Assessing the usefulness of toludine-blue staining, Oral*CDx*®, and VELscope® for oral cancer screening:

A Probabilistic Approach

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Background

Oral Cancer

- estimated prevalence in North America of :
  - oral lesions = 27.9% [1]
  - oral cancer = 0.08% (80 cases /100,000 people) [2]
- clinically challenging to identify oral lesions which could be potentially cancerous
- three devices available to public health programs and general dentists for oral cancer screening are:
  1. VELscope®; LED Dental Inc., White Rock, BC, V4B 1C5;
  2. Oral*CDx*®;OralCDx Laboratories Suffern, NY 10901-4164 ;
  3. toludine blue staining [3,4]
- to date, there is no scientific research supporting or refuting that adjunctive diagnostic screening devices saves lives [5,6]
- in the absence of such evidence, a probabilistic model can be helpful in determining the usefulness of adjunctive diagnostic screening devices [7]

Properties of Diagnostic Tests

- diagnostic devices are used as alternatives to the gold standard diagnostic test
- all diagnostic devices have a margin of error
- uncertainty of a diagnostic device is reflected in its properties of *sensitivity* (***Sn***), *specificity* (***Sp***), *positive predictive value* (***PPV***) and *negative predictive value* (***NPV***) [Table 1]
- likelihood of cancer ***before*** giving diagnostic test = ***pre-test probability***
- likelihood of cancer ***after*** a *positive* diagnostic test = ***post-test probability***
- ***PPV = post-test probability***
- oral cancer screening programs must assess the risk between a missed diagnosis by not testing versus the hazards of a false positive test

TABLE 1- Properties of Diagnostic Tests

Test Properties	Symbols	Definitions
Pre-test probability	***p***[pre-test]	▪ probability of ***cancer*** prior to doing the diagnostic test on the patient
Sensitivity	**Sn**	▪ probability of a **positive** test result when the patient is known to have ***cancer***
Specificity	**Sp**	▪ probability of a **negative** test result when the patient is known **NOT** to have ***cancer***
Positive Predictive Value*	**PPV**	▪ probability the patient has ***cancer*** when the test result is **positive**
Negative Predictive Value	**NPV**	▪ probability the patient does **NOT** have ***cancer*** when the test result is **negative**

**also referred to as the post-test probability*

Bayes' Theorem

- The ***PPV*** and the ***false-positive-rate*** are a function of the test's sensitivity, specificity and pre-test probability (see Equations 1 and 2) [8].

Equation 1. $PPV = Sn \times \boldsymbol{p}[\text{pre-test}] / (Sn \times \boldsymbol{p}[\text{pre-test}] + (1-Sp) \times (1- \boldsymbol{p}[\text{pre-test}]))$

Equation 2. False positive rate = 1-PPV

Objectives

- ***to evaluate the probabilistic performance of VELscope®, OralCDx® and toludine blue staining – as an adjunctive diagnostic procedure in the routine screening of oral cancer in clinical practice***

Methods

- The Sn and Sp for toludine-blue staining, Oral*CDx* and VELscope® were taken from current literature (Table 2).
- PPV's for each device were calculated using Bayes' Theorem under three clinical screening scenarios (Table 3) .

Table 2- Sensitivity and Specificity for diagnostic devices reported in the literature

Diagnostic device	Sn (%)	Sp (%)
toludine-blue staining [9]	77	67
VELscope ® [10]	97	94
Oral*CDx*® [11]	92	94

Table 3: Pre-test probability of three different types of screening scenarios

Screening scenarios	Pretest Probability		Commentary
	Per 100,000	***(%)***	
Screening all patients	80	.08	• Prevalence data for 2004 [12]
Screening only adults above the age of 40	160	.16	• *Median age in North America approx 40 years* [13] • *Assume all oral cancer occurs in people 40+*
Screening of only visible oral lesions in adults	573	.573	• = prevalence (adult) of oral cancer ÷ prevalence of oral lesions • assume all oral cancers are visible

Results

- The PPV's for each device under three screening scenarios is presented in tables 4-6.
- The PPV's for each device as a function of the pre-test probability is graphed in Figure 1.

Table 4: PPV and False Positive- Population based screening

Diagnostic Device	PPV (%)	False Positive (%)
toludine blue staining	0.19	99.81
VELscope	1.27	98.63

Table 5: PPV and False Positive - Screening all adults (≥40 years)

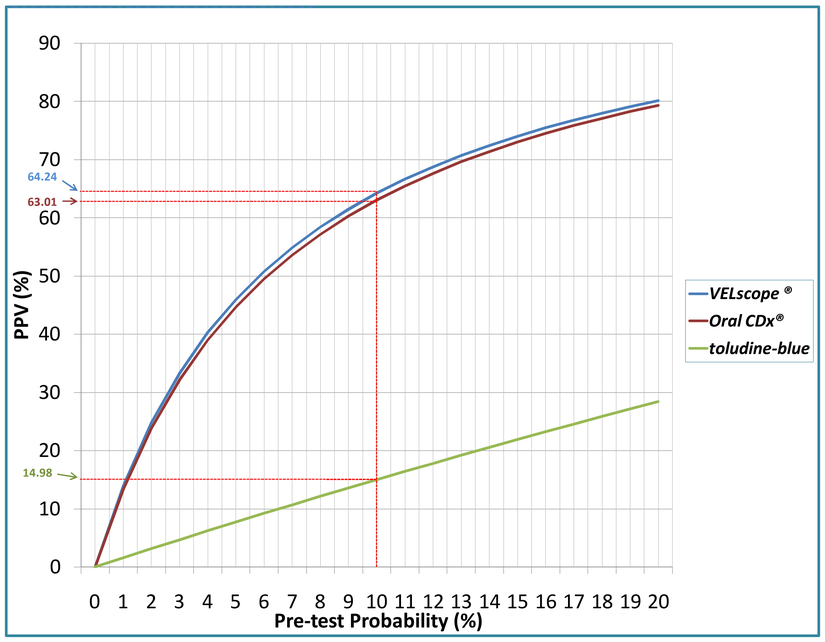
Device	PPV (%)	False Positive (%)
toludine blue staining	0.37	99.53
VELscope	2.53	97.47

Table 6: PPV and False Positive – Screening all visible oral lesions

Device	PPV (%)	False Positive (%)
toludine blue staining	0.90	99.10
VELscope	8.52	91.48
Oral*CDx**	8.11	91.89

∝ *only performed on visible suspicious oral lesions*

Figure 1: PPV *vs.* Pre-test Probability



Discussion

- ✓ In a cancer referral clinic, where the *pre-test probability* may likely be above 10%, then VELscope® and Oral*CDx*® have a PPV of over 60%.
- ✓ However, as a routine population screening device in public health programs or general practice, VELscope® and toludine blue staining will incorrectly test positive more than 97% of the time.
- ✓ The reported *Sn* and *Sp*'s for toludine blue, VELscope® and Oral*CDx*® are likely overestimated because of spectrum bias. [14,15]
- ✓ Therefore, the actual *false positive rates* for these devices are likely to be even higher than those reported here.

Conclusions

1. As a routine screening device in general practice, VELscope® and toludine blue staining have a **high *false positive rate.*** Consequently patients are likely to often undergo unnecessary surgical procedures and endure the stress of falsely believing they have oral cancer.
2. Scarce healthcare resources should not be directed to the use of these devices for general population based oral cancer screening
3. These devices may be beneficial in opportunistic screening programs or cancer referral clinics when the *pre-test probability* of oral cancer is likely to be above 10%.
4. Further research is needed to determine at which pre-test probabilities these adjunctive diagnostic devices would be cost-beneficial for the screening of oral cancer.

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