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Global Oral Cancer Forum: Group 4 White Paper

Clinical Assessment and Emerging Technology for Early Detection

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Introduction

Oral potentially malignant disorders (OPMDs) comprise a subset of epithelial lesions encountered clinically that do not have an obvious cause and therefore may represent either a malignancy or "premalignant" lesion with a higher risk of becoming malignant over time [1]. Estimates for the global prevalence of potentially malignant disorders are approximately 1-5% [2]. Oral leukoplakia is the most frequently encountered example of a potentially malignant disorder.

The current standard of care following the clinical detection of an OPMD is tissue biopsy and submission for histopathologic examination to rule out a malignancy (predominantly squamous cell carcinomas (SCCA)), or epithelial dysplasia. A minority of OPMDs are diagnosed as malignancies at the time of discovery. The remaining majority of OPMDs can have variable diagnoses including epithelial dysplasia or histologically benign entities. Collectively these non-malignant OPMDs have a low, albeit variable, propensity for malignant transformation of less than 5% [3]. Patients with lesions diagnosed with high-grade epithelial dysplasia are at the highest risk for malignant transformation [4], [3], yet the natural history and evolution of OPMDs is non-linear and malignant transformation is not predictable based on histopathology alone [5].

This may be explained by the underlying complexity of carcinogenesis: the "mutational" landscape of a OPMD is the result of an accumulation of genetic and epigenetic alterations. While some of the pathways driving carcinogenesis are more commonly operational across a population of patients with OPMDs, there is marked heterogeneity and every OPMD and patient is unique.

Adequate assessment of a lesion, or of patient with multifocal disease, is contingent upon the procurement of tissue (ie a biopsy) that represents the most significant pathology within a lesion (or patient), coupled with microscopic interpretation. Biopsy and histopathologic diagnosis requires expertise, both from the perspectives of procuring the actual sample (ie the technical aspects/instrumentation of/for performing biopsies and experience in biopsy site selection criteria), and in the interpretation of histopathology (which is fraught with a high degree of both intra and inter-pathologist variability [6, 7]).

The clinical diagnosis of mucosal abnormalities, such as OPMDs, is based on a visual and tactile examination (known as the conventional oral examination (COE)) followed by a synthesis of the history and clinical findings to render a clinical diagnosis. The "risk assessment" of lesion or lesions determines whether the a lesion meets the established clinical criteria for an OPMD. "Frontline examiners" such as dentists, have a reduced ability to perform such risk assessments to determine the significance of the abnormal epithelial lesions detected during an oral examination compared to experts [8]. From a global perspective, there are variable healthcare settings where access to oral health can be poor, and as such, frontline examiners may include community health workers with very little experience in performing oral examinations. Furthermore, easy access to tissue biopsy and histopathology may be limited in these settings.

The topics of screening and the reasons for delays in referral/diagnosis will be covered by groups 2 and 3 respectively. However, under the assumption that a patient has been examined and an abnormal epithelial lesion or lesions detected, our group will be exploring how current and emerging technologies might be applied, across variable resource settings, to facilitate the identification and diagnosis of patients with OPMDs. In particular we are interested in how these technologies can optimize the detection of patients with lower stage malignancies (ie stage I/II) or epithelial dysplasia, and

ultimately to predict which patients with non-malignant OPMDs are at the highest risk for developing a malignancy.

A diagnostic adjunctive technique is one that is applied, to an identified lesion (or patient) which aides in the characterization of the mucosal abnormalities to better identify and clinically classify lesions as OPMDs (particularly high-risk lesions such as early carcinomas, high-grade dysplasias, or those harbouring a phenotype that predict a high propensity for malignant transformation) and/or select appropriate regions for further evaluation (ie guide incisional or excisional biopsy site selection/mapping); its application should augment the risk assessment made following a COE and accelerate the pathway to a definitive diagnosis, improve diagnostic accuracy and reduce false negative rates due to COE or sampling error. It might also help predict the future nature of the lesion in terms of identifying lesions that are at increased risk for malignant transformation.

The performance of a number of adjunctive techniques as compared to the "gold standard" histopathologic endpoints has been studied (almost exclusively in the hands of experts), yielding information about their accuracy and applicability to facilitate the detection and assessment of OPMDs [9]. These adjunctive techniques have been developed based their ability to discriminate between the inherent differences in the underlying pathological, metabolic or biological behaviours of OPMDs compared to normal tissue or benign conditions with no malignant potential. Some are "point-of-care" techniques while others require samples to be analyzed outside of the clinical setting by a laboratory. They range from techniques that can instantly provide clinicians with broad "macroscopic" information about a lesion (or lesions), to those that can provide narrower "microscopic" information at the cellular level. Some technologies are based on reflectance/emission differences following exposure of lesions to various wavelengths of light, others work as vital stains, and yet others are based on the collection of non-invasive cellular samples (cytology and brush samples) that are processed and analyzed in various ways (ie to assess deviations in cytoplasmic versus nuclear morphology or various validated biomarkers). Unfortunately, there is a paucity studies exploring the value of these techniques to predict malignant transformation.

Our group will explore the utility of these adjunctive techniques in a number of ways: in the hands of frontline examiners in variable resource settings where they may be used to facilitate lesion risk assessment; by specialists where adjunctive technologies may facilitate diagnostic or treatment decisions, or help in the long-term surveillance of high risk patients with a history of malignancy or epithelial dysplasia. Furthermore, we will consider their performance across a number of domains including accuracy, ease of use, and cost (see Table 1).

In addition, our group will explore the use of "telemedicine" to facilitate the identification and referral of patients with OPMDs.

Visualization adjuncts/optical biopsy

A variety of imaging devices and techniques are now available to aid the clinician in visualizing and characterizing OPMDs in real time at the point of care [10], [11], [12]. These devices detect changes in optical properties (absorption, scattering, and fluorescence) associated with the development and progression of precancer and cancer in oral tissue [13], [14], [15]. In particular, recent technological advances in optical and electronic components (high-power LED illumination sources, cameras, tablet computers, other consumer electronics) have led to the development of a generation of low-cost, portable visualization methodologies which can be used as adjuncts during an evaluation of at risk tissue/lesions in the oral cavity. Some adjunctive technologies have received regulatory approval for clinical use, while others are in preclinical or clinical study stages.

Evaluation of the utility of these adjunctive technologies must take into account the diversity of users, user experience with these adjunctive technologies, the settings in which they would be used, and patient populations in which they are to be employed. Further the sensitivity, specificity and subsequent expected PPV and NPV when used on specific risk populations should be considered, particularly given the type and availability of subsequent likely patient follow-up procedures. This is true in both high-resource and low-resource settings.

Some adjunctive technologies are designed to image macroscopic regions of tissue. These devices are typically used to rapidly scan or view the oral cavity to map out areas of high risk and to help delineate the extent of lesions. Examples include direct viewing

enhanced by illumination and/or acetic acid [16], [17], [18], autofluorescence imaging [19], [20] [21], and narrow-band imaging [22] . These methods are generally preferentially designed to trade increased sensitivity at the expense of some specificity loss [23], [24], [25].

Other adjunctive technologies are designed to interrogate specific sites with high spatial resolution (in vivo microscopy) or high spectral resolution (spectroscopy). These devices, often implemented in a point probe format, are typically used to characterize lesions after they have been mapped out and as such have a tendency to be biased toward increased specificity relative to the macroscopic technologies. Examples include confocal microscopy [26], [27] , high-resolution microendoscopy [28], [29], , autofluorescence/reflectance spectroscopy [30], [31] [32] , time-resolved spectroscopy [33], and Raman spectroscopy [34], [35].

In the hands of a properly trained user, visualization adjuncts are useful diagnostic aids. The use of macroscopic imaging to map out areas of high risk, followed by high-resolution imaging or spectroscopy to characterize lesions, can aid the clinician in determining when and where to take a biopsy [36], [37]. In vivo microscopy allows real-time imaging of subcellular features that can otherwise only be seen via biopsy and histopathologic examination [38],[39]– hence the term "optical biopsy" is sometimes used, although in vivo microscopy is probably a more descriptive term. These imaging methods are also well suited to take advantage of continuing advances in molecular specific contrast agents [40].

What constitutes the optimal use of these adjunctive technologies depends to a large extent on the resources available in the setting they are being used and the follow-up procedures available or affordable in each particular setting.

In a resource rich environment, in which expert pathology is affordable and available, detection and biopsy of low to moderate risk (ie low to moderate risk of being cancer or transforming into cancer) lesions, pathologic interpretation, and sequent surveillance of the low risk lesions and possible treatment of the medium and treatment of the high risk lesions can be sustained. Even in this setting however indefinite surveillance with serial biopsies is not sustainable and so new technologies/ strategies which can further resolve these low/medium risk lesion patients into baseline population risk (return to regular screening behavior group) or patients in which treatment is indicated/required is needed.

In a resource poor environment in which the individual may only be seen once and the treatment options are limited, the detection of low-medium risk lesions which will not be treated or are not likely to be readily followed up is not of high value. Detecting the high risk lesions and enabling the determination of such with minimal resource (pathology/biopsy) use, enabling the decision to treat maximizing PPV could be the most effect use of resources. A further complication is the differing environmental risk agents and resultant differing developmental pathways of oral cancer. While alcohol and tobacco use are the predominate risk factors in the North American population, betel-quid (areca nut wrapped in piper betel plant leaf) and tobacco use are also predominate risk factors in Indo-Asian and Chinese populations [41]. Betel-quid use results in oral submucous fibrosis (a marked increase in collagen deposition in the oral submucosa) [42]. This increased collagen deposition can affect the performance of many of these visualization adjuncts/optical biopsy techniques introducing addition considerations for their use in some of the resource poor environments associated with betel quid use,

Other important considerations for adjunctive technologies include the capital cost, consumable costs, amount of user training required vs acceptable levels of performance, integration of the procedure into the workflow, patient acceptance, technical support and maintenance, and access to parts and supplies [43] [44]. In low-resource settings, the challenges associated with consumable costs, technical support, and maintenance can be especially significant barriers to successful implementation. Finally, even the simplest point-of-care technologies require continuous, ongoing user training and effective quality control procedures.

Vital Staining

Toluidine blue (TB) vital staining as a diagnostic adjunctive technique for assessing OPMDs was first reported by Neibel et al more than half a century ago [45]. The mechanism by which it works remains somewhat of a mystery, but it is likely related to the affinity for nuclear material in the context of increased permeability in squamous cell carcinoma and high grade dysplasia. Toluidine blue has been used both as a screening adjunct and a diagnostic adjunct. Its use as a screening adjunct for the general population has not been validated [8] and this section will focus on it's use as a diagnostic adjunct. It

may be prepared as a 1 or 2% solution or is available commercially in pre-prepared packages, and it's application is used in conjunction with a 1% acetic acid solution (acetic acid is applied first, followed by toluidine blue, and then acetic acid). A recent meta-analysis of 14 vital staining studies using toluidine blue revealed a sensitivity and specificity of 0.84 (95% CI 0.74-0.90) and a specificity of 0.70 (95% CI 0.59-0.79) for dysplasia or SCCa [9]. There was a trend of increasing sensitivity with worsening disease and the broad ranges of values for sensitivity and specificity may be attributed to several factors including the population of PMDs tested (a higher percentage of high-grade dysplasias and SCCa will lead to higher sensitivity [46], variability in the testing protocols and in the interpretation of cases of light or equivocal staining patterns (some authors assigned a light-blue stained lesion as positive and others as negative), and differences in the clinical expertise of reporting authors. There is a potential for both false positives and false negatives and clinician experience is important. False positives may result when inflammatory, ulcerative, and regenerating tissues are stained blue. In addition, the dye is mechanically retained in the crevices of rough/fissured lesions and the filiform papillae. False negatives can occur and may be due to the inability of the dye to penetrate through thick hyperkeratotic tissue in some leukoplakias. Given that frontline clinicians will encounter of blend of lesions that are most likely traumatic and inflammatory and less likely to be high risk OPMDs, higher false positive and false negative rates may be anticipated. A follow-up visit for repeated staining may improve specificity. Specialists, however, use toluidine blue in three ways: to help guide biopsy site selection (in an attempt to reduce sampling error) at baseline, particularly in non-homogeneous, mixed or multifocal lesions where variable histopathology can exist within a lesion or across multiple lesions; to help identify/map high-risk disease prior to surgical excision; and for facilitating the long-term surveillance of high-risk patients with a past history of SCCA or dysplasia, thereby minimizing the need for serial biopsies.

Lugol's iodine, named after the French physician Jean Lugol, preferentially stains normal non-keratinized mucosa due to it's higher glycogen content compared to SCCA and epithelial dysplasia. It has been used for the identification of esophageal SCCA and dysplasia and there is limited evidence suggesting that this inexpensive vital stain may be

useful to delineate surgical margins for resection of oral SCCA and epithelial dysplasia [47, 48].

Oral Cytology

Final diagnosis of OSCC and OPMD is almost exclusively established through scalpel biopsy which due to its invasive nature is only indicated in cases with highly suspicious clinical appearance (e.g., erythroplakia, non-homogeneous leukoplakia, erythroleukoplakia). It also confines the sampling to a limited area which is particularly problematic in case of multiple lesions. A false negative rate of up to 23% also poses a serious challenge to the current complete reliance on scalpel biopsy; [49, 50] this and the above mentioned limitations may partly be responsible for the late detection and consequent poor prognosis of OSCC.

An important adjunctive diagnostic technique is oral cytology which has been defined as microscopic examination of surface epithelium which has been harvested via non-invasive methods such as brush, spatula and curette.[51] Due to its ease of use, and its inexpensive and non-invasive nature exfoliative cytology (EC) can be routinely used for screening and early diagnosis of oral lesions, in addition to identification of potential biomarkers. Cytology is advantageous as it can be repeated for follow-up and research purposes, and although a definitive diagnosis is generally reached by conventional scalpel biopsy, EC has a supportive role in management of OSCC.

Compared to incisional biopsy, exfoliative cytology provides the diagnostician with a rich collection of cells harvested from a wider area. Although the concept is the same, based on different collecting devices, the sensitivity and specificity of exfoliative cytology differs. EC is generally seen as a good approach in resource poor environments and for front line oral health practitioners providing opportunities to assess patients and lesions with additional ease and limited technical requirements, although it must be acknowledged that differences in cytology approaches exist.

The most commonly used exfoliative cytology instruments include wooden tongue depressor, metal spatula and cotton tip applicators. Both the wooden tongue depressor and metal spatula are readily available in a dental practice and can be used with relative ease; however when scraped over sensitive areas such as gingival margins or the

muco-gingival junction they can cause discomfort. In addition due to their inflexibility, size and shape, the wooden tongue depressor and metal spatula cannot be adapted to all parts of the oral cavity. Cytoplasmic and nuclear distortion has been reported in smears collected using wooden tongue depressors and metal spatulas due to collection of epithelial cells in a thick aggregate.[52] Cotton tipped-applicators are more convenient for the patient, however fewer cells are harvested with their use and many remain trapped in the cotton resulting in a smaller number of cells for diagnostic purposes, and these are mostly collected from superficial layers thus limited accurate interpretation of the presence of epithelial dysplasia.

The next evolution of exfoliative cytology are newer platforms using specially designed brushes to procure higher yield cellular samples. OralCDx® (OralCDx Laboratories®, Suffern, NY, USA) is the most widely available and well known brush "biopsy" system available, implementing a patented brush followed by a computerised program to interpret the morphologic and cytologic changes of collected cells and "microbiopsies".[53] OralCDx® comes with the promise of overcoming the inherent limitations of conventional cytopathologic examination; particularly the tedious visual search for potentially rare abnormalities through using an image analysis system.

Although significant discussion still rages as to the applicability of OralCDx® in routine clinical practice for assessment of oral mucosal lesions, it must be emphasised that the proprietary OralCDx® collection brush must be used with the computer assisted neural network software analysis system for maximum potential and accurate results. Attempting to use the brush without the computer assisted software, with other software packages, or using a different brush with the neural network software or with liquid based cytology, will compromise sensitivity and specificity findings, and therefore the overall utility of the OralCDx® oral brush biopsy system. Despite this, many authors have used the OralCDx® brush to obtain cellular material for various applications including liquid based cytology, DNA-image cytometry (DNA-ICM), and also molecular biomarker analysis. Obviously given these issues, the use of OralCDx® system may be seen as useful in resource rich environments and the costs and practicalities would limit its use in resource poor settings.

Given the disparate results surrounding the use of OralCDx® oral brush biopsy system with computer assisted neural network analysis and DNA-ICM in diagnosing oral cancer and precancerous conditions, a recent meta-analysis was conducted to compare the accuracy of the two systems in diagnosing both conditions. Bibliographic databases were systematically searched for original relevant studies on the early diagnosis of oral cancer and precancer. Thirteen studies (eight of OralCDx® brush biopsy and five of DNA-ICM) were identified as having reported on 1981 oral mucosal lesions. The meta-analysis found that the area under the summary receiver operating characteristic curves of the OralCDx® brush biopsy and DNA-ICM were 0.8879 and 0.9885, respectively. The pooled sensitivity, specificity, and diagnostic odds ratio of the OralCDx® brush biopsy were 86%, 81%, and 20.36, respectively, while these were 89%, 99%, and 446.08 for DNA-image cytometry, respectively. Results of a pairwise comparison between each modality demonstrated that specificity, area under the curve, and Q^* index of DNA-ICM was significantly higher than that of the OralCDx® brush biopsy, but no significant difference in sensitivity was found. Based on available published studies, DNA-ICM was more accurate than OralCDx® brush biopsy in diagnosing oral cancer and precancerous mucosal lesions.[54]

Salivary adjuncts

Saliva is an ideal diagnostic fluid because it is so simple to collect. There are number of different analytes that may be detected in the saliva including hormones, endogenous steroids (eg estrogen and testosterone), antibodies, cytokines and chemokines, human and microbial nucleic acids (DNA, RNA, microRNA), growth factors, a myriad of proteins, and drugs (eg drugs of abuse and therapeutic drugs) [55]. Depending on the analyte(s) under investigation, it is feasible for patients to perform self-testing (and send/take the sample to a lab), for a sample to be collected and analyzed chairside by a clinician (point-of-care), or to be collected and sent to a laboratory for analysis. Research on salivary diagnostics for oral cavity and oropharyngeal cancer has identified a number of putative biomarkers revealed from studies comparing cohorts of cancer patients with various control groups (healthy patients or patients with benign mucosal conditions) which have

been recently reviewed in detail by others [56], [57], [58], [59], and this topic is beyond the scope of our group. The process for the commercialization of salivary diagnostics for potential use in dental offices has been reviewed by Jacobson [60]. From a diagnostic standpoint, there are a number of research questions: (a) Can saliva be used to screen a population and identify "at risk" patients ie those with clinically detectable disease versus those with clinically undetectable disease. (b) Can saliva be used to determine the significance of an oral lesion (or lesions) that has (or have) been detected by a frontline examiner? (c) Can saliva be used to serially monitor "high risk" patients? ie those that have a history of SCCA or dysplasia.

There are a number of salivary diagnostic platforms, with approval for use in certain countries, some indicated as screening adjuncts and others as diagnostic adjuncts. Ora-Risk HPV from Oral-DNA labs can detect HPV-DNA in saliva. Its utility as a screening adjunct to detect or predict HPV-associated oropharyngeal cancer has not been studied and a single positive test cannot distinguish between virus in the saliva because of an ongoing infection (there is an estimated 1% prevalence of oral HPV-16 infection in the US [61]) versus virus in the saliva because of malignancy (there are less than 17,000 pharyngeal cancers diagnosed annually in the US [62]) . More studies are needed to elucidate the natural history of oral oncogenic HPV infection. OncAlert from Vigilant Biosciences offers a screening platform where the patients perform a salivary rinse and the sample may be analyzed chairside with a point of care platform and/or sent for a quantitative laboratory assay. The biomarkers are CD44 and "total protein" levels, and validation studies comparing 102 patients with known head and neck SCCA (ie not exclusively oral cavity) versus 84 controls have demonstrated sensitivity and specificity of 80.4% and 65.5% respectively [63], although data from screening studies in cohorts of patients representative of the general population seeking dental care have not been published as yet.

Salimark from PeriRx is marketed to dentists as a salivary diagnostic adjunct performed following the detection of an OPMD. Patients perform a salivary rinse which is sent to a laboratory for PCR analysis of a battery of mRNA biomarkers. The validation for this platform appears to be a single study enrolling 168 patients with oral lesions "suspicious" for cancer, of which 28 had SCCA/carcinoma-in-situ and 140 were labelled

as “benign” (and containing a subset of dysplastic lesions) [64]. The authors report the performance of several three marker “models” of which the biomarker combination of DUSP1/SAT/OAZ1 were reported to generate a sensitivity of >90% and corresponding specificity of 60%.

Telemedicine in oral cancer surveillance

There are several novel point-of-care technologies currently emerging for early detection of oral cancer. For these technologies to have maximum impact it should reach `at risk' population. Adapting the point-of-care technologies with wireless telecommunication devices can overcome many drawbacks as well as extent its use in both low- and high-resource countries. Boppart et al., identified four broad areas where one can use telemedicine to improve efficacy of point-of care diagnostics [44]. (1) Health surveillance: Lack of knowledge and awareness of health conditions at population level may delay seeking medical advice. There are several studies demonstrating poor knowledge and awareness of high-risk population both in terms of risk factors as well as early signs of oral cancer. (2) Lack of knowledge of primary care physicians on low-prevalent diseases such as oral can significantly delay diagnosis and referral. Studies have reported that on average patients consult physicians three times before diagnosis of oral cancer. (3) Delay in diagnosis at referral centers. Diagnosis of disease such as oral cancer requires invasive biopsy and imaging studies. This requires processing of tissues as well as review by a specialist. This can delay diagnosis. (4) Post treatment surveillance often require clinical review and investigations. Poor compliance at this stage can delay recognition of recurrence or second primary tumors. Optical imaging technology adopted with mobile telemedicine where one can potentially obtain real-time diagnosis and transmit for expert opinion can improve the efficacy of point-of-care in both primary care and referral centers both in low and high resource countries. Specifically, for oral cancer, the population with highest prevalence of oral cancer is in low-resource countries and even within the high-resource countries it tends to occur among low-socio-economic setting. There is a significant disparity between the access to advanced health care and prevalence of oral cancer. Mobile telemedicine has the potential to bridge this gap by remote access of advanced health care.

Most of the oral cancer diagnostic methods such as visual examination, light-based adjuncts, vital stains and oral cytology utilize images. All images can be digitized. The digitized images can be transmitted to a remote center with clinical expertise for interpretation. With the availability of broadband, image compression and analysis algorithms and encryption technology in mobile devises, even large diagnostic quality data can be transmitted efficiently and safely. These technologies have now extensively penetrated the low-resource settings offering us the opportunity to harness the power of telemedicine.

Birur et al studied the use of mobile phone for remote diagnosis of oral cancer in high-risk individuals (n=3440) in a low-resource population [65]. They have demonstrated 100% concordance of the interpretation between direct clinical examination and remote diagnosis using mobile phone transmitted images when dentists were using the device at the remote location. The concordance dropped to 46% with frontline health workers.

Telemicroscopy was investigated by Sunny et al in a similar setting (manuscript under review). This study used automated tablet computer to capture images from liquid based cytology. The study enrolled 55 subjects with oral potentially malignant lesions (OPML) (n=19) and malignant lesions (n=36). The cytology diagnosis correlated with histopathology in 34 (94%) subjects. The concordance of direct microscopy and tele-microscopy in malignant lesions was 97%. However with respect to OPML, cytology identified atypical cells only in 4 (21%) of lesions. The concordance of direct microscopy and tele-microscopy was 75%. The poor efficacy of cytology in OPML can be attributed to lack of well-defined diagnostic criteria as well as technical limitation of brush biopsy to sample basal layers of epithelium.

By attaching appropriate filters fluorescent images and images from optical coherence tomography could be transmitted to a specialist center for remote diagnosis. Once diagnosed, photodynamic therapy may be adopted for treatment of OPML using similar device. Light with specific wavelength could be delivered to activate photosensitizer.

Overall, oral cancer is well suited for mobile telemedicine. Technological improvements may be able to rectify many current limitations of telemedicine in oral cancer.

Summary

None of the numerous oral cancer adjunctive diagnostic techniques meet all criteria for an ideal test. Furthermore, our understanding of the natural history of carcinogenesis has not been well elucidated through longitudinal studies which makes it challenging to appreciate the significance of a lesion detected at a single point in time along it's evolution. The true nature of lesions diagnosed histopathologically as epithelial dysplastia are difficult to predict let alone lesions with an abnormal test outcome yielded by an adjunctive technique.

In primary care settings where the clinician (or community health worker) has minimal experience in the diagnosis of mucosal diseases, the aim of the adjunctive technique is to help non-experts better triage a patient with a lesion (which they have already determined clinically to be a OPMD) by helping to dichotomize lesions/patients into high versus low risk, thereby facilitating referral to a higher level of care and accelerating a definitive diagnosis and management. In such settings, the research question is: what threshold of accuracy (sensitivity/specificity/PPV/NPV) is acceptable for determining high vs low risk? Given that accuracy is validated against gold standard histopathology, what histopathologic endpoint should be used as the threshold for a true positive? These questions are difficult to answer and require a detailed analysis of resources, clinician expertise, and healthcare infrastructure. In a low resource setting, particularly in a high prevalence setting, where there are barely enough resources to diagnose and manage patients with oral cancer, adjunctive techniques that can accurately detect OPMDs that are early SCCAs (or high grade dysplasia) would seem to have the greatest utility. By contrast, in high resource settings with low disease prevalence, altered thresholds to capture a wider spectrum of disease may be feasible. Point-of-care diagnostics seem more imperative in low resource settings where patient follow-up is challenging. The use of telemedicine and mobile technology to facilitate the dissemination of information from the field is an attractive and we expect this area will evolve as the world becomes increasingly more connected. Studies conducted by primary

care clinicians in these different settings to explore the utility of these adjunctive techniques (and coupled to telemedicine) are needed.

In higher care settings, where most of the published diagnostic adjunctive validation studies have been conducted, clinicians with experience in mucosal diseases are better able to interpret false positive and false negative adjunctive technique results. This is the venue for a more detailed assessment of new technologies, which may be applied to new referrals for the purpose of baseline lesion assessment/diagnosis, to the surveillance setting, or to facilitate patient treatment (eg mapping of margins prior to excision). Multi-center collaborations are needed to generate OPMD patient populations with the power to run meaningful studies in these domains, linked to chemopreventive trials where possible. The question is, will conventional tissue biopsies and histopathology become obsolete? Will they be replaced by optical biopsies, surveillance using predictive biomarkers, and nanotechnology used to localize and treat disease?

The technological and information age has provided opportunities to both deepen our understanding about oral carcinogenesis and to generate exciting new diagnostics. Yet, embracing these new technologies without careful consideration about their utility across different settings and in the context of escalating healthcare costs, we must rely on the results meticulous research studies with rigorous inclusion criteria and validated endpoints and endeavor not to oversell their benefits.

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Tables:

Table 1: Ideal attributes of a diagnostic adjunct

Widely available
Can be easily and consistently used by non-experts
High patient acceptance
Immediate results
Inexpensive/covered by insurance or healthcare system
Separates high vs low risk lesions/ patients
Helps move patients into higher care settings
High accuracy (sensitivity/specificity)