	Visual Exam Only	Visual Exam (Early-Stage)
Image Count	110	20
Sensitivity	70%	38%
Specificity	63%	N/A
Negative Predictive Value	67%	N/A
Positive Predictive Value	66%	N/A

Table 1

For step 1 of Round 2, the study dentists performed a re-review and categorization of the now shuffled, image dataset, and achieved a 100% agreement with their original visual lesion classification and management plan. In step 2 of Round 2, each dentist had accessed the individual patient OraFusion test results and were then asked to re-evaluate the same image collection and re-evaluate with this additional information. The average sensitivity was 100% (95%CI) , specificity 99% (95%CI), NPV 100% (95%CI) and PPV 99% (95%CI). (Table 2) Two dentists now correctly identified all lesions while one dentist missed one cancer and another missed two malignant lesions. There was an overall statistical and clinical improvement in lesion discrimination and resultant management plan when the results of the OraFusion test were included as part of the 'physical' image exam.

	Visual Exam + BeVigilant Test	Visual Exam (Early-Stage) + BeVigilant Test
Image Count	110	20
Sensitivity	100%	100%
Specificity	99%	N/A
Negative Predictive Value	100%	N/A
Positive Predictive Value	99%	N/A

Table 2

Discussion

Head and neck squamous cell carcinoma (HNSCC) of the oral cavity and oropharynx is a curable disease if identified and treated at an early stage. Despite evidence of histological progression from cellular atypia through high grade dysplasia, ultimately leading to invasive Head and Neck (Oral) OSCC, most patients are diagnosed with late-stage OSCC without a clinically evident pre-malignant lesion. Furthermore, as OSCC incidence and prevalence continue to decline due to smoking cessation, the incidence of oral pharyngeal (OPSCC) has increased most likely due to concomitant increases in Human Papilloma Virus (HPV, primarily HPV-16)-related disease. (12,13) The social and biological evolution of the disease combined with the role of dentists as front-line oral health professionals (OHP), highlights the need for an easy to use, low cost POC device which broadly enables early diagnosis and ultimately improving outcomes.

In the current utility study we observed that four dental practitioners relying on their standard of care physical exam, or in this setting a digital inspection of mucosal lesions, were able to successfully categorize up to two-thirds of mucosal abnormalities as malignant a / high grade dysplasia with a sensitivity of 70% and a PPV of 66%,; however, they mis-classified approximately one third of the cases with a specificity of 63% and NPV of 67%. These results are comparable to prior studies where the oral cavity physical exam remains highly subjective and not very accurate with a reported sensitivity of 64% and a specificity of 31-76%. (14,15) More recent studies from the Netherlands further establish that dentists are not sufficiently prepared to differentiate benign from malignant oral mucosal lesions, and typically default to referral. This unfortunately leads to an increased burden on the oral specialty services creating potential delays in appropriate care.

Our primary objective was to determine whether dentists would utilize additional information such as the OraFusion risk categorization, to modify and or change their assessment and subsequent management of patients with oral lesions. We observed a significant improvement of greater than 30% in the dentists ability to accurately discriminate malignant / high grade dysplasia from benign / potentially malignant lesions with a combined sensitivity of 100% and PPV of 99%. The OHP's in this study incorporated the OraFusion risk level (which is based on clinical risk factors such as age, gender, race, smoking (yes/no), drinking (yes/no) history combined with protein levels of p16 and EGFR) into their lesion classification process and as a result changed their management recommendation.

Currently, the American Dental Association (ADA) proactively encourages OHP's to perform an oral cancer screening (OCS) in all adult patients with a visual and tactile examination (CVTE). (6) Evidence from the United States suggests that 28% of patients presenting to the dentist have some type of oral mucosal abnormality. (17) A recent report on an oral screening questionnaire from National Health and Nutrition Examination Survey (NHANES) for years 2011-2017 found that oral cancer screening rates have been declining, and most pronounced in low income adults. (18) It was noted that the Affordable Care Act did increase oral cancer screening by 5-6% with the majority of this being performed by dentists.

Furthermore, low resource, minority and underserved populations have the highest rate of OC in the US along with a higher prevalence of oral potentially malignant lesions. (19) Collectively this data further emphasizes the need to educate and support the OHP community through a variety of channels which includes easy to use devices such as the OraFusion platform that are subject specific and supportive adjuncts in the oral lesion assessment / decision process.

The study has limitations including the engagement of only 4 dentists to assess 110 lesions which were restricted to the oral cavity and provided in a digital manner. The design of the study did provide for a histologic confirmation of each lesion thereby correlating a visual impression with a pathology diagnosis. Finally, the OraFusion assay was not performed in real-time during the image review process. This was intentional to stream-line the study design and to limit OHP time commitments.

Conclusion

The introduction of risk categorization based on clinical and biomarker data from a point of care device into the dentists oral cancer screening process improves the dentists ability to correctly discriminate benign vs. malignant / high grade dysplastic lesions. Additional studies are underway to further expand this design by including more dentists geographically distributed across the US and to incorporate mucosal lesions of the visible oropharynx as well as the oral cavity.

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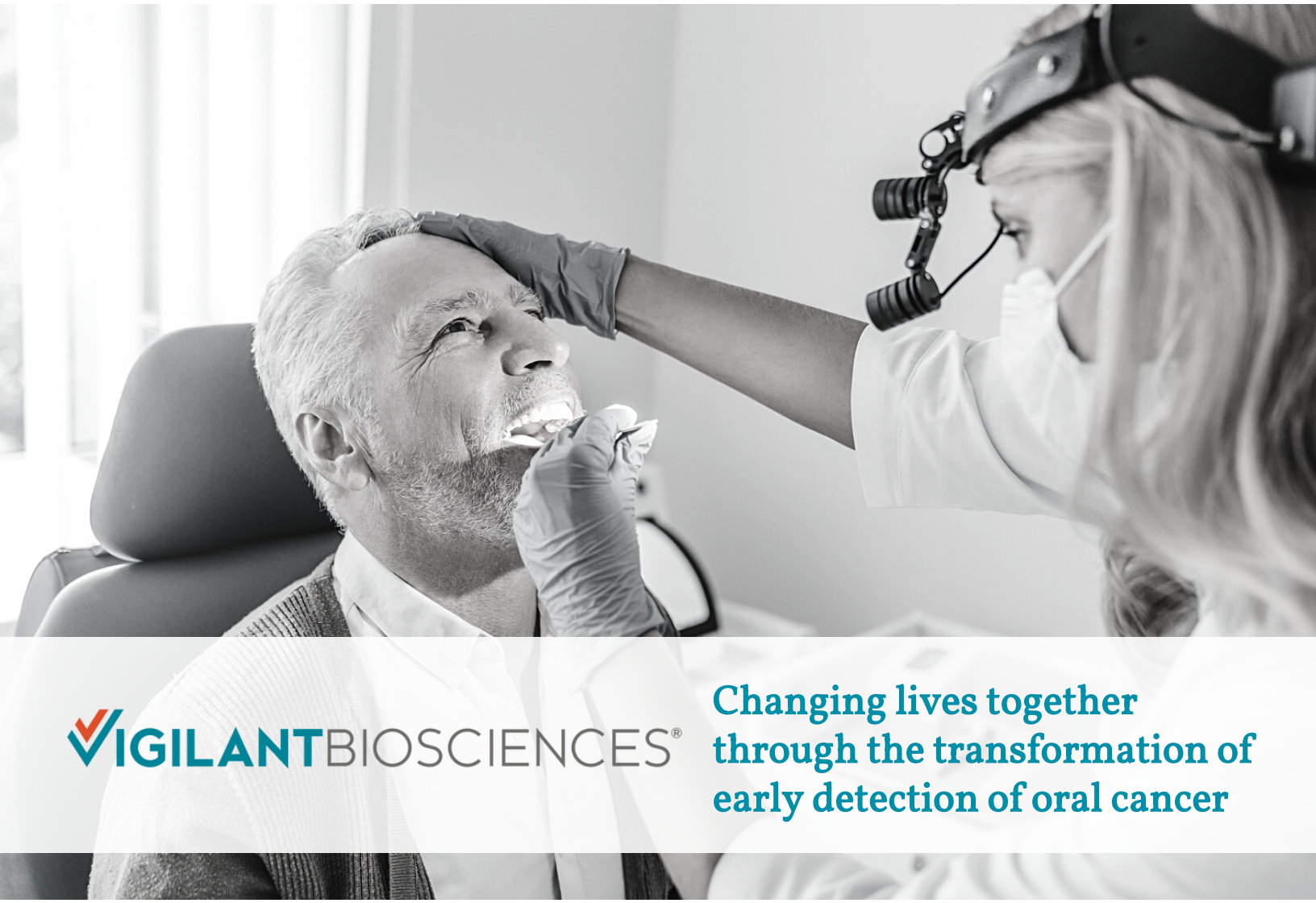

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