Screening for oral cancer—a perspective from the Global Oral Cancer Forum

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Screening for oral cancer should be defined as the application of a test to people who are apparently free of disease to identify those who may have oral cancer and to distinguish them from those who may not. The aim of the test is not to be diagnostic but to identify changes that may be the earliest signs of impending disease. Defined in this way, screening is an ongoing public health measure, often funded by governments. A screening program must do no harm and must be cost effective. Governments demand that strict evidence of benefits and cost effectiveness be met before a program may be implemented. Although many studies have investigated the utility of potential screening tests, there have been few evaluations of screening programs and only one randomized controlled trial. Systematic reviews have concluded that there is insufficient evidence to show that oral cancer screening can reduce mortality from oral cancer, and to date, no country has implemented a formal oral cancer screening program. This paper reviews this evidence and tries to identify the barriers to screening and suggests areas of focus for future research. (Oral Surg Oral Med Oral Pathol Oral Radiol 2017;123:680-687)

To date, no national screening programs for oral cancer have been introduced despite many studies attempting to evaluate screening methodologies and at least one well-organized clinical trial. This review paper, the first of a series of papers from the Global Oral Cancer Forum (GOCF), summarizes the current international status of oral cancer screening. The GOCF was an internationally coordinated meeting held in New York in March 2016,[1] where invited experts discussed issues related to gaps and innovations in prevention, early detection, patient care, technologies, and services across the oral cancer continuum. The authors of this paper reviewed the world literature and presented a global perspective of oral cancer screening in a symposium at the forum.

Screening is defined as the application of a test to people who are apparently free of disease to identify those who may have the disease from those who may not.[2] A screening test or examination is not diagnostic but is intended to identify tissue changes that may indicate the likelihood of having or developing the disease in question. Screening must be clearly distinguished from case finding or early detection, which have the objective of identifying specific lesions either by examination or by application of a test. It must also be distinguished from "screening" studies, which survey cohorts of a population, often with the objective of determining the prevalence of a specific disease or lesion or for the purpose of bringing patients to treatment. As properly defined, the term *screening* encompasses an ongoing process of examination and referral at periodic intervals, applied to a defined population and managed most often by a regional or national program. Screening programs for cervical, breast, and colorectal cancers are well known examples of screening programs that have been implemented across many countries.

In the context of oral cancer, screening would involve the application of an oral examination or a test with the objective of identifying changes, which may precede or predict, with a high likelihood, the development of oral cancer. Patients identified as likely to have the disease, would then be referred to a specialist

Statement of Clinical Relevance

Screening for oral cancer should be an ongoing public health endeavor that must have proven benefits and be cost effective. This review tries to show why screening for oral cancer has not been implemented so far and suggests areas for further research.

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for a definitive diagnosis. The screening test would be applied to a defined population at regular intervals. Such a program would be very similar to programs for screening for cervical cancer. However, before implementation, the aspects of a screening program must be properly evaluated, and a number of criteria must be met.

In 1968, Wilson and Jungner[2] first defined *screening* and enumerated the ideal properties of a health screening program. These are considered essential to ensure that the program achieves maximum public health gains in a cost-effective manner. These criteria have been modified in subsequent decades to reflect the more rigorous standards of evidence required to prove effectiveness and increasing concerns about overdiagnosis (false-positive results or lead time bias), whereby patients may be overinvestigated or overtreated without receiving any benefits and with possible additional risks or costs. The United Kingdom's National Screening Committee requires that 19 criteria be met before a screening program may be funded and implemented[3] (Table I). In the United States, the National Cancer Institute[4] and the U.S. Preventive Services Task Force[5] have similar criteria.

It can be seen from Table I that these criteria are rigorous and may be considered overly stringent. They are designed to address all issues regarding the disease as well as concerns over public acceptability, costs, and, when applied to a state-funded health system, evidence of value to the taxpayer and consumer. Some of these criteria may have a political element and may be debatable, and others clearly require hard scientific evidence or widely accepted guidelines or policies. All who work in the field of oral cancer research or clinical management will see that many of these criteria have not yet been met, and for some, it may not be possible to demonstrate compliance. In the table, we have indicated with a check mark those criteria that we believe have been met, or should be easy to meet, if a program were to be implemented. These are only nine of 19 criteria. We have also indicated with a cross mark four areas in which the evidence is still not clear and further research is needed. Other issues that have yet to be considered or are uncertain are indicated by a question mark. This paper will address some of these key issues.

Table I. Criteria that must be met for the implementation of a screening program

The Condition:		
1.	Must be an important health problem	✓
2.	The epidemiology and natural history must be understood, and there must be a detectable latent asymptomatic or early symptomatic phase	✗
3.	All cost-effective primary prevention interventions should have been implemented, where possible	?
The Test		
4.	Should be simple, safe, and validated	✓
5.	The distribution of test values should be known (e.g., sensitivity and specificity), and the criteria for a positive test should be agreed upon	✗
6.	Should acceptable to the population	✓
7.	There should be an agreed-upon policy and process for the further referral and diagnostic investigation of individuals who test positive	?
The Treatment		
8.	Should be an effective treatment or intervention for patients found to have disease and evidence that this early treatment leads to better outcomes	✓
9.	Should be evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered	✗
10.	Clinical management of the condition and patient outcomes should be optimized	✓
The Screening program		
11.	There must be evidence from randomized clinical trials (RCTs) that the screening program is effective in reducing mortality or morbidity	✗
12.	Should be clinically, socially, and ethically acceptable	✓
13.	Benefit should outweigh any physical or psychological harm	?
14.	Must be cost effective	✓
15.	There must be a clear plan for managing the programme and agreed-upon quality assurance standards	✓
16.	There must be adequate staffing and facilities for the program and for referrals, diagnosis, and treatment	?
17.	All other options for managing the condition should have been considered	✓
18.	Evidence-based information explaining the positive and negative aspects of the program must be available to participants	✓
19.	Screening intervals, eligibility for screening and the testing process should be scientifically justifiable to the public	?

Based on the UK National Screening Committee criteria.[3]

IS SCREENING FOR ORAL CANCER FEASIBLE, AND WHY SHOULD WE CONSIDER IMPLEMENTING SCREENING PROGRAMS?

Oral cancer is a serious health problem, and despite slight improvements in survival rates, approximately 50% of patients still die as a result of this disease. In addition, there is clear evidence that oral and oropharyngeal cancers are increasing in incidence, and although there is a shift in the site of lesions—with a greater increase in the oropharynx—intraoral or mouth lesions are still the most common and the greatest cause of morbidity and mortality.[6]

For these reasons, oral cancer meets criterion 1 in Table I, and for many working in oral health care, it is inconceivable that an oral cancer screening program

Table II. Reports of evaluations of conventional oral examinations in which sensitivity and specificity of the test have been calculated

Reference (no.)	*N*	*% positive*	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*
Chang et al.[14]	13,606	2.1	0.99	0.99		
Downer et al.[15]	309	5.5	0.71	0.99	0.86	0.98
Ikeda et al.[16]	154	9.7	0.60	0.94	0.67	0.96
Jullien et al.[17]	2027	2.7	0.74	0.99	0.67	0.99
Mathew et al.[18]	2069	10.3	0.94	0.98	0.87	0.99
Mehta et al.[19]	1921	1.4	0.59	0.98	0.31	0.99
Warnakulasuriya et al.[20]	1872	21.6	0.95	0.81	0.58	0.98
Monteiro et al.[21]	727	3.4	0.96	0.98	0.96	0.98
Nagao et al.[22]	137	58*	0.92	0.64	0.78	0.86
Sweeney et al.[23]	88	4.5	0.50	0.98		

*% positive relates to the proportion positive who attended for follow-up.

should not be easily implemented. The oral cavity is easy to examine, oral lesions are relatively easy to detect, and oral cancer is, in most cases, preceded by an oral potentially malignant disorder (OPMD). The term *OPMD* refers to a precancerous state in the oral cavity, carrying an increased risk of progression to squamous cell carcinoma.[7,8] The most common disorders recognized as potentially malignant are *leukoplakia* and *erythroplakia*,[7,9] which have characteristic clinical features. However, although these disorders have a statistically increased risk of progression to cancer,[8,10] they may remain stable or regress. At present, the prognostic significance of an individual lesion is difficult to determine; none of the currently available histologic or molecular markers has proven to be prognostically significant, and a few have yet to be evaluated in large prospective studies.[11,12]

The existence of OPMD suggests that oral cancer screening is feasible, since this is evidence for a preclinical ("latent/asymptomatic") phase of the disease that can be detected early. Although this partly meets criterion 2 in Table I, uncertainty remains regarding the natural history of OPMD because it is not known which actual lesions will progress and it has been difficult to define clear criteria for a positive screening test. This is discussed further in the next section.

EVALUATION OF ORAL CANCER SCREENING TESTS

The validity of a screening test is measured by the frequency with which the result of that test is confirmed by an acceptable diagnostic procedure. The ability of a test to classify persons as being positive for the presence of disease is termed *sensitivity* and the ability to classify those without the disease is termed *specificity*; that is, sensitivity is a measure of the false-negative rate, and specificity is a measure of the false-positive rate.[2] For population-based (organized) screening, the most sensitive test may not be chosen for a nationwide program, since it risks a higher rate of false-positives. However, high specificity is important in reducing avoidable costs resulting from unnecessary workup of false-positive results and the associated adverse effects.[13] At the population level, higher test specificity and less frequent screening help minimize both physical and psychological harms by reducing unnecessary diagnostic evaluations and the risk for overtreatment.[13]

Although many studies have evaluated the conventional oral examination (COE) as a screening test for oral cancer screening, only 10 have tested negative cases against a gold standard that enables effectiveness to be determined in terms of sensitivity and specificity.[14-23] These are summarized in Table II.

Walsh et al.[24] included a number of these studies[14-20,23] in a Cochrane systematic review undertaken to estimate the diagnostic accuracy of COE, vital rinsing, light-based detection, biomarkers, and mouth self-examination, used singly or in combination, for the early detection of oral cancer and OPMDs in apparently healthy adults. The review found that the test accuracy of COE may depend on disease prevalence and showed a variable degree of sensitivity (0.50-0.99), but a consistently high value for specificity (>0.80). Additionally, one randomized controlled trial (RCT) found a higher detection rate for oral cavity cancer in the "COE plus vital rinsing" adjunct trial arm. Furthermore, there was insufficient evidence to satisfactorily determine the diagnostic test accuracy of mouth self-examination as part of an organized screening program. Downer et al.[25] undertook a meta-analysis of some of these studies[15-20] and reported pooled values of sensitivity and specificity of 0.85 (95% confidence interval [CI] 0.73-0.92) and 0.97 (95% CI 0.93-0.98), respectively.

In a more recent systematic review of studies on the effectiveness of oral cancer screening tests in Europe, Warnakulasuriya et al.[26] further demonstrated the feasibility of screening for OPMD and oral cancer using COE. They reviewed 16 studies that used COE

Table III. Advantages and shortcomings of conventional oral examination (COE) and possible future approaches

Advantages	*Shortcomings*	*Future approaches*
Minimally invasive	May depend on the quality of the examiner	Establish a clear definition of a positive screen and continuous training program
High validity (sensitivity and specificity, in case of experienced examiners)	Training and calibration of the screeners is needed	
Applicable in primary care setting	Cannot distinguish between benign lesions, cancer, and oral potentially malignant disorders (OPMDs)	Need scientifically evaluated adjunctive tests or biomarkers
Minimum examination time once trained	Low compliance and screen positives may not attend for secondary examinations	Basic strategies for health promotion, "advocacy, enabling, and mediating."[16] Need well-developed referral and monitoring
Can be repeated, no morbidity	Cost-effectiveness is uncertain	Cost of studies must be carefully determined
No special facilities needed	Difficult to maintain a simple record of COE	Lesions can be photographed; standardization can be desirable
Can be undertaken together with any other general and dental examinations		

to detect relevant lesions, but none was an RCT or a screening program as properly defined (see previously). Nine of the studies were descriptive only, and the validity of the data could not be evaluated. The review postulated that opportunistic screening in dental practices or screening of selected high-risk population groups may be considered but that further studies were needed to determine the effectiveness of such interventions in these settings.

Overall, these studies and reviews indicated that COE results in a satisfactory test performance with sensitivities and specificities similar to those reported for breast and cervical cancer screening programs. Furthermore, a number of these studies utilized nonmedical or nondental health care workers as screeners[18-20] and showed similar results. This indicates that trained health care workers or dental care professionals (dental auxiliaries) are equally able to examine the mouth and detect lesions of significance. This has been confirmed by a number of studies that have directly evaluated lesion identification by trained health care workers, including primary care physicians, or have compared the accuracy of different members of the dental care team to identify lesions.[18,27-30] Although these studies have identified both the advantages and shortcomings of COE (summarized in Table III), the data do suggest that screening is feasible in that dentists and allied health care workers can accurately detect oral lesions.

However, in the review of the studies mentioned, care must be taken not to arrive at the interpretation that a good screening test is available. Most of these studies have used the presence of lesions consistent with OPMDs or early oral cancer as the criterion for a positive screening result. In most cases, such lesions have been a white patch, a red patch, or a persistent ulcer. Leukoplakia is the most common OPMD, and although these lesions have been detected with a prevalence rate of between 1.4% and 22%[31,32] (see Table II), it is important to remember that clinical appearance does not correlate well with histology and that overall only about 5% of the lesions progress to cancer.[8] This means that about 95% of detected lesions will not progress to oral cancer and are therefore not relevant to a test designed to detect lesions with a high likelihood of progressing to oral cancer.

Although some molecular markers, especially loss of heterozygosity,[33] and some salivary markers[34] have the potential to be useful for screening tests, at the present time, no biomarkers have been shown to have utility in screening trials.[11,12] Many new and emerging diagnostic aids and adjunctive techniques have been described to assist clinical diagnosis, but these have mostly been used to aid in categorization of clinical lesions. Evaluation of these adjuncts has taken place in secondary care facilities, often with patients at increased risk of mucosal change and not in primary care settings, and therefore, there is still no evidence that they may assist in the screening of healthy asymptomatic patients to detect OPMD or otherwise occult oral cancerous lesions.[35-38]

Patton et al.[36] reviewed 23 articles describing use of adjunctive techniques. Although they found evidence of the utility of these techniques as diagnostic aids in high-risk individuals in a hospital setting, they identified a lack of studies in primary care or community settings and found no evidence of utility in the use of these techniques as tests for screening. A Cochrane systematic review concluded that none of the evaluated tests that were adjuncts to visual examination can be recommended as a replacement for the currently used diagnostic standard of scalpel biopsy and histologic assessment.[38] For these reasons, oral cancer screening fails to meet criteria 2, 5, and 9 in Table I.

Table IV. The Kerala screening study*

Participation
Screen positivity
Prevalence of oral cancer and precancer†
Compliance with referral
Sensitivity and specificity of the oral examination
Positive predictive value for detection of oral precancerous lesions.
Program sensitivity and specificity for detection of oral cancer
Incidence rate of oral cancer in the study groups per 100,000 person-years†
Characteristics of oral cancer (TNM Staging)†
Mortality for oral cancer cases†

*Parameters recorded in the screen positive groups.
†These parameters were also recorded in the control arms.

EVALUATION OF ORAL CANCER SCREENING PROGRAMS

Although many studies have evaluated potential screening tests (see Table II), few have evaluated actual screening programs. Only one properly conducted RCT used mortality as the primary outcome. This oral cancer screening trial was a community-based, cluster RCT carried out in North Trivandrum (in the state of Kerala in India) from 1996 to 2004.[39-43] The study was undertaken in 13 municipalities, or clusters, which were dichotomized into two arms: an intervention (screened) arm (7 clusters; n = 96,517) and a control (not screened) arm (6 clusters; n = 95,356). Screening included healthy residents age 35 years or older. Nonmedical university graduates performed the screening. They were trained for 3 months in recording sociodemographic features and in performing visual examination to identify potentially malignant diseases, including white or red patches, oral submucous fibrosis, lichen planus, and ulcers suspicious of malignancy. Over a 15-year period, there were four rounds of screening, which were performed in 1998, 2002, 2004, and 2009. A detailed analysis of the outcomes was reported in 2005 after three rounds of screening.[41] For the intervention arm, oral findings were recorded as normal, nonreferable lesions or referable lesions (screen positive). Referable lesions (screen positive) were referred to a dentist or oncologist for final diagnosis by visual examination or biopsy, and a number of parameters were recorded (Table IV). For the control arm, the participants were not screened and only received awareness education and general health care. The primary outcome was the difference in mortality resulting from oral cancer in the intervention and control groups.

Ninety-one percent in the intervention arm and 84% in the control arm were interviewed; 87,655 individuals (91%) were screened at least once, and 5145 (6.55%) of them screened positive. Of these, only 3218 (62%) complied with referral. The detection rate of OPMD or oral cancer per 1000 screened individuals was 28, 11.6, and 11.3 in the first, second, and third rounds, respectively. In the intervention clusters, 205 (131 screen-detected, 59 interval cancers, and 15 nonparticipants) cases of oral cancer were diagnosed; 158 were diagnosed in the control group. Seventy-seven (37.6%) persons died as a result of oral cancer in the intervention arm and 87 (55%) died in the control arm, but this difference was not significant. There was a significant difference in 5-year survival (intervention arm: 50%; control arm: 34%) and in the number of cases diagnosed in stages I and II (42% and 23%, respectively). However, in the population as a whole, there was no significant reduction in mortality (16.4% and 20.7%).

The data were further analyzed to determine if the effects were greater in high-risk groups (defined as users of tobacco and/or alcohol). In males who used tobacco and/or alcohol, there was a significant (43%) reduction in mortality from 42.9% in the control group to 24.6% in the intervention group. There was no significant reduction among females.

A subsequent (fourth) round of screening was completed in 2009.[43] After four rounds, there was an overall significant improvement in 5- and 10-year survival rates and in early detection (stage shift), but there was no significant improvement in mortality rates or in overall mortality. However, for those individuals who participated in all four cycles of screening, there was an overall reduction in mortality of 79% in the intervention arm (reduced from 17.1 to 3 per 100,000) and a reduction of 81% in the high-risk group (39 vs 7.1). This reduction in mortality was significant. However, it is important to note that only 19,288 persons completed four rounds of screening—20% of the eligible population.

Data from these studies show that oral cancer screening using COE, even in high-prevalence settings, does not reduce mortality in the population. The data do suggest, however, that screening of high-risk groups may be effective in reducing mortality. The authors concluded that opportunistic screening of high-risk groups is likely to be an effective intervention.[43]

The results from the Kerala studies suggested that oral cancer screening only partly meets criterion 11 in Table I.

EVIDENCE-BASED RECOMMENDATIONS FOR ORAL CANCER SCREENING

The rationale for a systematic review is to establish whether findings are consistent and can be generalized across populations, settings, and treatment variations and to limit bias and provide recommendations and guidance for practice.[44]

A Cochrane systematic review was undertaken to assess the effectiveness of oral cancer screening

programs.[45] The primary outcome was evidence of reduced mortality from oral cancer, with secondary outcomes including early stage detection (stage shift), reduced incidence, and reduced costs. The review identified 30 potentially eligible studies, but only one RCT—the Kerala study just described—met the inclusion criteria.[39-41] Although this systematic review acknowledged the significant findings of the Kerala study, the reviewers identified a number of methodologic weaknesses that might affect the validity of the study findings. The reviewers found insufficient evidence to recommend population-based screening programs. However, visual screening may reduce the mortality rate in users of tobacco, alcohol, or both and can produce a stage shift. The review concluded that targeted screening programs could be effective in reducing oral cancer mortality. Nevertheless, further RCTs are warranted to provide the highest level of evidence for practice. The Cochrane review concluded that there is insufficient evidence from RCTs to satisfy criterion 11 in Table I.

IS SCREENING FOR ORAL CANCER COST EFFECTIVE?

The Kerala group undertook costing analyses of their screening programs and interventions.[43] The overall benefit obtained from screening was 270 life-years saved per 100,000 population, but this rose to 1438 life years per 100,000 in the high-risk groups. The cost per life-year saved was US$835 for the whole population and $156 for the high-risk groups. The cost per screening examination was only $6 per person. The results of this study show that oral visual examination screening may be cost effective, especially when applied to high-risk groups in which there is a larger yield and the potential to increase the number of life-years saved. These financial calculations may be very different in Western settings, thus affecting any discussion of cost-effectiveness.

RCTs are very difficult or impossible to conduct in populations in which the prevalence of the disease under study is low. For this reason, it is extremely unlikely that a funding agency will fund an oral cancer screening RCT in any country with a low prevalence, and cost-effectiveness analyses will be a challenge to perform. An alternative to RCTs for the evaluation of interventions is computer simulation modeling.[46] An interesting study used a decision-analysis simulation model to determine the incremental costs and outcomes of alternative oral cancer screening programs conducted in primary care environments.[47] The study found that opportunistic high-risk screening, particularly in general dental practice, may be cost effective. The cost per life-year saved was £22,850 and was only marginally greater if screening was performed in medical practice (£23,728). Screening may be targeted more effectively at younger age groups, particularly those aged between 40 and 60 years. Although these costs are considerably more than those found in the Kerala study, they are still within the acceptable cost per life saved, which is considered value for money by the National Health Service in the United Kingdom.[48] These data suggest that oral cancer screening may meet criterion 14 in Table I.

SUMMARY AND FUTURE DIRECTIONS

The cumulative evidence suggests that it is feasible to screen for oral cancer but that there is considerable uncertainty regarding a number of key issues (see Table I). Clinicians recognize OPMD, and there is evidence that these can be detected with sensitivity and specificity sufficient to justify COE as a screening test. However, the criteria for detected lesions (for a positive test result) are not specific to lesions that have a high likelihood of progression because, overall, only about 5% of lesions detected at screening are likely to progress to cancer.[8] Even for those that will progress, the rates of progression and the significance of individual markers are still uncertain. In their decision model, Speight et al.[47] undertook a value of information analysis, which showed that the greatest source of uncertainty in determining the outcomes of screening lies in our lack of understanding of malignant transformation of OPMD and disease progression. More accurate tests are needed, and further research on the natural history of the disease and the use of adjunctive aids is needed.

Although research on potential screening tests has been considerable, there has been only one evaluation of a screening program—that is, the Kerala study. However, a systematic review[45] suggested that there is considerable uncertainty in this study, and the findings have not been accepted by national governments as sufficient evidence to justify the implementation of screening programs.[4,5,49] An expert panel for the American Dental Association also reviewed the literature[37] and found insufficient evidence to show that community-based screening may alter disease-specific mortality, although it did suggest that screening by COE may reduce mortality in high-risk groups. The panel also found no evidence for the effectiveness of adjunctive tests except by expert providers in high-risk patients. It could not advocate population-based screening but recommended that clinicians opportunistically screen all patients for signs of OPMD or early oral cancer.[37] It is now generally agreed that patients, especially those in high-risk groups, should be opportunistically examined for any signs of oral cancer or precancer as part of their routine dental care.[50] The use

Table V. Suggested priority areas for further research

Natural History of the Disease
Malignant transformation rates
Rates of progression through stages of disease from precancer to cancer
Clinical and molecular biomarkers of the high-risk lesion
Screening Tests
Evaluation of adjunctive tests
Criteria for positive and negative tests
Evaluations in appropriate populations with sensitivity and specificity as endpoints
Evaluations of diagnostic accuracy among different groups of health care workers
Screening Programs
Further evaluations of programs: randomized controlled trials, but also simulation and demonstration studies
Evaluation of opportunistic programs in different health care settings
Identification of relevant high-risk groups and methods of targeting
Evaluation of risk reduction advice at time of screening

of adjunctive tests does, however, show promise, but further studies are needed in primary care settings and on populations relevant to a screening test.[36]

Ideally, further large-scale RCTs are needed, but these would be extremely costly to undertake, especially if population mortality is used as the endpoint in populations with a low prevalence of oral cancer. It is unlikely that any funding agency will underwrite an RCT of the required scale. Consideration needs to be given to further simulation studies or to trials using surrogate endpoints, such as yield, stage shift, or rates of disease progression. Demonstration studies could also be undertaken, using demographically similar populations as controls.

The accumulated evidence does support the view that opportunistic screening of high-risk groups may be cost effective.[43,44,47] However, it has been suggested that relevant high-risk groups do not visit a dentist on a sufficiently regular basis to make opportunistic screening in dental practice feasible.[51] Further research is needed to determine how opportunistic screening may be implemented and in which health care environments. Screening by nonmedical or nondental health care workers has been shown to be effective, and utilizing this group may be the best and most cost-effective way of improving early detection. Table V summarizes key areas that should be considered for further research.

REFERENCES

1. The global oral cancer forum. March, 2016. Available at: http://www.globaloralcancerforum.org. Accessed July 1, 2016.
2. Wilson JMG, Jungner G. *Principles and practice of screening for disease*. Geneva, Switzerland: World Health Organization; 1968. Available at: http://apps.who.int/iris/bitstream/10665/37650/1/WHO_PHP_34.pdf. Accessed July 1, 2016.
3. UK National Screening Committee. Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. London, UK: National Screening Committee, 2003. Updated 2015: Available at: https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes. Accessed July 1, 2016.
4. Oral cancer screening. National Cancer Institute: U.S. National Institutes of Health. Available at: http://www.cancer.gov/cancertopics/pdq/screening/oral/healthprofessional. Accessed July 1, 2016.
5. *U.S. Preventive Services Task Force: Screening for oral cancer: recommendation statement*. Rockville, MD: U.S. Preventive Services Task Force; 2004. Available at: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/oral-cancer-screening1. Accessed July 1, 2016.
6. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol*. 2009;45:309-316.
7. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med*. 2007;10:575-580.
8. Napier SS, Speight PM. Natural history of potentially malignant oral lesions and conditions: an overview of the literature. *J Oral Pathol Med*. 2008;37:1-10.
9. Gale N, Pilch BZ, Sidransky D, et al. Tumours of the oral cavity and oropharynx. epithelial precursor lesions. In: Barnes L, Eveson JW, Reichart P, Sidransky D, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours 2005*. Lyon, France: IARC Press; 2005: 177-179.
10. Bouquot J, Speight PM, Farthing PM. Epithelial dysplasia of the oral mucosa—diagnostic problems and prognostic features. *Curr Diagn Pathol*. 2006;12:11-22.
11. Warnakulasuriya S, Reibel J, Bouquot J, Dabelsteen E. Oral epithelial dysplasia classification systems: predictive value, utility, weaknesses and scope for improvement. *J Oral Pathol Med*. 2008;3:127-133.
12. Warnakulasuriya S. Lack of molecular markers to predict malignant potential of oral precancer. *J Pathol*. 2000;190:407-409.
13. Miles A, Cockburn J, Smith RA, Wardle J. A perspective from countries using organized screening programs. *Cancer*. 2004;101:1201-1213.
14. Chang IH, Jiang RS, Wong YK, Wu SH, Chen FJ, Liu SA. Visual screening of oral cavity cancer in a male population: experience from a medical center. *J Chinese Med Assoc*. 2011;74:561-566.
15. Downer MC, Evans AW, Hughes Hallett CM, Jullien JA, Speight PM, Zakrzewska JM. Evaluation of screening for oral cancer and precancer in a company headquarters. *Commun Dent Oral Epidemiol*. 1995;23:84-88.
16. Ikeda N, Downer MC, Ishii T, Fukano H, Nagao T, Inoue K. Annual screening for oral cancer and precancer by invitation to 60 year-old residents of a city in Japan. *Community Dent Health*. 1995;12:133-137.
17. Jullien JA, Downer MC, Zakrzewska JM, Speight PM. Evaluation of a screening test for the early detection of oral cancer and precancer. *Community Dent Health*. 1995;12:3-7.
18. Mathew B, Sankaranarayanan R, Sunilkumar KB, Kuruvila B, Pisani P, Nair MK. Reproducibility and validity of oral visual inspection by trained health workers in the detection of oral precancer and cancer. *Br J Cancer*. 1997;76:390-394.
19. Mehta FS, Gupta PC, Bhonsle RB, et al. Detection of oral cancer using basic health workers in an area of high oral cancer incidence in India. *Cancer Detect Prev*. 1986;9:219-225.
20. Warnakulasuriya S, Pindborg JJ. Reliability of oral precancer screening by primary health care workers in Sri Lanka. *Community Dent Health*. 1990;7:73-79.

21. Monteiro LS, Salazar F, Pacheco JJ, Martins M, Warnakulasuriya S. Outcomes of invitational and opportunistic oral cancer screening initiatives in Oporto, Portugal. *J Oral Pathol Med*. 2015;44:145-152.
22. Nagao T, Ikeda N, Fukano H, Miyazaki H, Yano M, Warnakulasuriya S. Outcome following a population screening programme for oral cancer and precancer in Japan. *Oral Oncol*. 2000;36:340-346.
23. Sweeny L, Dean NR, Magnuson JS, Carroll WR, Clemons L, Rosenthal EL. Assessment of tissue autofluorescence and reflectance for oral cavity cancer screening. *J Otolaryntol Head Neck Surg*. 2011;145:956-960.
24. Walsh T, Liu JL, Brocklehurst P, et al. Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults. *Cochrane Database Syst Rev*. 2013;11:CD010173.
25. Downer MC, Moles DR, Palmer S, Speight PM. A systematic review of test performance in screening for oral cancer and precancer. *Oral Oncol*. 2004;40:264-273.
26. Warnakulasuriya S, Fennell N, Diz P, Seoane J, Rapidis A; LDV Lifelong Learning Programme. An appraisal of oral cancer and pre-cancer screening programmes in Europe: a systematic review. *J Oral Pathol Med*. 2015;44:559-570.
27. Warnakulasuriya KA, Nanayakkara BG. Reproducibility of an oral cancer and precancer detection program using a primary health care model in Sri Lanka. *Cancer Detect Prev*. 1991;15:331-334.
28. Warnakulasuriya KA, Ekanayake AN, Sivayoham S, et al. Utilization of primary health care workers for early detection of oral cancer and precancer cases in Sri Lanka. *Bull World Health Organ*. 1984;62:243-250.
29. Brocklehurst P, Pemberton MN, Macey R, Cotton C, Walsh T, Lewis M. Comparative accuracy of different members of the dental team in detecting malignant and non-malignant oral lesions. *Br Dent J*. 2015;218:525-529.
30. Epstein JB, Gorsky M, Cabay RJ, Day T, Gonsalves W. Screening for and diagnosis of oral premalignant lesions and oropharyngeal squamous cell carcinoma: role of primary care physicians. *Can Fam Physician*. 2008;54:870-875.
31. Petti S. Pooled estimate of world leukoplakia prevalence: a systematic review. *Oral Oncol*. 2003;39:770-780.
32. Lim K, Moles DR, Downer MC, Speight PM. Opportunistic screening for oral cancer and precancer in general dental practice: results of a demonstration study. *Br Dent J*. 2003;194:487-502.
33. Lingen MW, Kalmar JR, Karrison T, Speight PM. Critical evaluation of diagnostic aids for the detection of oral cancer. *Oral Oncol*. 2008;44:10-22.
34. Zhang L, Poh CF, Williams M, et al. Loss of heterozygosity (LOH) profiles validated risk predictors for progression to oral cancer. *Cancer Prev Res (Phila)*. 2012;5:1081-1089.
35. Elashoff D, Zhou H, Reiss J, et al. Prevalidation of salivary biomarkers for oral cancer detection. *Cancer Epidemiol Biomarkers Prev*. 2012;21:664-672.
36. 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;139:896-905.
37. Rethman MP, Carpenter W, Cohen EE, et al. Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas. *J Am Dent Assoc*. 2010;141:509-520.
38. Macey R, Walsh T, Brocklehurst P, et al. Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions. *Cochrane Database Syst Rev*. 2015;5:CD010276.
39. Sankaranarayanan R, Mathew B, Jacob BJ, et al. Early findings from a community-based, cluster-randomized, controlled oral cancer screening trial in Kerala, India. The Trivandrum Oral Cancer Screening Study Group. *Cancer*. 2000;88:664-673.
40. Ramadas K, Sankaranarayanan R, Jacob BJ, et al. Interim results from a cluster randomized controlled oral cancer screening trial in Kerala, India. *Oral Oncol*. 2003;39:580-588.
41. Sankaranarayanan R, Ramadas K, Thomas G, et al. Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. *Lancet*. 2005;365:1927-1933.
42. Sankaranarayanan R, Ramadas K, Thara S, et al. Long term effect of visual screening on oral cancer incidence and mortality in a randomized trial in Kerala, India. *Oral Oncol*. 2013;49:314-321.
43. Subramanian S, Sankaranarayanan R, Bapat B, et al. Cost-effectiveness of oral cancer screening: results from a cluster randomized controlled trial in India. *Bull World Health Organ*. 2009;87:200-206.
44. Mulrow CD. Rationale for systematic reviews. *Br Med J*. 1994;309:597-599.
45. Brocklehurst P, Kujan O, O'Malley LA, Ogden G, Shepherd CS, Glenny AM. Screening programmes for the early detection and prevention of oral cancer. *Cochrane Database Syst Rev*. 2013;11:CD004150.
46. Fone D, Hollinghurst S, Temple M, et al. Systematic review of the use and value of computer simulation modelling in population health and health care delivery. *J Public Health Med*. 2003;25:325-335.
47. Speight PM, Palmer S, Moles DR, et al. The cost-effectiveness of screening for oral cancer in primary care. *Health Technol Assess*. 2006;10:1-144.
48. National Institute for Healthcare Excellence (NICE). *Judging whether public health interventions offer value for money*; September 2013. Available at: https://www.nice.org.uk/advice/lgb10/chapter/judging-the-cost-effectiveness-of-public-health-activities. Accessed July 1, 2016.
49. UK National Screening Committee. *The UK NSC recommendation on oral cancer screening in adults*. London, UK: National Screening Committee; January 2016. Available at: http://legacy.screening.nhs.uk/oralcancer. Accessed July 1, 2016.
50. Epstein JB, Huber MA. The benefit and risk of screening for oral potentially malignant epithelial lesions and squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2015;120:537-540.
51. Netuveli G, Sheiham A, Watt RG. Does the "inverse screening law" apply to oral cancer screening and regular dental check-ups? *J Med Screen*. 2006;13:47-50.

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