Exfoliated cytology for early detection of oral cancer and risk stratification of OLK:

1.       As a well-established and widely used method for early detection of oral cancer, exfoliated cytology provides qualitative result of diagnosis. For example, OralCDx reports “negative or benign”, “positive” (defined as definitive cellular evidence of epithelial dysplasia or carcinoma), or “atypical” (defined as abnormal epithelial changes of uncertain diagnostic significance). OralCDx has been proved to be a very good method for early detection of oral cancer (see attached report).

2.       As for risk stratification for OLK patients, OralCDx does NOT do a good job because qualitative results “negative, positive or atypical” are vague. Clinicians have to reply on multiple tests during follow-up before the patient is definitely proved to be “negative” or “positive”. That’s why a quantitative risk stratification of OLK is needed. This is our niche!

3.       The advantages of this technique: minimally invasive and inexpensive.

Challenge of statistical data analysis of exfoliated cytology for quantitative risk stratification:

1.       Big population of diploid cells, relatively small population of tetraploid cells, and a very small population of aneupoid cells

2.       Therefore, the signal of aneuploid cell population needs to be “amplified” for data analysis.

Other methodologies for quantitative risk stratification of OLK:

1.       Clinical data-based cancer risk index, for example Harvard Cancer Risk Index (J Clin Epidemiology 2004:57:332-40): “Discriminatory accuracy was modest for ovarian cancer (age-adjusted concordance statistic = 0.59), and relatively good for pancreatic cancer (concordance statistic of 0.72), and colon cancer in men and women (concordance statistics of 0.71, 0.67 respectively).” Limitation of this method is obvious, not tissue or cancer specific.

This method has been used for risk stratification of OLK. Yao, you know these clinical parameters in your clinical practice.

2.       Molecular data-based cancer risk index, for example, mRNA expression data (using gene expression array, qRT-PCR), protein expression data (using immunohistochemical staining): This method has been developed for clinical use in other cancers, for example, breast cancer (Breast 2013;109-120), colon cancer (JNCI 2014;106 (10). pii: dju247). Performance of this approach is not that great, according to the colon cancer paper. “The four tested gene expression-based risk scores provide prognostic information but contribute only marginally to improving models based on established risk factors.”. Why? According to a recent paper (Cancer Res 2014;74:4612-21), “Different prognostic gene lists have very few shared genes, the biological meaning of most signatures is unclear, and the published success rates are considered to be overoptimistic.” “Two approaches that may hold hope for obtaining improved prognosis are presented with both based on using existing prior knowledge. One proposes combining molecular data with clinical data, and the second infers biologically relevant pathway deregulation scores”. Further studies are needed to validate these approaches. Overall, limitations of this methodology are two-fold: (1) it is expensive and special expertise is required for sample analysis and data analysis; (2) Since sample quality is critical for this method, clinical sampling, sample storage and processing will be a challenge to clinicians.

This method has been used to generate an Oral Cancer Index using biopsy samples from OLK patients (Cancer Prevention Res 2011;4:218-29). Three models, Model 1 (only microarray data), Model 2 (microarray data, clinical data and protein data), Model 3 (clinical data and protein data), were tested. “The prediction error curves in figure 1 demonstrated that microarray data can markedly improve the prediction accuracy over Model 3 that used only clinical and protein data. Model 1 and Model 2 have similar performance (Model 2 is slightly better) with prediction error around 8% beyond 2 years of follow-up time.”

Therefore, we believe exfoliated cytology is a potentially good method for quantitative risk stratification of OLK if we can improve the statistical model.

Future perspective: This study used only DI as the parameter for model construction. If other parameters are taken into consideration (Yao, list all parameters Classify reports), performance of this model may be further improved.