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Response

Response to Brandt, Bednarz-Knoll, Kleinheinz et al.

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We thank Brandt and colleagues for their interest in our article. In a population-based study of oral leukoplakia and risk of progression to oral cancer, we reported that the decision to biopsy a leukoplakia had modest predictive ability for the identification of prevalent or incident oral cancers (sensitivity of 59.6%, specificity of 62.1%, and positive predictive value [PPV] of 5.1%). Furthermore, although grade of dysplasia was statistically significantly associated with risk of progression to cancer, a high proportion of oral cancers (39.6%) arose from leukoplakias without evidence of dysplasia. We concluded that our results underscore the need for tools to improve triage and reduce sampling errors of the biopsy of oral leukoplakia.

Brandt and colleagues (1) suggest that molecular analysis of epidermal growth factor receptor (EGFR)—number of CA single sequence repeats (SSR) in intron 1 or gene copy number—could guide accurate identification of high-risk oral leukoplakias.

In theory, we agree with Brandt and colleagues (1) that molecular markers could enable the accurate identification of high-risk oral leukoplakias. In practice, however, we submit that neither EGFR nor any other currently available biomarker provides adequate discrimination of oral leukoplakias. The current state of the science includes numerous biomarkers with statistically significant associations with risk of prevalent or incident oral cancer in patients with oral leukoplakia. However, the translation of promising biomarkers into clinically useful tests mandates a transition from measures of association (eg, odds ratios, risk ratios) to measures of clinical and public health utility, such as sensitivity, specificity, area under the receiver operating characteristic curve, PPV, negative predictive value (NPV), and the complement of the NPV (cNPV = 1-NPV) (2,3).

In the context of biopsy of oral leukoplakia, a clinically useful molecular triage test needs to have high sensitivity to ensure biopsy of patients with prevalent cancer and those with high risk of incident cancer, high specificity to minimize the number of unnecessary biopsies, and high NPV–low cNPV to provide appropriate reassurance against current and future disease to patients who do not receive a biopsy. As shown in Table 1, both the number of EGFR CA SSR (based on data presented by Brandt et al.) (1) and EGFR copy number (based on data from the Erlotinib prevention of oral cancer [EPOC] trial) (4) have poor performance. Specifically, the high sensitivity of EGFR CA SSR is counterbalanced by low specificity and low PPV, whereas for EGFR copy number, both sensitivity and specificity are low and cNPV is unacceptably high.

We note that accurate triage of oral precancers for biopsy represents an important, yet initial, clinical step. Our data, as well as numerous reports in the literature (5), demonstrate that a histopathologic definition of disease (presence and grade of dysplasia) provides unsatisfactory discrimination between oral leukoplakias that do or do not progress to cancer. This

Table 1. Performance of EGFR markers for the identification of oral leukoplakias at high risk of progression to oral cancer

Characteristic	EGFR CA SSR in Muenster cohort, %[a]	EGFR copy number in EPOC trial, %[b]
Sensitivity	83.3	55.3
Specificity	38.1	67.1
AUC	60.7	61.2
PPV	3.9	34.2
NPV	98.7	82.9
cNPV	1.3	17.1

[a]Calculated based on numbers derived from figure 1 presented by Brandt et al. ([a]): low EGFR CA repeats, oral cancer = 10; low EGFR CA repeats, no oral cancer = 242; high EGFR CA repeats, oral cancer = 2; high EGFR CA repeats, no oral cancer- = 149. AUC = area under the receiver operating characteristic curve; cNPV = complement of the NPV; EGFR = epidermal growth factor receptor; EPOC = Erlotinib prevention of oral cancer; NPV = negative predictive value; PPV = positive predictive value.

[b]Calculated from numbers in figure 3B presented by William et al. (4): high EGFR copy number, oral cancer = 26; high EGFR copy number, no oral cancer = 50; low EGFR copy number, oral cancer = 21; low EGFR copy number, no oral cancer = 102.

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underscores a much-needed change in the definition of oral precancer from a macroscopic (clinical identification of leukoplakia) and microscopic (histopathology) definition to a molecular definition based on genomic features.

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