TITLE: Screening for Oral Cancer using Light-based Techniques: A Review of the Diagnostic Accuracy, Cost-effectiveness, and Guidelines

DATE: 10 September 2013

CONTEXT AND POLICY ISSUES

Oral cancer is any malignant tissue growth located in the oral cavity. Risk factors for oral cancer include heavy smoking, drinking alcohol and pan chewing.[1]

The Canadian estimates for cancer published by the Public Health Agency of Canada[2] for 2013 reported approximately 4,100 new cases of oral cancer; that is equivalent to 8.7 per 100,000 age-adjusted incidence rate. These incidence rates are relatively lower than prostrate, breast, and colorectal cancer, but are almost three times higher than for cervical cancer and almost double those of liver cancer.[3] The five year survival rate for oral cancer is 63 percent compared to the survival rates of cervical cancer (75 %) and prostate cancer (95 %).[2,3] The projected rate of age-adjusted mortality for the year 2013 is 2.3 per 100,000 which translates to 1,150 deaths.[2]

Early detection of oral cancer is believed to reduce the morbidity and increase the survival of patients. The histopathological analysis of suspected lesions is the gold standard for oral cancer diagnosis;[4] however, it can only be provided for patients with highly suspicious lesions to confirm the clinical diagnosis. On the other hand, screening tests, which included conventional visual examination, diagnostic adjuncts such as Toluidine Blue, and light-based screening methods, are provided for asymptomatic individuals to ameliorate the early detection of malignant or premalignant lesions.[5] The effectiveness of screening tests can be evaluated by the diagnostic values in terms of sensitivity, specificity, positive and negative predictive values, and the number of additional cases detected by the new test which were not detected by the standard procedure.[6]

There is evidence that screening for oral cancer with conventional visual examination can reduce mortality in high-risk individuals.[5,7] Visualization adjuncts may be used in combination with conventional examination or alone. The light-based screening methods include applying a chemisluminescent- or LED-greenrated light emitted from a hand held device. The oral tissues can retain fluorescent characteristics after excitation with ultra-violet light or applied chemicals and the malignant lesion shows up as bright white or dark, depending on the device used.[8,9]

A previous report produced by the Canadian Agency for Drugs and Technologies in Health concluded that there wasn't a strong evidence to suggest that these adjunctive technologies could help the clinician to identify premalignant lesions before they are detectable by conventional visual examination.[10] The current review had the objective to update the evidence supporting the use of light-based adjuncts in oral cancer screening.

RESEARCH QUESTIONS

1. What is the diagnostic accuracy of light-based screening techniques compared with conventional oral examination for the detection of oral cancer?

2. What is the cost-effectiveness of light-based oral cancer screening compared with conventional oral examination?

3. What are the evidence based guidelines for oral cancer screening?

KEY FINDINGS

Two guidelines, two systematic reviews, and 13 primary studies were included in this review. The included studies evaluated three light-based screening adjuncts: VELscope, ViziLite and Identafi. No cost-effectiveness studies were found. The available evidence does not support the use of the evaluated tools for the screening of cancer in the general population or those at low risk for malignancy.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 7), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type for research questions one and two. A guideline filter was used for research question three. The search was also limited to English language documents published between January 1, 2008 and August 12, 2013.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed for relevance. Full texts of relevant titles/abstracts were retrieved, and assessed for inclusion. The final article selection was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults
Intervention	Light-based oral cancer screening techniques such as ViziLite, MicroLux DL, VELscope or Identafi
Comparator	Conventional oral examination
Outcomes	Q1: Diagnostic accuracy Q2: Cost-effectiveness Q3: Evidence-based guidelines
Study Designs	Health technology assessment, systematic review, meta-analysis, randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines

Exclusion Criteria

Observational and retrospective studies, case series, and studies without comparative or reference tests were excluded from this review. Studies on indirect visualization methods were excluded; indirect visualization is based on capturing the fluorescent reflection with special spectrometers. Experimental or commercially unavailable devices were also excluded. Two cost-effectiveness studies were excluded from the review because they did not specifically evaluate light-based screening adjunct; instead they conducted a general evaluation of screening programs. Studies with a more recent update were considered duplicates and were excluded; the most recent update was considered the primary publication, and previous versions were used as secondary source of data.

Critical Appraisal of Individual Studies

Critical appraisal of the included studies was based on study design.

The Appraisal of Guidelines Research and Evaluation (AGREE) instrument[11] was used to evaluate the quality of the included guidelines. The methodological quality of the included systematic reviews was evaluated using the "assessment of multiple systematic reviews" (AMSTAR).[12] AMSTAR is an 11-item checklist that has been developed to ensure reliability and construct validity of systematic reviews. The methodological quality of the included randomized controlled trial was evaluated using the SIGN50 checklist for controlled studies.[13] The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool[6] was used to evaluate the included diagnostic studies. The QUADAS tool is a 14-item questionnaire that is used to evaluate bias, data variability, and quality of reporting in diagnostic studies.

For the included studies a numeric score was not calculated. Instead, the strengths and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 491 potential citations were identified by searching the bibliographic databases; nine additional articles were identified in the grey literature and by hand search. Of the 500 citations, 453 were excluded during the title and abstract screening based on their irrelevance to the questions of interest. The full text documents of the remaining 47 articles were retrieved. Of these articles, 30 did not meet the inclusion criteria and were excluded, leaving 17 articles that reported two guidelines, two systematic reviews, one randomized controlled trial, and 12 diagnostic studies. The search did not identify any cost-effectiveness study.

A PRISMA diagram demonstrating the study selection process is presented in Appendix I.

Summary of Study Characteristics

Details on studies characteristics are tabulated in Appendix II.

Two guidelines were included and gave recommendations on the use of light-based adjuncts.[14,15] The remainder of the articles addressed the diagnostic accuracy of the light-based adjuncts for oral cancer screening: The two included systematic reviews reported on two adjunct devices, VELscope and ViziLite.[16,17] In addition, VELscope was evaluated in eight studies,[18-25] ViziLite was evaluated in four studies,[26-29] and Identafi was evaluated in one study.[30]

*Evidence-based guidelines (***Table 2***)*

One guideline was produced by the HealthPartners Dental Group in 2007 and was summarized by the Agency for Healthcare Research and Quality (AHRQ) in 2012.[14] The guideline intended to provide guidance on risk assessment for early oral cancer detection. The guideline was not specific for light-based visualization adjuncts, but it reported recommendations on these tools; a total of 26 articles supported the recommendations of this guideline. The other guideline was produced in 2010 by Rathman et al.[15] The guideline was produced in collaboration with the American Dental Association; the guideline was based on five systematic reviews and four clinical trials.

*Systematic reviews (***Table 3***)*

The included systematic reviews were published in 2009[16] and 2008.[17] The inclusion of these reviews provides a glimpse on the evidence anterior to the search limits of the current review. One review, by Trullenque et al,[16] included six studies on ViziLite and four studies on VELscope.[16] The results were reported as a narrative conclusion for each included article. The review by Patton et al.[17] included four studies on VELscope and ViziLite, and it was reported that no relevant articles were identified on Microlux or Orascoptic. The results were reported in terms of diagnostic values.

*Primary studies on VELscope (***Table 4***)*

Eight studies that evaluated VELscope and met the inclusion criteria were published since 2010. Two studies were conducted in Canada,[18,19] three in Germany,[20,24,25] and one study each was conducted in Australia,[21] USA,[22] and Italy.[23] In six studies, patients were recruited after referral

to a specialist due to a preliminary diagnosis of suspicious lesions.[19-21,23-25] One study recruited individuals from the general population through public invitation,[18] and the last study recruited dental clinic patients who consulted the clinic for routine dental care.[22] Conventional visual examination was the comparator test in all these studies, and they used the histopathology evaluation as the reference test. Biopsies or histopathology was conducted for all included patients in four trials;[21,23-25] the other four trials however, conducted the histopathology only for suspicious lesions as judged by the clinical and or the index examination (VELscope).

*Primary studies on ViziLite (***Table 4***)*

Studies that evaluated ViziLite were conducted in India,[26,29] Poland,[27] and UK.[28] The four studies included patients at high-risk for oral cancer, either by preliminary diagnosis of suspicious lesions or cancer. Two studies compared ViziLite with the Toluidine Blue staining test,[26,27] one study compared it with the conventional visual examination,[28] and one study compared ViziLite with VELscope.[29] The histopathology testing was provided for all patients as the reference test; however, in one study the histopathology results were missing for 10 patients, and the reason for this was not provided.[28]

*Primary study on Identafi (***Table 4***)*

The included patients in this study were treated for head and neck cancer, and were recruited during their follow-up routine. The trial compared the use of Identafi with the conventional oral examination, and the histopathology testing was the reference test. However, histopathology was conducted only if the lesion was detected positive by either of the index tests.

Summary of Critical Appraisal

Details on studies appraisal are tabulated in Appendix III.

Quality of the evidence-based guidelines

The two guidelines were based on systematic reviews of the literature. The quality of evidence was evaluated in Rethman's guideline[15] but not reported in the AHRQ guideline.[14] The two guidelines did not report if patients' preferences and values were considered in producing the final recommendations.

Quality of the systematic reviews

The review by Trullenque et al. included cross-sectional studies, case series and opinion articles; the last two types of publications are not a reliable source of evidence. Furthermore, the review did not report the inclusion criteria nor patients' characteristics, and the quality of the included studies was not evaluated.[17] Conversely, Patton's review was based on a priori design and selection criteria, and literature search was supplemented by hand searching.[17] The quality of the included studies was evaluated and considered in the recommendations. However, Patton's review did not specify if the literature selection was done in duplicate by more than one reviewer.[17]

Primary studies

The main limitation of the included primary studies was the recruitment of high-risk individuals or even cancer patients who were already treated for cancer. Only two studies included patients from the general population or low-risk individuals.[18,22] The validation of screening tests should be conducted on asymptomatic individuals; the use of high-risk patients might limit the generalizability of findings to the general population for whom the screening tests will be used. All other primary studies included in this review were conducted on patients who have high risk of developing cancer or have a high probability of having cancer based on a preliminary screening.

Another important limitation is the partial testing with the reference test. The true status of the lesions could not be confirmed or refuted without a reliable diagnostic tool. In the case of cancer, the histopathology of biopsies in the gold standard diagnostic method; however, it is neither realistic nor ethical to conduct a biopsy screening for asymptomatic individuals. Another method of refuting cancer is by long term follow-up. This can be helpful if the clinician suspects that the origin of the oral lesion is inflammatory or traumatic; these lesions tend to resolve spontaneously in two to three weeks. If lesions persist after this follow-up, a biopsy is warranted. The deferred biopsy method was done in two studies;[18,22] the two studies are the ones that included individuals from the general population. In three studies, biopsy was offered only if the index tests showed positive results.[19,20,30]

Summary of Findings

Details on studies' findings are tabulated in Appendix IV.

Recommendations from the evidence-based guidelines

The guideline summarized by the AHRQ reported that further studies are needed to determine whether ViziLite has a role in oral cancer screening.[14] The document reported that ViziLite may be of benefit for patients who are already diagnosed with oral cancer.

Rethman's guideline reported that the available evidence was insufficient to support the use of ViziLite or VELscope for the detection of potentially malignant lesions.[15]

Results of the systematic reviews

Trullenque et al. reported the diagnostic values of ViziLite from two studies; the sensitivity of the test was 100% in both studies, but the specificity was 14.2% in one trial and 0% in the other one.[16] The diagnostic values for the VELscope studies in Trullenque's review were obtained from one observational study, case series and opinion article. These sources are not a reliable source for evidence, and the reported diagnostic values could not be used with confidence.[16]

Patton's review included six studies.[17] Four studies evaluated ViziLite and reported 100% sensitivity in all studies; specificity ranged from 0% in two studies to 55%. On the other hand, the two studies that evaluated VELscope reported a sensitivity of 98% to 100% and a specificity of 100% to 78%.

Results of the primary studies on VELscope

The study by Laronde et al.[18] reported the Akiake Information Criteria (AIC) as an indicator of the utility of the screening test (VELscope) in predicting the persistence of suspicious lesions after three weeks of follow-up. The AIC showed that the model fit was better when the VELscope results, at the initial visit, were included in the model compared to the clinical evaluation results. However, these results could not be used to conclude on the diagnostic validity of the test because the model fit did not provide information on how many additional cases were detected by the new technology when compared with the standard methods.

Four studies reported the diagnostic values of the VELscope.[23,23-25] Sensitivity ranged from 30%[23] to 100%,[24] and specificity ranged from 16%[25] to 97.4%.[23] Two of these studies reported the diagnostic values of the conventional clinical examination and showed that VELscope provided comparable results as the conventional examination.

Three studies did not report the results for the histopathology, or partially reported them. Marzouki's study reported values of sensitivity, specificity, and positive and negative predictive values for VELscope and the clinical examination.[19] However, the reference test was not provided for lesions that were diagnosed negative by the two index tests; the results of the reference test, for all included patients, are essential to calculate the sensitivity, specificity and negative predictive values. For this reason, there is no known method to calculate these values; nevertheless, the authors reported such values but without justifications on the methods used for these calculations. The only diagnostic value that could be calculated is the positive predictive value that was 47% for VELscope and the clinical examination. The same issue was encountered in Rana et al.[20] The study reported the sensitivity and specificity of VELscope; however, the reported data did not include the results for the reference test (histopathology), and for this reason these values could not be used without providing justification on the method and data used to estimate them.[20] A third study by McNamara et al. had the histopathology evaluation missing for ten patients, and therefore the diagnostic values could not be calculated.[22]

Results of the primary studies on ViziLite

The reported sensitivity of ViziLite ranged from 0%[29] to 84%,[26,28] and the specificity ranged from 15%[28] to 91%.[26] When ViziLite was compared with Toluidine Blue, it showed better diagnostic values; however, it did not provide additional diagnostic value compared to the conventional clinical examination. ViziLite provided better specificity results than VELscope, but its sensitivity was lower.[29]

Results of the primary study on Identafi

The study showed sensitivity and negative predictive values equivalent to the conventional clinical study, 50% and 98% respectively. However, the specificity and positive predictive values were lower than what was reported for the conventional clinical examination, 81% versus 98% and 11% versus 50% for the specificity and positive protective value of Identafi and the conventional test respectively.

Limitations

The majority of the included trials evaluated light-based screening adjuncts in patients at high-risk for oral cancer. This type of population might not be representative of the general population for whom screening tests should be designed and validated. Furthermore, the quality of some of the included studies, or at least their reporting quality, did not allow for full evaluation of the diagnostic values of the assessed screening tools.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This report aimed to evaluate the diagnostic value of light-based adjuncts for oral cancer screening. A total of two guidelines, two systematic reviews, and 13 primary studies were retrieved. The included studies evaluated three light-based screening adjuncts: VELscope, ViziLite and Identafi. No cost-effectiveness studies were found.

In general, the evaluated tools showed high sensitivity and low specificity values, but these results were not consistent across the trials. When these tools were compared with results of the conventional clinical examination, they did not provide superior diagnostic values. It can be concluded that the reviewed light-based screening tools are not suitable for cancer screening in the general population due to their high potential of false positive screening. For patients already treated for cancer, light-based screening tools may be helpful as an adjunct tool during the follow-up evaluation.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Elango KJ, Anandkrishnan N, Suresh A, Iyer SK, Ramaiyer SK, Kuriakose MA. Mouth self-examination to improve oral cancer awareness and early detection in a high-risk population. Oral Oncol. 2011 Jul;47(7):620-4.

2. Canadian cancer statistics 2013: special topic: liver cancer [Internet]. Toronto: Canadian Cancer Society; 2013. [cited 2013 Aug 19]. Available from: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/canadian-cancer-statistics-2013-EN.pdf

3. Health Canada [Internet]. Ottawa: Health Canada; 2013. Oral cancer; 2009 [cited 2013 Sep 4]. Available from: http://www.hc-sc.gc.ca/hl-vs/oral-bucco/disease-maladie/cancer-eng.php

4. Sankaranarayanan R, Ramadas K, Thomas G, Muwonge R, Thara S, Mathew B, et al. Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. Lancet. 2005 Jun 4;365(9475):1927-33.

5. Subramanian S, Sankaranarayanan R, Bapat B, Somanathan T, Thomas G, Mathew B, et al. Cost-effectiveness of oral cancer screening: results from a cluster randomized controlled trial in India. Bull World Health Organ. 2009 Mar;87(3):200.

6. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol [Internet]. 2003 Nov 10 [cited 2013 Aug 13];3(25). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC305345

7. Brocklehurst P, Kujan O, Glenny AM, Oliver R, Sloan P, Ogden G, et al. Screening programmes for the early detection and prevention of oral cancer. Cochrane Database Syst Rev. 2010;(11):CD004150.

8. Pavlova I, Williams M, El-Naggar A, Richards-Kortum R, Gillenwater A. Understanding the biological basis of autofluorescence imaging for oral cancer detection: high-resolution fluorescence microscopy in viable tissue. Clin Cancer Res [Internet]. 2008 Apr 15 [cited 2013 Aug 15];14(8):2396-404. Available from: http://clincancerres.aacrjournals.org/content/14/8/2396.full.pdf+html

9. Huber MA. Adjunctive diagnostic aids in oral cancer screening: an update. Tex Dent J. 2012 May;129(5):471-80.

10. Canadian Agency for Drugs and Technologies in Health. Detection of oral cancer: quidelines and a clinical effectiveness review [Internet]. Ottawa: The Agency; 2008 May 20. [cited 2013 Aug 19]. (Health technology inquiry service (HTIS)). Available from: http://www.cadth.ca/media/pdf/htis/Detection%20of%20Oral%20Cancer%20Guidelines%20and%20a%20Clinical%20Effectiveness%20Review.pdf

11. The AGREE Collaboration. Appraisal of guidelines for research and evaluation (AGREE) instrument [Internet]. London: The AGREE Research Trust; 2001 Sep. [cited 2013 Sep 10]. Available from: http://www.agreetrust.org/?o=1085

12. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2013 Sep 6];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

13. Scottish Intercollegiate Guidelines Network. Methodology checklist 2: randomized controlled trials [Internet]. In: SIGN 50: a guideline developer's handbook. Edinburgh: SIGN; 2008 [cited 2013 Sep 10]. Available from: http://www.sign.ac.uk/guidelines/fulltext/50/checklist2.html.

14. National Guideline Clearinghouse [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); c2009 -. Health Partners Dental Group and Clinics oral cancer guideline; 2012 Nov [cited 2013 Aug 15]. Available from: http://www.guideline.gov/content.aspx?id=39245

15. Rethman MP, Carpenter W, Cohen EE, Epstein J, Evans CA, Flaitz CM, et al. Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas. J Am Dent Assoc. 2010 May;141(5):509-20.

16. Trullenque-Eriksson A, Munoz-Corcuera M, Campo-Trapero J, Cano-Sanchez J, Bascones-Martinez A. Analysis of new diagnostic methods in suspicious lesions of the oral mucosa. Med Oral Patol Oral Cir Bucal [Internet]. 2009 May [cited 2013 Aug 15];14(5):E210-E216. Available from: http://www.medicinaoral.com/pubmed/medoralv14_i5_p210.pdf

17. Patton LL, Epstein JB, Kerr AR. Adjunctive techniques for oral cancer examination and lesion diagnosis: a systematic review of the literature. J Am Dent Assoc. 2008 Jul;139(7):896-905.

18. Laronde DM, Williams PM, Hislop TG, Poh C, Ng S, Bajdik C, et al. Influence of fluorescence on screening decisions for oral mucosal lesions in community dental practices. J Oral Pathol Med. 2013 Jun 10. Epub ahead of print.

19. Marzouki HZ, Tuong Vi Vu T, Ywakim R, Chauvin P, Hanley J, Kost KM. Use of fluorescent light in detecting malignant and premalignant lesions in the oral cavity: a prospective, single-blind study. J Otolaryngol Head Neck Surg. 2012 Jun 1;41(3):164-8.

20. Rana M, Zapf A, Kuehle M, Gellrich NC, Eckardt AM. Clinical evaluation of an autofluorescence diagnostic device for oral cancer detection: a prospective randomized diagnostic study. Eur J Cancer Prev. 2012 Sep;21(5):460-6.

21. Farah CS, McIntosh L, Georgiou A, McCullough MJ. Efficacy of tissue autofluorescence imaging (VELScope) in the visualization of oral mucosal lesions. Head Neck. 2012 Jun;34(6):856-62.

22. McNamara KK, Martin BD, Evans EW, Kalmar JR. The role of direct visual fluorescent examination (VELscope) in routine screening for potentially malignant oral mucosal lesions. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012 Nov;114(5):636-43.

23. Paderni C, Compilato D, Carinci F, Nardi G, Rodolico V, Lo ML, et al. Direct visualization of oral-cavity tissue fluorescence as novel aid for early oral cancer diagnosis and potentially malignant disorders monitoring. Int J Immunopathol Pharmacol. 2011 Apr;24(2 Suppl):121-8.

24. Scheer M, Neugebauer J, Derman A, Fuss J, Drebber U, Zoeller JE. Autofluorescence imaging of potentially malignant mucosa lesions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011 May;111(5):568-77.

25. Koch FP, Kaemmerer PW, Biesterfeld S, Kunkel M, Wagner W. Effectiveness of autofluorescence to identify suspicious oral lesions--a prospective, blinded clinical trial. Clin Oral Investig. 2011 Dec;15(6):975-82.

26. Rajmohan M, Rao UK, Joshua E, Rajasekaran ST, Kannan R. Assessment of oral mucosa in normal, precancer and cancer using chemiluminescent illumination, toluidine blue supravital staining and oral exfoliative cytology. J Oral Maxillofac Pathol [Internet]. 2012 Sep [cited 2013 Aug 15];16(3):325-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3519202/?report=printable

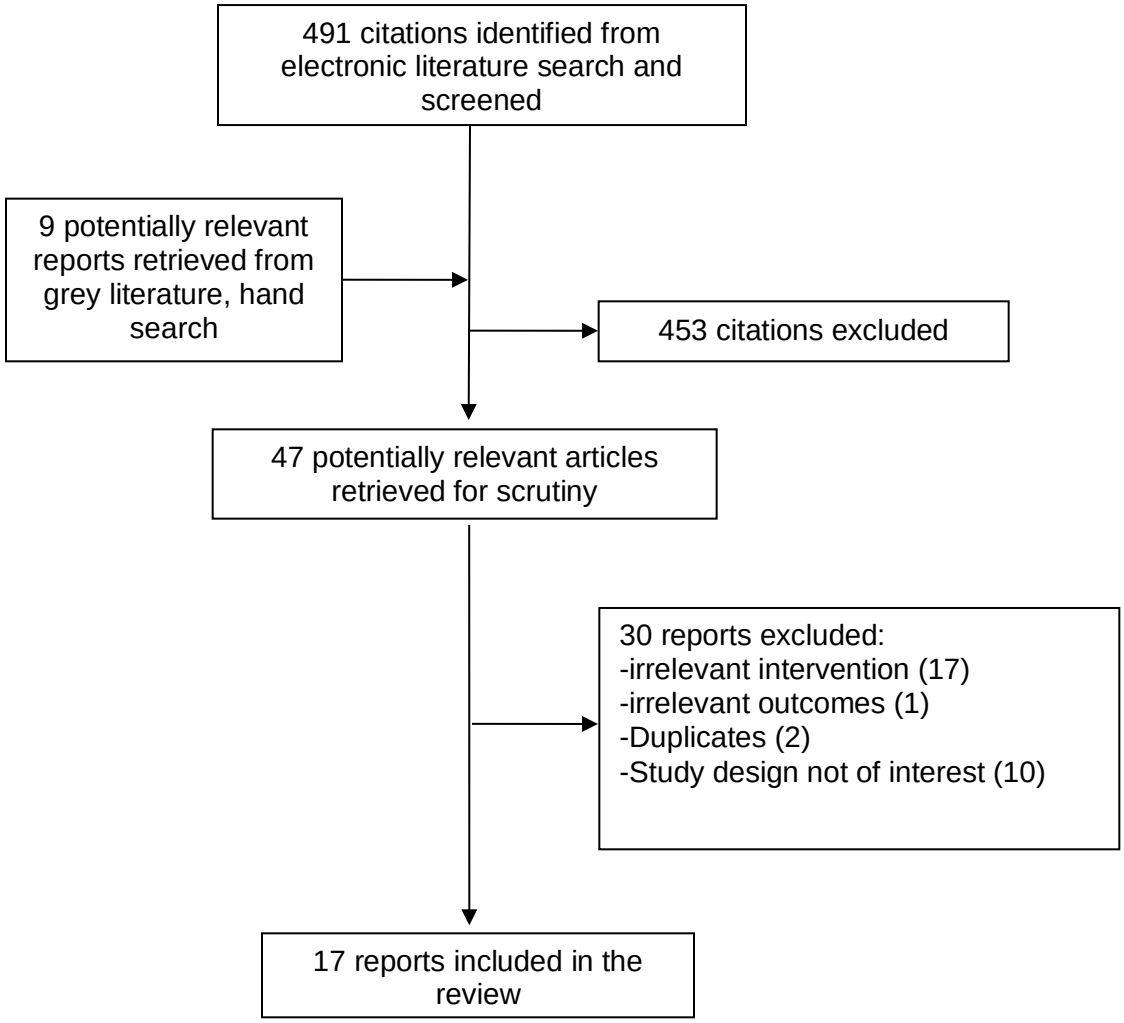
27. Mojsa I, Kaczmarzyk T, Zaleska M, Stypulkowska J, Zapala-Pospiech A, Sadecki D. Value of the ViziLite Plus System as a diagnostic aid in the early detection of oral cancer/premalignant epithelial lesions. J Craniofac Surg. 2012 Mar;23(2):e162-e164.

28. Awan KH, Morgan PR, Warnakulasuriya S. Utility of chemiluminescence (ViziLite) in the detection of oral potentially malignant disorders and benign keratoses. J Oral Pathol Med. 2011 Aug;40(7):541-4.

29. Mehrotra R, Singh M, Thomas S, Nair P, Pandya S, Nigam NS, et al. A cross-sectional study evaluating chemiluminescence and autofluorescence in the detection of clinically innocuous precancerous and cancerous oral lesions. J Am Dent Assoc. 2010 Feb;141(2):151-6.

30. Sweeny L, Dean NR, Magnuson JS, Carroll WR, Clemons L, Rosenthal EL. Assessment of tissue autofluorescence and reflectance for oral cavity cancer screening. Otolaryngol Head Neck Surg [Internet]. 2011 Dec [cited 2013 Aug 15];145(6):956-60. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3594780/pdf/nihms-341248.pdf

APPENDIX I: SELECTION OF INCLUDED STUDIES



APPENDIX II: CHARACTERISTICS OF THE INCLUDED STUDIES

Table 2: Characteristics of the Included Guidelines

Scope and purpose	Involved stakeholders	Methods of development	Notes
Agency for Healthcare Research and Quality – National Guideline Clearinghouse – Guideline summary-9498, 2012[14] – USA			
To provide a model to assess an individual patient's risk for developing an oral cancer and to recommend tools for early oral cancer detection Oral cancers including squamous cell carcinoma, melanoma, metastatic neoplasm, kaposi's sarcoma and other oral cancers	Dentists were identified as the intended users of the guideline. However, there involvement in the development of the guideline was not specified. No other stakeholders were identified in the reviewed document.	Evidence was synthesized through a systematic review of published primary trials, systematic reviews and meta-analyses. A total of 26 articles were reviewed by the developing committee, and recommendations were formulated by expert consensus	The guideline was not specific for adjunctive diagnostic or screening aids. ViziLite was the only light-based diagnostic adjunct reported in this guideline
Rethman et al., 2010[15] – USA			
To address the benefits and limitations of oral cancer screening and the use of adjunctive screening tools for early visual detection of malignant and potentially malignant oral lesions Squamous cell carcinoma of the lips and cancers of the oropharynx were excluded.	The American Dental Association	Evidence was synthesized through a systematic review of published primary trials, systematic reviews and meta-analyses. A total of five systematic reviews and four clinical trials were reviewed by a panel of experts. The panel evaluated the evidence and used to develop their recommendations. Recommendations were produced through a consensus or voting process	

Table 3: Characteristics of the Included Systematic Reviews

Objectives/Scope	Type of primary studies	Population/ Medical context	Intervention/ Comparator	Outcomes
Trullenque-Eriksson et al. 2009[16] – Spain				
To review the evidence on the utility of adjunctive tools for oral cancer identification. Published literature between 2002 and 2008. Technology assessed: light-based (ViziLite and VELscope) and trans-epithelial cytology-based (OralCDx)	Criteria for inclusion and exclusion of studies were not reported. Five cross-sectional studies and one pilot study were included for the ViziLite; one cross-sectional study, one case series and two opinion articles were included for VELscope.	Patients' characteristics were not reported. A total of 563 patients were included in the six ViziLite trials. In the VELscope trials, 24 patients were included in two studies; number of patients was not provided for the other two studies.	**Interventions:** ViziLite, VELscope and OralCDx **Comparators:** Not specified	Narrative conclusion of each included article
Patton et al. 2008[17] – USA				
To evaluate the role of adjunctive tools in early oral cancer detection. Published literature between 1966 and 2008. Technology assessed: vital tissue staining (tolonuim chloride), light-based (ViziLite, VELscope, Microlux DL, and Orascoptic DK) and trans-epithelial cytology-based (OralCDx)	The review excluded case reports and statements of expert opinion. To be included, studies had to have histopathologic confirmation as a reference test. Four studies evaluating ViziLite and VELscope were included; the review did not identify any relevant studies for Microlux DL, and Orascoptic DK	The adjunctive tools (ViziLite and VELscope) were evaluated as diagnostic adjunct in patients who had oral lesions; performance of these tools as screening tools in the general population was not assessed in the included studies	**Interventions:** ViziLite, VELscope **Comparators:** Histopathology	Diagnostic performance in terms of specificity, sensitivity, and positive and negative predictive values.

Table 4: Characteristics of the Included Studies

Study objective and design	Population	Intervention	Comparator	Outcomes
Laronde et al. 2013[18] – Canada – (VELscope 1/8)				
To test the utility of fluorescence visualization as an adjunct screening tool for oral cancer and other oral lesions Diagnostic study	The general population in Vancouver – Canada was called to participate in the study. A total of 2404 individual were recruited in the study	VELscope; according to tissue retention for the green autofluorescence light, lesion were classified: - FV negative: normal green light that indicates normal tissue - FV positive: reduction in the green light that appears as dark patches indicates tissue anomaly - FV equivocal: this class was used when the dentist could not classify the tissue in one of the previous classes	Visual screening examination; lesions were classified as: - Low-risk: obvious trauma, aphthous lesions, melanotic macules, candidiasis, and geographic tongue - High-risk: anomalies without apparent cause, non-healing ulcers, red or white patches, and Lichenoid lesions.	• Descriptive association analysis between the autofluorescence and VELscope assessments. • Prediction value for the lesion persistence; this was measured by logistic regression models that fitted either the autofluorescence or the visual exam values, both of them or neither value. The Akaike Information Criteria was obtained from the four models, and was used to evaluate the predictive utility of each test.
		After three weeks, patients with low-risk lesions without an obvious cause and patients with high risk lesions were followed-up after 3-weeks from the initial exam. These patients had another visual and autofluorescence exams. Any suspicious lesions were referred to oral medicine specialist who decided if a biopsy was necessary or not. The decision of the specialist and the biopsy were considered the reference		
Marzouki et al. 2012[19] – Canada – (VELscope 2/8)				
To determine the usefulness of the VELscope in detecting malignant oral cavity lesions. Diagnostic study	Patients referred to the oncology clinic at the McGill University Health Centre. Patients had strong history of smoking and alcohol consumption and suspicious	VELscope examination for the oral cavity. • The exam was conducted after the clinical exam • The examiner was blinded to the results of the clinical examination	Full clinical examination for the head and neck and the oral cavity.	• Diagnostic performance in terms of specificity, sensitivity, and positive and negative predictive values.

Table 4: Characteristics of the Included Studies

Study objective and design	Population	Intervention	Comparator	Outcomes
	lesions seen by primary care providers. A total of 85 patients were included	Biopsy was taken for all suspicious sites detected by the clinical examination and/ or VELscope. A total of 33 biopsies were analyzed by an experienced pathologist.		
Rana et al. 2012[20] – Germany – (VELscope 3/8)				
To evaluate an adjunctive device for the diagnosis of oral cancer. Randomized trial	Patients were referred to a specialized maxillofacial surgery department for suspicious oral lesions. Patients were included in the study only if they presented with premalignant lesions (leukoplakia, erythroplakia, lichen planus, or pemphigus vlugaris) A total of 289 patients were included in the study	• Autofluorescence visualization examination (VELscope) in addition to the conventional oral examination with white light • N = 123	Conventional oral examination with white light N = 166	• The diagnostic value in terms of sensitivity and specificity
		Suspicious lesions from both groups were biopsied. If the lesions were suspected to be from acute inflammatory origin, a recall visit after two weeks was planned to reduce the false positive. N = 52		
Farah et al. 2012[21] – Australia – (VELscope 4/8)				
To evaluate the efficacy of direct tissue autofluorescence imaging Visually Enhanced Lesion Scope (VELscope) in the detection of oral mucosal lesions. Diagnostic study	Patients were recruited from an oral medicine specialist unit. Patients were referred to the clinical because of suspected oral lesions. A total of 112 patients were included	• Oral examination using the VELscope device N = 112 patients	Clinical examination under incandescent operatory light N = 112 patients	• Diagnostic value in terms of sensitivity, specificity, accuracy, and positive and negative predictive values
		All suspected lesions were biopsied and examined histologically. A total of 118 biopsies were evaluated		
McNamara et al. 2012[22] – USA – (VELscope 5/8)				
To evaluate the benefit of VELscope in routine screening for potentially malignant oral mucosal	Patients were recruited from a university dental clinic. Patients consulted the clinic for routine dental care	• Oral examination using the VELscope device N = 130 patients	Clinical oral examination under incandescent operatory light N = 130 patients	• Association between the clinical oral examination, VELscope and the histopathology

Table 4: Characteristics of the Included Studies

Study objective and design	Population	Intervention	Comparator	Outcomes
lesions in a general population of patients. Diagnostic study	A total of 130 consecutive patients were included	All patients were followed-up after 2 weeks; suspected lesions were biopsied and examined histologically. A total of 95 clinical lesions were biopsied		
Panderni et al. 2011[23] – Italy – (VELscope 6/8)				
To evaluate the diagnostic value of the an autofluorescence device for the visualization potentially malignant oral lesions Diagnostic study	Patients were recruited form a University department of oral sciences. Patients were referred to the department because of suspected oral lesions detected by conventional oral examination. A total of 175 patients were recruited	• Oral examination using the VELscope device N = 175 patients	Clinical examination under incandescent operatory light N = 175 patients	• Diagnostic value in terms of sensitivity, specificity, accuracy, and positive and negative predictive values
		All visualized lesions were biopsied and examined histologically. A total of 175 biopsies were evaluated		
Scheer et al. 2011[24] – Germany – (VELscope 7/8)				
To evaluate the diagnostic value of the fluorescence loss with the VELscope device in oral cancer Diagnostic study	Patients were recruited from a university department for oral surgery. Patients were referred to the department for suspected invasive squamous cell carcinoma. A total of 64 patients were included. Twenty patients had history of oral squamous cell carcinoma	• Oral examination using the VELscope device N = 64 patients	Clinical examination under incandescent operatory light N = 64 patients	• Diagnostic value in terms of sensitivity, specificity, and positive and negative predictive values
		All visualized lesions were biopsied and examined histologically.		
Koch et al. 2010[25] – Germany – (VELscope 8/8)				

Table 4: Characteristics of the Included Studies

Study objective and design	Population	Intervention	Comparator	Outcomes
To evaluate the effectiveness of the autofluorescence investigation to differentiate between suspicious and benign oral lesions, dysplasia and squamous cell carcinoma. Diagnostic study	Patients were recruited from a university clinic of oral and maxillofacial surgery. Patients had to have clinical diagnosis of squamous cell carcinoma or suspicious lesion requiring histological evaluation. A total of 78 patients were included	• Oral examination using the VELscope device o Two reading were recorded: the green light and red light reflection o N = 78 patients	Clinical examination under incandescent operatory light N = 78 patients	• Diagnostic value in terms of sensitivity, specificity, and positive and negative predictive values
		All visualized lesions were biopsied and examined histologically.		
Rajmohan et al. 2012[26] – India – (ViziLite 1 of 4)				
To evaluate the efficacy of chemiluminescent illumination (ViziLite) for the diagnosis of premalignant and malignant oral lesions Diagnostic study	The trial included 3 groups of patients. Group I had normal appearing mucosa, group II had a clinical diagnosis of pre-cancer lesions, and group III had a clinical diagnosis of oral cancer lesion. A total of 30 patients were included, 10 patients in each group. The setting in which the trial was conducted was not specified.	• Oral examination using the ViziLite device o N = 30	• Toluidine blue staining o N = 30 • Oral exfoliative cytology o N = 30	• Number of positive and negative cases based on each test
		All visualized lesions were biopsied and examined histologically. Biopsies were taken from the sites that showed positive results with the ViziLite or Toluidine blue; if these two test showed different sites multiple biopsies were taken for the same patient		
Mojsa et al. 2012[27] – Poland – (ViziLite 2 of 4)				
To evaluate the value of chemiluminescent and 1% tolonium chloride in the early diagnosis of malignant and premalignant epithelial lesions Diagnostic study	Patients were included if they had premalignant oral lesions, as per the clinical evaluation. A total of 30 patients were included	• Oral examination using the ViziLite device o N = 30 patients/ 41 lesions	• Toluidine blue staining o N = 41 lesions • Clinical evaluation o N = 41 lesions	• Diagnostic value in terms of sensitivity, specificity, positive and negative predictive values.
		All visualized lesions were biopsied and examined histologically.		

Table 4: Characteristics of the Included Studies

Study objective and design	Population	Intervention	Comparator	Outcomes
Awan et al. 2011[28] – UK – (ViziLite 3 of 4)				
To evaluate the utility of ViziLite examination as an adjunct in the identification of oral potentially malignant disorders. Diagnostic study	Patients were recruited form two hospital clinics of oral medicine. Consecutive patients with white, red, and mixed patches were recruited in the study. A total of 126 patients were included in the study	• Oral examination with ViziLite procedure o N = 126	• Clinical examination using white light o N = 126	• Diagnostic value in terms of sensitivity, specificity, positive and negative predictive values.
		A total of 116 lesions were biopsied and examined histologically. The reason for the missing 10 lesions was not reported.		
Mehrotra et al. 2010[29] – India (ViziLite 4 of 4)				
To evaluate the use of ViziLite with toluidine blue and VELscope as adjunct aids in the diagnosis of suspicious oral lesions. Diagnostic study	Patients were recruited from a District Hospital in India; patients had to have clinically innocuous oral lesions to be included in the trial. A total of 258 patients were included in the trial. Patients were divided into two groups.	• Oral examination using the ViziLite plus Toluidine blue o N = 102	• Oral examination using the VELscope device o N = 156	• Diagnostic value in terms of sensitivity, specificity, positive and negative predictive values.
		All visualized lesions were biopsied and examined histologically.		
Sweeny et al. 2011[30] – USA (Identafi 1 of 1)				
To evaluate the diagnostic validity of an autofluorescence visualization device (Identafi) for the screening of oral and oropharynx cancer Diagnostic study	Patients treated for head and neck cancer were included in the trial. A total of 88 patients were included in the study	• Oral examination using the Identafi device o Tissue autofluorescence o Tissue reflectance o N = 88	• Oral examination using conventional white light o N = 88	• Diagnostic value in terms of sensitivity, specificity, positive and negative predictive values.
		Any suspected lesion, by any of the above tests, was biopsied and examined histologically.		

[a]

APPENDIX III: CRITICAL APPRASIAL OF THE INCLUDED STUDEIS

Strengths	Limitations
Clinical Practice Guidelines	
Agency for Healthcare Research and Quality – National Guideline Clearinghouse – Guideline summary-9498, 2012[14] – USA	
Evidence was collected by a systematic review of the published medical literature The guidelines were validated though an external peer review process	• The quality of evidence was not reported, and it was not clear if it was evaluated or considered in the development of recommendations • Recommendations were formulated through expert consensus; however, details on these experts or their area of expertise were not provided. • It was not clear whether patient's preferences and values were considered in the recommendations or not.
Rethman et al., 2010[15] – USA	
Evidence was searched and synthetized with a systematic review process Quality of the evidence was evaluated and integrated in the produced recommendations Recommendations were reviewed by external and internal (from the ADA) peer review process	Guideline did seek patients opinion on the assessed technology, and patients' values and preferences were not considered in the recommendations
Systematic Reviews	
Trullenque-Eriksson et al. 2009[16] – Spain	
	• The review did not report the inclusion criteria. • Patient's characteristics were not provided. • The quality of the included studies was not evaluated.
Patton et al. 2008[17] – USA	
• The review was based on a priori design • The search was based on electronic literature search that was supplemented by grey literature and hand searching • The quality of the included studies was evaluated and reported as part of the results.	• It was not specified in the report whether study selection and data extraction was done in duplicate
Primary Studies	
Laronde et al. 2013[18] – Canada – (VELscope 1/8)	
- The trial recruited individuals from the general population; this type of recruitment reflects the clinical practice for screening asymptomatic patients. - The index test (VELscope) was sufficiently described and the range of outcome was provided.	- The trial based the call for reassessment on the visual screening examination and not the autofluorescence evaluation. According to the visual examination, here were a total of 135 patients with risk level that required reassessment; however, there were 218 patients with autofluorescence risk level requiring reassessment. The exclusion of the 83 (38%) of patients who were labeled as positive with the VELscope assessment would mask the high rate of false positive (low specificity) of the device. - The analysis plan considered the visual and the VELscope examination as explanatory factors in predictive models for lesion persistence. This type of analysis does not provide all the information needed to evaluate the utility of the new screening technology. - The reference test was not sufficiently declared. Visual screening was use as a comparator in one analysis and as reference in another. The declared reference test was the opinion of a specialist and biopsy results (if the specialist justified it). However, specialists were

Strengths	Limitations
	not consulted to control all the screened cases. Instead, they were consulted for persistent lesions only. Therefore, results from this trial might be generalizable to high risk patients only, since these are the only patients who had true reference test.
Marzouki et al. 2012[19] – Canada – (VELscope 2/8)	
• Different investigators conducted each test. Investigators of each test were blinded to the results of the other test. • The index screening test and the comparator screening test were both validated by a reference test (biopsy)	• The trial included high risk population who were already screened by their primary healthcare giver and had suspicious lesions that require referral to specialist. Results for this population might not be representative to the general population for which the light-based cancer screening is intended to be used.
Rana et al. 2012[20] – Germany – (VELscope 3/8)	
• Investigators, who conducted the VELscope evaluation, were unaware of the results of the conventional oral exam	• The trial included patients who already had been screened for oral cancer and had suspicious oral lesions. This might limit the generalizability of the trial's findings for the general population who is expected to receive the screening evaluation with VELscope • The randomized design is inappropriate for the validation of a diagnostic test. The verification by the gold standard method (biopsy) wasn't applied for all included patients; it was only provided for patients whose lesions were classified as suspicious by one of the examination methods assessed in the trial.
Farah et al. 2012[21] – Australia– (VELscope 4/8)	
• Investigators were blinded for the clinical examination results • All included patients benefited from the index test (VELscope), the comparator test (clinical evaluation), and the reference test (histopathological analysis) • The reference test was conducted by two investigators	• The trial included patients who already had been screened for oral cancer and had suspicious oral lesions. This might limit the generalizability of the trial's findings for the general population who is expected to receive the screening evaluation with VELscope
McNamara et al. 2012[22] – USA – (VELscope 5/8)	
• All included patients benefited from the index test (VELscope), the comparator test (clinical evaluation), and the reference test (histopathological analysis) • The trial included patients representative to the general population who did not have suspected lesions before the inclusion in the trial	•
Paderni et al. 2011[23] – Italy– (VELscope 6/8)	
• Investigators were blinded for the clinical examination results • All included patients benefited from the index test (VELscope), the comparator test (clinical evaluation), and the reference test (histopathological analysis) • Two investigators conducted the clinical visualization and pathological analyses	• The trial included patients who already had been screened for oral cancer and had suspicious oral lesions. This might limit the generalizability of the trial's findings for the general population who is expected to receive the screening evaluation with VELscope
Scheer et al. 2011[24] – Germany– (VELscope 7/8)	

Strengths	Limitations
• All included patients benefited from the index test (VELscope), the comparator test (clinical evaluation), and the reference test (histopathological analysis)	• The trial included patients who had suspicious lesions, and they were referred to specialty department to rule out the presence of invasive squamous cell carcinoma. This might limit the generalizability of the trial's findings for the general population who is expected to receive the screening evaluation with VELscope
Koch et al. 2010[25] – Germany – (VELscope 8/8)	
• All included patients benefited from the index test (VELscope), the comparator test (clinical evaluation), and the reference test (histopathological analysis)	• The trial included patients who had suspicious lesions or had clinical diagnosis of squamous cell carcinoma, and they were referred to specialty clinic to rule out the presence of invasive squamous cell carcinoma. This might limit the generalizability of the trial's findings for the general population who is expected to receive the screening evaluation with VELscope
Rajmohan et al. 2012[26] – India – (ViziLite 1 of 4)	
• All included patients benefited from the index test (ViziLite), the comparator tests (toluidine blue and exfoliative cytology), and the reference test (histopathological analysis)	• The setting at which the patients were recruited was not specified. This information is important to evaluate the applicability of the findings to the general population. • The three diagnostic tests (reference and comparators) were conducted on the same session; it was not specified if these tests were conducted without knowing the results of the preceding tests (blinded testing).
Mojsa et al. 2012[27] – Poland – (ViziLite 2 of 4)	
• All included patients benefited from the index test (ViziLite), the comparator tests (toluidine blue and clinical oral evaluation), and the reference test (histopathological analysis)	• It was not clear if the difference tests were conducted with or without knowledge of the results of the other tests. • The article reported two datasets for the toluidine blue group; the results were not consistent in the two sets. This raised doubts about the accuracy of the ViziLite group.
Awan et al. 2011[28] – UK (ViziLite 3/4)	
• The reference test and the index test were conducted without knowing the results of the clinical evaluation	• Patients were selected based on the results of the clinical examination. Patients who had suspicious lesions were included in this trial. This might limit the generalizability of findings to the general population and the use of ViziLite as screening tests. • Not all lesions were evaluated by the reference test (histopathology). Ten lesions were not evaluated by the reference test, and the reason for this discrepancy was not reported.
Mehrotra et al. 2010[29] – India (ViziLite 4/4)	
• All included patients benefited from the index test (ViziLite plus Toluidine blue), the comparator tests (VELscope), and the reference test (histopathological analysis)	• Patients were selected based on the results of the clinical examination. Patients who had suspicious lesions were included in this trial. This might limit the generalizability of findings to the general population and the use of ViziLite and VELscope as screening tests.
Sweeny et al. 2011[30] – USA (Identafi 1 of 1)	

Strengths	Limitations
•	• The trial included patients treated for head and neck cancers; this population might not be representative to the general population. • The reference test was provided for patients who had suspicious lesions by the index tests.

APPENDIX IV: MAIN FINDINGS OF THE INCLUDED STUDIES

<table>
<tr><th>Study findings</th><th>Conclusions/ Comments</th></tr>
<tr><td colspan="2">Guideline – Agency for Healthcare Research and Quality – National Guideline Clearinghouse – Guideline summary-9498, 2012[14] – USA</td></tr>
<tr><td>Under the recommendations about the screening and diagnostic tools, the guideline reported that ViziLite may be of benefit in the follow-up of patients who are already diagnosed with oral cancer. This recommendation was justified by the low false-negative value of this technology in the detection of oral cancer. However, the guideline also reported that further studies are needed to determine what role, if any, ViziLite should play in oral cancer screening.</td><td></td></tr>
<tr><td colspan="2">Guideline – Rethman et al., 2010[15] – USA</td></tr>
<tr><td>The guideline did not provide recommendations specific for light-based screening techniques. However, the guideline did report that the available evidence was insufficient to support the use of devices based on tissue reflectance (ViziLite and ViziLite Plus) and autofluorescence (VELscope) for the detection of potentially malignant lesions.

The guideline did not identify relevant evidence regarding the utility of MicroLux/DL, Orascoptic DK or Identafi 3000.</td><td></td></tr>
<tr><td colspan="2">Systematic review – Trullenque-Eriksson et al. 2009[16] – Spain – (Systematic review 1/2)</td></tr>
<tr><td>ViziLite:
- Results were obtained from 6 articles published between 2004 and 2007
- Sample size ranged from 40 to 150; a total of 563 patients were included in the six trials
- Diagnostic values were reported for two trials (N= 40 and 55); sensitivity was 100% in both trials, and specificity was 14.2% in one trial and 0% in the other one.
VELscope:
- Four articles published between 2006 and 2007 were used in the review
- Sample size was provided for 2 articles, 20 patients in the first and 4 in the other one
- Sensitivity was reported in three articles; it was 97% in a cross-sectional study and 98% in one case series study and another opinion article. Specificity was 94% in the cross-sectional study (N=20), and it was 100% in the two other articles.</td><td>Authors' conclusions:
Authors concluded that the clinical examination and histopathological confirmation remain the "gold standard" in oral cancer detection.</td></tr>
<tr><td colspan="2">Patton et al. 2008[17] – USA – (Systematic review 2/2)</td></tr>
<tr><td>All included studies were controlled with histopathological testing.
All studies included patients who had highly suspected oral lesions or history of oral cancer
<table>
<tr><th>Adjunctive tool/ Study identifier</th><th>No. of patients/ biopsies</th><th>SN</th><th>SP</th><th>PPV</th><th>NPV</th><th>Quality score - 0 to 100</th></tr>
<tr><td>ViziLite</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Ram et al. 2005</td><td>40/31</td><td>100%</td><td>14%</td><td>80%</td><td>100%</td><td>32.5</td></tr>
<tr><td>Farah el al. 2007</td><td>55/55</td><td>100%</td><td>0</td><td>18%</td><td>0</td><td>42.5</td></tr>
<tr><td>Epstein et al 2007</td><td>84/97</td><td>100%</td><td>0</td><td>21%</td><td>0</td><td>55</td></tr>
<tr><td>ViziLite Plus with TBlue</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Epstein et al 2007</td><td>84/97</td><td>100%</td><td>55%</td><td>37%</td><td>100%</td><td>55</td></tr>
<tr><td>VELscope</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Lane et al. 2006</td><td>44/50</td><td>98%</td><td>100%</td><td>100%</td><td>86%</td><td>42.5</td></tr>
<tr><td>Poh et al. 2006</td><td>20/122</td><td>100%</td><td>78%</td><td>66%</td><td>100%</td><td>60</td></tr>
</table>
NPV = negative predictive value; PPV = positive predictive value; SN = sensitivity; SP = specificity</td><td>Authors' conclusions:
The evaluated technologies may contribute in the diagnosis oral cancer and treatment response evaluation

Reviewer's comments:
The evaluated technologies showed high sensitivity values; however, specificity was very low. This low specificity indicates that a large number of false positive readings will undergo unnecessary biopsies and will impact patients' morbidity.</td></tr>
</table>

<table>
<tr><th>Study findings</th><th>Conclusions/ Comments</th></tr>
<tr><td colspan="2">Laronde et al. 2013[18] – Canada (VELscope 1/8)</td></tr>
<tr><td colspan="2">
- A total of 2404 individuals were screened
- The florescence visualization (VELscope) is considered the index (new) test
- The clinical exam and visual screening (white light) is considered the comparator test
- The reference test is considered the lesion status after 3 weeks or the opinion of clinical specialist or biopsy results
</td></tr>
<tr><td colspan="2">
<table>
<tr><td colspan="4">Initial screening</td></tr>
<tr><td colspan="2">Total number screened, N</td><td colspan="2">2404</td></tr>
<tr><td colspan="2">Total number of lesions detected by initial visual screening and FV, N</td><td colspan="2">375[a]</td></tr>
<tr><td colspan="2" rowspan="2">Results of FV status, n (%)</td><td>FV+</td><td>FVE</td><td>FV-</td></tr>
<tr><td>192 (54%)</td><td>26 (7%)</td><td>139 (39)</td></tr>
<tr><td colspan="2">Results of the reference test</td><td colspan="2">Not evaluated</td></tr>
<tr><td colspan="2">Diagnostic value based on the reference test</td><td colspan="2">Not evaluated</td></tr>
<tr><td rowspan="2">Results of white light exam, n (%)</td><td>Low risk lesion</td><td>175 (91%)</td><td colspan="2">150 (91%)</td></tr>
<tr><td>Intermediate to high risk lesion</td><td>17 (9%)</td><td colspan="2">15 (9%)</td></tr>
<tr><td colspan="2">Correlation between FV status and clinical exam judgment</td><td colspan="2">Not evaluated</td></tr>
<tr><td colspan="4">Recall screening</td></tr>
<tr><td colspan="2">Total number of patients (lesions) recalled for reassessment after 3 weeks, N</td><td colspan="2">135[b]</td></tr>
<tr><td colspan="2" rowspan="2">Status of the lesion after 3 weeks[c], n (%)</td><td>Persistent</td><td colspan="2">Regressed</td></tr>
<tr><td>50 (100%)</td><td colspan="2">85 (100%)</td></tr>
<tr><td rowspan="2">Results of FV status, n (%) – (N=121)[d]</td><td>FV+</td><td>9 (21%)</td><td colspan="2">22 (29%)</td></tr>
<tr><td>FVE and FV-</td><td>35 (80%)</td><td colspan="2">55 (71%)</td></tr>
<tr><td colspan="2">Diagnostic value based on the reference test (status of the lesion)</td><td colspan="2">Not evaluated</td></tr>
<tr><td colspan="2">Akiake Information Criteria[e]:
Model fit when the FV exam was included</td><td colspan="2">102.484</td></tr>
<tr><td rowspan="2">Results of clinical exam, n (%)</td><td>Low risk lesion</td><td>31 (62%)</td><td colspan="2">78 (92%)</td></tr>
<tr><td>Intermediate to high risk lesion</td><td>19 (38%)</td><td colspan="2">7 (9%)</td></tr>
<tr><td colspan="2">Akiake Information Criteria:
Model fit when the clinical exam was included</td><td colspan="2">108.486</td></tr>
<tr><td colspan="2">Correlation between FV status and clinical exam judgment</td><td colspan="2">Not evaluated</td></tr>
<tr><td colspan="2">Akiake Information Criteria:
Model fit when both the FV exam and the clinical exam were included in the model</td><td colspan="2">96.488</td></tr>
</table>
FV = fluorescence visualization; FV+ = positive screening; FV- = negative screening; FVE = equivocal screening;
[a] it was not clear if this number of lesions was detected by each method separately.
[b] the number of lesions/patients recalled for reassessment did not correlate with the results of the initial evaluation. Other six patients were referred directly without doing the screening tests.
[c] It was not clear how the judgment about lesion status was made. Typically this is done through the visual and clinical examination; however in this trial, the clinical examination seemed to be used as the reference test and the comparator test at the same time
[d] Of the total 135 patients recalled for reassessment only 121 patients had FV reassessment results; the reviewed article did not provide explanation for this discrepancy
[e] Akiake Information Criteria is a measure of the relative quality of a statistical model. The lower values indicate better fit of the model for the given data. In this trial this measure was used to compare a logistic model that used to explain the persistence of lesions. The FV and visual exams were used as explanatory variables in the model
</td><td>
Authors' conclusions:
The authors concluded that the integration of fluorescence visualization (VELscope) in a protocol of oral cancer screening would improve the model.

The specificity of the fluorescence visualization can be improved by a reassessment of the suspected lesions after 3 weeks of the initial assessment.

Reviewer's comments:
The authors used a logistic model to explain the persistence of lesions after 3 weeks of the initial assessment. In this model, the FV, visual assessment or both were included as explanatory variables. The model fit value was used as a judgment factor for the utility of florescence visualization. This is a methodological flaw, because the model fit does not provide information on how many additional cases were detected by the new technology when compared with the standard methods.

Moreover, the reassessment did not ameliorate the specificity because 29% of the reassessed lesions were classified as FV positive while they showed lesion regression in the clinical and visual exam.

The reviewed report did not provide evidence on the added value from using the FV in oral cancer screening.
</td></tr>
</table>

Study findings	Conclusions/ Comments
Marzouki et al. 2012[19] – Canada (VELscope 2/8)	

Outcome measure	VELscope (N= 85)		Clinical exam (N= 85)	
Results for the screening tests	Positive	Negative	Positive	Negative
	28	57	17	68
Results of the pathological testing (biopsy), n= 33[a]				
• Positive for dysplasia	13	NE[a]	8	NE[a]
• Negative for dysplasia	15	NE[a]	9	NE[a]
Sensitivity				
• calculated by the reviewer[b]	Can't be evaluated			
• reported by the trial authors	92%		61.5%	
Specificity				
• calculated by the reviewer[b]	Can't be evaluated			
• reported by the authors	77%		87.5%	
Positive predictive value				
• calculated by the reviewer[b]	46.6%		47%	
• reported by the authors	42%		47%	
Negative predictive value				
• calculated by the reviewer[b]	Can't be evaluated			
• reported by the authors	98%		92.6%	
Suspicious lesions detected in one test but not the other	16		5	
• No. of dysplastic lesions	5		1	

NE = not evaluated;

[a] the reference test (pathological evaluation of biopsy) was conducted on the lesions which were screened positive by either screening test. Lesions which were screened negative were not biopsied for ethical reasons.

[b] All calculations were based on the following contingency table and formulae:

		Screening test: Positive	Screening test: Negative
Reference test (true status)	Disease	A	B
	No disease	C	D

- $Sensitivity = a/(a+b)$
- $Specificity = d/(c+d)$
- $Positive\ pridictive\ value = a/(a+c)$
- $Negative\ pridictive\ value = d/(b+d)$

Authors conclusions:
It was concluded that the results from this trial support the use of VELscope as a screening adjunct in identifying oral dysplastic lesions in high risk patients.

Reviewer's comments:
Given the reported results, the sensitivity, specificity and negative predictive values for either VELscope or the clinical exam could not be calculated due to the trial protocol. The only diagnostic value that could be calculated was the positive predictive value that was equivalent between VELscope and the clinical examination.

It was noticed that VELscope could detect four dysplastic lesions which were not detected by the clinical exam; however, this was at?? the expense of 11 more false positive screens. On the other hand, clinical exam could detect one dysplastic lesion that wasn't detected by VELscope at the expense of only four false positive screens.

Study findings	Conclusions/ Comments
Rana et al. 2012[20] – Germany (VELscope 3/8)	

Outcome measure	VELscope + conventional evaluation (N= 123)		Conventional evaluation (N= 166)	
Results for the screening tests	Positive	Negative	Positive	Negative
	79 (64.2)	44 (35.8)	NR	NR
Results of the pathological testing (biopsy)				
• Total number of biopsies	31 (25.1)[b]		NR	
• Positive for cancer	NR	NR[b]	NR	NR[b]
• Negative for cancer	NR	NR[b]	NR	NR[b]
Number of cancer lesions[c]				
• Cancer	6 (4.9)		4 (2.4)	
• No cancer	117 (95.1)		162 (97.6)	
Sensitivity				
• calculated by the reviewer[b]	Can't be evaluated			
• reported by the trial authors	100%		17%	
Specificity				
• calculated by the reviewer[b]	Can't be evaluated			
• reported by the authors	74%		97%	

NR = not reported;

[a] this was obtained from the number of biopsied lesions because, as per the protocol, lesions were biopsied if they were classified by either test as "suspicious".

[b] the reference test (pathological evaluation of biopsy) was conducted on the lesions which were screened positive by either screening test. Lesions which were screened positive by VELscope were biopsied if the diascopy exam was negative for that lesion.

[c] The method used to conclude about the presence or absence of cancer was not reported. It can't be concluded that this was obtained from the biopsy and pathological evaluation because only74.8% of these lesions were biopsied in the VELscope group.

[b] All calculations were based on the following contingency table and formulae:

		Screening test: Positive	Screening test: Negative
Reference test (true status)	Disease	A	B
	No disease	C	D

- $Sensitivity = a/(a+b)$
- $Specificity = d/(c+d)$

Authors' conclusions: Authors reported that VELscope lead to increase the sensitivity but decreased the specificity of the conventional oral diagnosis. Thus they concluded that VELscope is a useful diagnostic device for oral cancers.

Reviewer's comments: Given the reported results, the sensitivity and specificity for either VELscope or the conventional oral evaluation could not be calculated due to the trial protocol. Therefore, the diagnostic values of the VELscope device could not evaluated or compared with the conventional oral examination.

Study findings	Conclusions/ Comments

Farah et al. 2012[21] – Australia (VELscope 4/8)

Outcome measure	VELscope examination (N= 118)		Clinical examination (N= 118)		Combined clinical and VELscope examination (N = 118)	
	Test results		Test results		Test results	
Histology findings	+ve	-ve	+ve	-ve	+ve	-ve
• Cancer	8	19	7	21	11	15
• No Cancer	34	57	16	74	29	63
Sensitivity	30%		25%		46%	
Specificity	63%		82%		68%	
Positive predictive value	19%		30%		29%	
Negative predictive value	75%		78%		82%	
Accuracy	55%		69%		63%	

-ve = negative; +ve = positive

Authors' conclusions:
- VELscope seemed to be of use in the visualization of potentially malignant, malignant and inflammatory lesions. However, the device could not differentiate between these lesions.
- VELscope could not be used to provide a definitive diagnosis of oral cancers

Reviewer's comments: The trial included patients who had suspected lesions; results couldn't be generalized for the general population.

McNamara et al. 2012[22] – USA – (VELscope 5/8)

Outcome measure	VELscope (N = 130)		Oral examination (N 130)	
Results for the screening tests	+ve	-ve	+ve	-ve
	59	36	5	90
Results of the pathological testing (biopsy), n= 34[a]				
• Malignant/ premalignant	2	1	2	1
• Benign	37[b]	3[c]	3	47[d]
Sensitivity[e]	66.7%		66.7%	
Specificity[e]	Can't be evaluated[f]		Can't be evaluated[f]	
Positive predictive value[e]	Can't be evaluated[f]		40%	
Negative predictive value[e]	Can't be evaluated[f]		Can't be evaluated[f]	

NE = not evaluated;

[a] lesions that resolved at the follow-up visit were included in this table; these were considered in the benign category.
[b] 10 patients did not have follow-up data
[c] 32 patients did not have follow-up data or biopsy evaluation
[d] 42 patients did not have follow-up data or biopsy evaluation
[e] All calculations were based on the following contingency table and formulae:

		Screening test: Positive	Screening test: Negative
Reference test (true status)	Disease	A	B
	No disease	C	D

- $Sensitivity = a/(a+b)$
- $Specificity = d/(c+d)$
- $Positive\ pridictive\ value = a/(a+c)$
- $Negative\ pridictive\ value = d/(b+d)$

[f] missing data could not imputed, and any calculation made with missing values would not be credible

Authors' conclusions : It was concluded that VELscope did not provide diagnostic benefit beyond the clinical examination alone in routine screening for potentially malignant oral mucosal lesions.

Study findings			Conclusions/ Comments
Paderni et al. 2011[23] – Italy (VELscope 6/8)			
Outcome measure	**VELscope examination (N= 175)**		**Authors' conclusions:** It was concluded that the VELscope device could not fully replace histopathology procedure. For the trial authors, VELscope should be seen as complementary device to the conventional visual examination and the histopathological assessment during oral cancer diagnosis and monitoring steps.
Histological classification: high-risk versus low-risk lesions			
	VELscope positive	VELscope negative	
• High risk oral premalignant lesion	12	4	
• Low risk oral premalignant lesion	10	121	
Sensitivity	75%		
Specificity	92.3%		
Positive predictive value	54.5%		
Negative predictive value	97%		
Histological classification: Mild to severe dysplasia versus no dysplasia			
	VELscope positive	VELscope negative	
• Lesions with dysplasia (mild to severe)	46	12	
• Lesions without dysplasia	3	114	
Sensitivity	65.5%		
Specificity	97.4%		
Positive predictive value	86.3%		
Negative predictive value	92.0%		
Histological classification: Mild dysplasia versus no dysplasia			
	VELscope positive	VELscope negative	
• Lesions with dysplasia (mild)	9	6	
• Lesions without dysplasia	3	114	
Sensitivity	60%		
Specificity	97.4%		
Positive predictive value	75%		
Negative predictive value	95%		
Histological classification: Moderate to severe dysplasia versus no dysplasia			
	VELscope positive	VELscope negative	
• Lesions with dysplasia (moderate to severe)	37	6	
• Lesions without dysplasia	3	114	
Sensitivity	71.4%		
Specificity	97.4%		
Positive predictive value	77%		
Negative predictive value	96.6%		

<table>
<tr><th>Study findings</th><th>Conclusions/ Comments</th></tr>
<tr><td colspan="2">Scheer et al. 2011[24] – Germany (VELscope 7/8)</td></tr>
<tr><td>
<table>
<tr><th>Outcome measure</th><th colspan="2">VELscope examination (N= 64)</th></tr>
<tr><td></td><td>VELscope positive</td><td>VELscope negative</td></tr>
<tr><td>• Dysplastic lesions[a]</td><td>12</td><td>0</td></tr>
<tr><td>• Benign lesions</td><td>10</td><td>42</td></tr>
<tr><td>Sensitivity</td><td colspan="2">100%</td></tr>
<tr><td>Specificity</td><td colspan="2">80.8%</td></tr>
<tr><td>Positive predictive value</td><td colspan="2">54.5%</td></tr>
<tr><td>Negative predictive value</td><td colspan="2">100%</td></tr>
</table>
[a] dysplastic lesions included either squamous intraepithelial neoplasia or squamous cell carcinoma
</td><td>Authors' conclusions:
"VELscope results should be interpreted with caution because benign reactive lesions may show similar autofluorescence patterns as the malignant lesions. Histology controlled prospective studies in a general population are required to assess the role of autofluorescence as a screening adjunct." (page 576)</td></tr>
<tr><td colspan="2">Koch et al. 2010[25] – Germany (VELscope 8/8)</td></tr>
<tr><td>
<table>
<tr><th rowspan="2">Outcome measure</th><th colspan="2">VELscope (N = 78)</th><th rowspan="2">White light (N = 78)</th></tr>
<tr><th>Green reflection</th><th>Red reflection</th></tr>
<tr><td colspan="4">Histological classification: squamous cell carcinoma versus benign lesions[a]</td></tr>
<tr><td>Sensitivity</td><td>93%</td><td>20%</td><td>96.6%</td></tr>
<tr><td>Specificity</td><td>15%</td><td>98%</td><td>95.8</td></tr>
<tr><td>Positive predictive value</td><td>41%</td><td>87%</td><td>93.5</td></tr>
<tr><td>Negative predictive value</td><td>78%</td><td>63%</td><td>97.9%</td></tr>
<tr><td colspan="4">Histological classification: squamous cell carcinoma or dysplasia versus benign lesions[a]</td></tr>
<tr><td>Sensitivity</td><td>94%</td><td>22%</td><td>93.8%</td></tr>
<tr><td>Specificity</td><td>16%</td><td>98%</td><td>97.8%</td></tr>
<tr><td>Positive predictive value</td><td>45%</td><td>87%</td><td>96.8</td></tr>
<tr><td>Negative predictive value</td><td>77%</td><td>67%</td><td>95.7</td></tr>
</table>
-ve = negative; +ve = positive;
[a] the actual numbers of screen and test positive and negative were not provided
</td><td>Authors' conclusions:
The autofluorescence examination was not able to differentiate between benign and malignant oral lesions. The red reflection from the autofluorescence should be used as an indication for biopsy because of its high positive predictive value.

Reviewer's comment:
The autofluorescence examination didn't provide better diagnostic values than the conventional examination with white light</td></tr>
</table>

Study findings	Conclusions/ Comments

Rajmohan et al. 2012[26] – India – (ViziLite 1 of 4)

Outcome measure	ViziLite (N= 30)		Toluidine Blue (N= 30)		Clinical diagnosis (N = 30)	
Histological classification: Dysplastic (mild to severe) or cancerous versus benign lesions						
Histopathology	+ve	-ve	+ve	-ve	+ve	-ve
• Dysplastic/ cancerous lesion	16	3	6	13	19	0
• Benign lesion	1	10	1	10	1	10
Sensitivity[a]	83.3%[a]		77.8%[a]		100%[b]	
Specificity[a]	90.9%		90.9%		90.9%	
Positive predictive value[a]	88.2%[a]		76.9%[a]		95%	
Negative predictive value[a]	76.9%		43.5%		100%	

[a] values as reported in the article
[b] values were not reported in the article; they were calculated by the reviewer based on the following contingency table and formulae:

		Screening test: Positive	Screening test: Negative
Reference test (true status)	Disease	a	b
	No disease	c	d

- $Sensitivity = a/(a+b)$
- $Specificity = d/(c+d)$
- $Positive\ pridictive\ value = a/(a+c)$
- $Negative\ pridictive\ value = d/(b+d)$

Authors' conclusions:
The trial findings indicated that chemiluminescent illumination test was relatively reliable and accurate than toluidine blue.

Reviewer's comment:
The evaluated tests, ViziLite and Toluidine blue, did not provide better diagnostic values than the clinical diagnosis done before conducting these adjunctive tests.

Mojsa et al. 2012[27] – Poland - (ViziLite 2 of 4)

Outcome measure	ViziLite + Toluidine blue (N = 41)		Toluidine blue – 1st dataset[a] (N = 41)		Toluidine blue – 2nd dataset[a] (N = 41)		Visual test (N = 41)	
Histopathology results	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve
• Dysplastic or SSC	19	14	27	6	7	0	33	0
• benign lesions	5	3	5	3	25	9	8	0
Sensitivity[b]	57.6%		81.8%		100%		100%	
Specificity[b]	37.5%		37.5%		26.5%		0	
Positive predictive value[b]	79.2%		84.4%		21.9%		80.5%	
Negative predictive value[b]	17.6%		33.3%		100%		NA	

SSC = squamous cell carcinoma

[a] the article reported two datasets for the toluidine blue test; the two sets provided different numbers for the positive and negative cases. Both sets were reported here; however, there was one dataset for the ViziLite and the visual examination. The confidence in the accuracy of these results is compromised

[b] values were not reported in the article; they were calculated by the reviewer based on the following contingency table and formulae:

		Screening test	
		Positive	Negative
Reference test (true status)	Disease	a	b
	No disease	c	d

- $Sensitivity = a/(a+b)$
- $Specificity = d/(c+d)$
- $Positive\ pridictive\ value = a/(a+c)$
- $Negative\ pridictive\ value = d/(b+d)$

Authors' conclusions: The false-positive and negative values for the ViziLite plus toluidine should be considered when it is used for the diagnosis of oral cancer. The use of ViziLite plus does not replace the thorough clinical examination and histopathology.

Awan et al. 2011[28] – UK – (ViziLite 3/4)

Outcome measure	ViziLite (N= 126)		Clinical diagnosis (N= 126)	
Results for the screening tests	Positive	Negative	Positive	Negative
	21	105	NR	NR
Results of the pathological testing (biopsy)				
• Total number of biopsies	116		116	
• Positive for dysplasia	37	7	NR	NR
• Negative for dysplasia	61	11	0	NR
Sensitivity	84.1%		NR	
Specificity	15.3%		NR	
Positive predictive value	37.8%		NR	
Negative predictive value	61.1%		NR	

NR = not reported;

Authors' conclusions : The trial showed that ViziLite had very low specificity in discriminating dysplastic from benign lesions.

<table>
<tr><th>Study findings</th><th>Conclusions/ Comments</th></tr>
<tr><td colspan="2">Mehrotra et al. 2010[29] – India (ViziLite 4/4)</td></tr>
<tr><td>
<table>
<tr><th>Outcome measure</th><th colspan="2">ViziLite + Toluidine blue
(N = 102)</th><th colspan="2">VELscope
(N = 156)</th></tr>
<tr><td colspan="5">Results of the pathological testing (biopsy)</td></tr>
<tr><td>• Total number of biopsies</td><td colspan="2">102</td><td colspan="2">156</td></tr>
<tr><td>• Positive for dysplasia or cancer</td><td>0</td><td>4</td><td>6</td><td>6</td></tr>
<tr><td>• Negative for dysplasia or cancer</td><td>24</td><td>74</td><td>88</td><td>56</td></tr>
<tr><td>Sensitivity</td><td colspan="2">0</td><td colspan="2">50%</td></tr>
<tr><td>Specificity</td><td colspan="2">75.5%</td><td colspan="2">38.9%</td></tr>
<tr><td>Positive predictive value</td><td colspan="2">0</td><td colspan="2">6.4%</td></tr>
<tr><td>Negative predictive value</td><td colspan="2">94.8%</td><td colspan="2">90.3%</td></tr>
</table>
</td><td>Authors' conclusions :
The results of the trial indicated that neither the ViziLite nor the VELscope added any benefits to a conventional screening examination involving the use of a standard overhead light.</td></tr>
<tr><td colspan="2">Sweeny et al. 2011[30] – USA (Identafi 1 of 1)</td></tr>
<tr><td>
<table>
<tr><th rowspan="2">Outcome measure</th><th colspan="4">Identafi (N =88)</th><th colspan="2" rowspan="2">Wight light
(N =88)</th></tr>
<tr><th colspan="2">Tissue fluorescence</th><th colspan="2">Reflectance</th></tr>
<tr><td>Results for the screening tests</td><td>+ve
9</td><td>-ve
79</td><td>+ve</td><td>-ve
71</td><td>+ve
17</td><td>-ve
71</td></tr>
<tr><td colspan="7">Status of the lesions by biopsy (n = 9[a]) or after six months follow-up</td></tr>
<tr><td>• Dysplastic/ cancerous lesion</td><td>2</td><td>2</td><td>0</td><td>4</td><td>2</td><td>2</td></tr>
<tr><td>• Benign lesion</td><td>16</td><td>68</td><td>12</td><td>72</td><td>2</td><td>82</td></tr>
<tr><td>Sensitivity[a]</td><td colspan="2">50%</td><td colspan="2">0</td><td colspan="2">50%</td></tr>
<tr><td>Specificity[a]</td><td colspan="2">81%</td><td colspan="2">86%</td><td colspan="2">98%</td></tr>
<tr><td>Positive predictive value[a]</td><td colspan="2">11%</td><td colspan="2">0</td><td colspan="2">50%</td></tr>
<tr><td>Negative predictive value[a]</td><td colspan="2">97%</td><td colspan="2">95%</td><td colspan="2">98%</td></tr>
<tr><td colspan="7">[a] the nine biopsies were from the 17 lesions identified by the one Identafi tests.</td></tr>
</table>
</td><td>Authors' conclusions:
It was concluded that the standard clinical lightening had a higher sensitivity than tissue reflectance and autofluorescence visualization for the detection of head and neck cancers.</td></tr>
</table>