Separating the Good from the Bad and Ugly

The Use of Non-Invasive Optical and Molecular Tests in the Management of an Oral Lesion

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Faculty Disclosure

I have no conflict of interest in relation to the devices or tools used in this presentation.

Vancouver, British Columbia, Canada

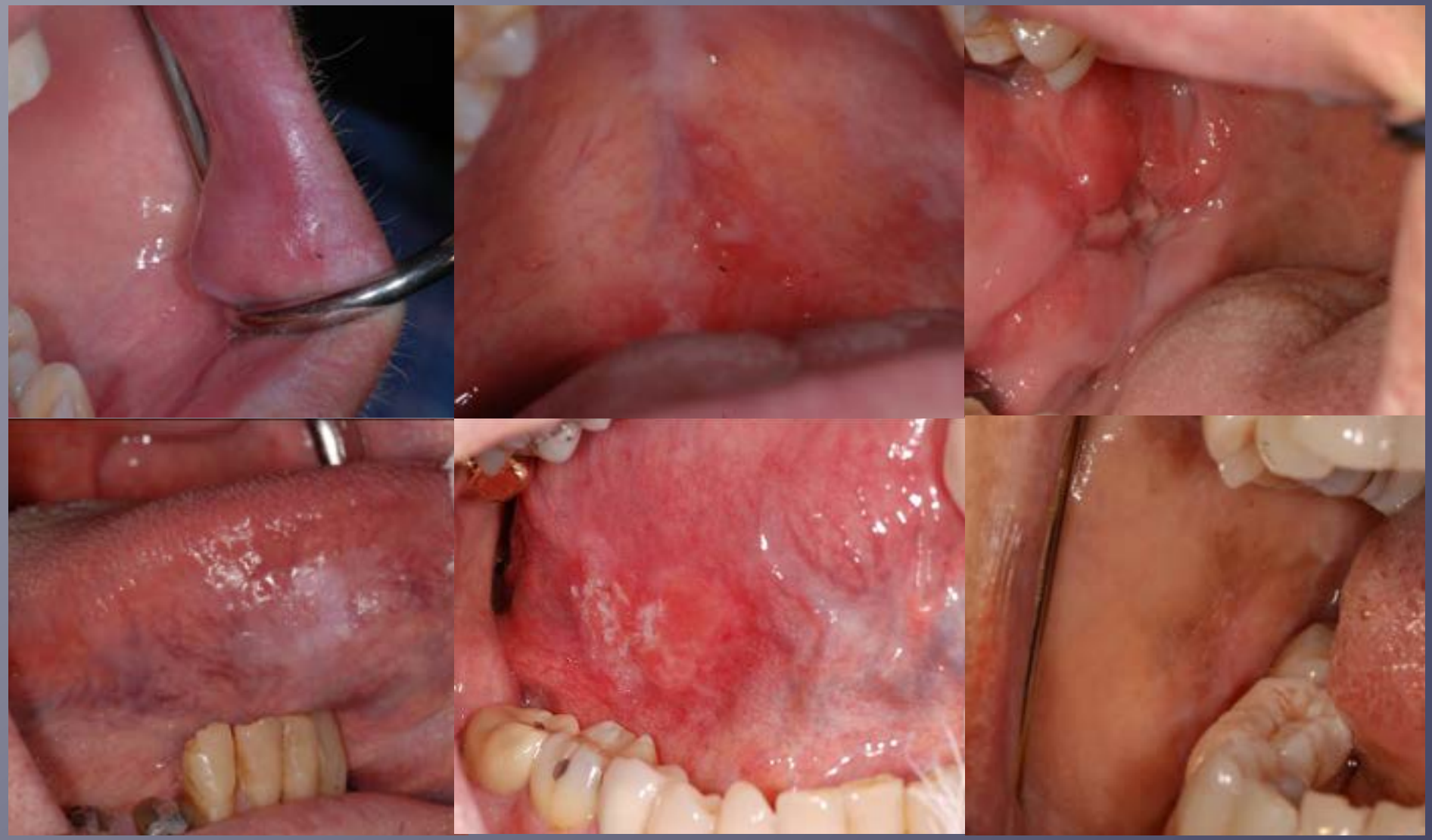
University of British Columbia


UBC


Oral Health Centre


BC Cancer Agency
VANCOUVER CENTRE

Oral Mucosal Lesions



Early Detection and Risk Assessment

Finding Solutions through Research !!

Non-invasive Optical and Molecular Tests

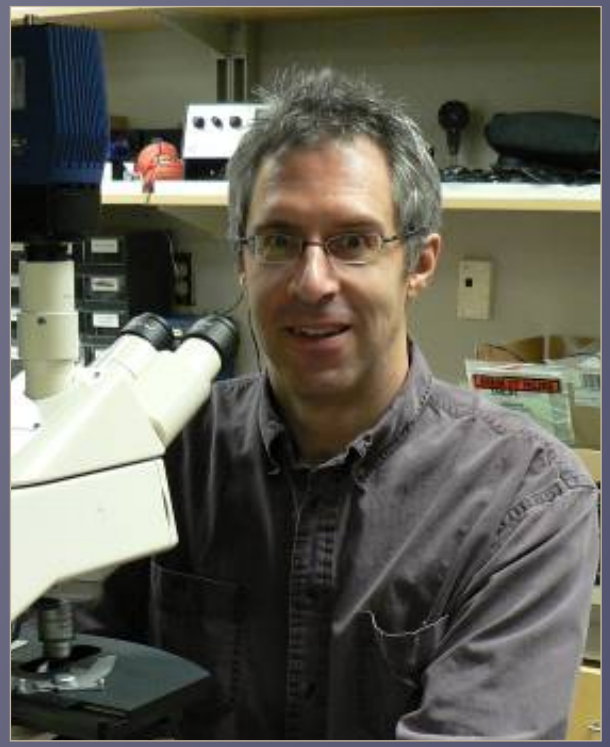
1. VELScope®
2. Quantitative Cytology
3. Loss of Heterozygosity

VELScope®


Introducing the
VELscope Vx™
Shining Blue Light on Oral Health
VELSCOPE Vx
Enhanced Oral Assessment

Building a Visualization Device

Calum MacAulay



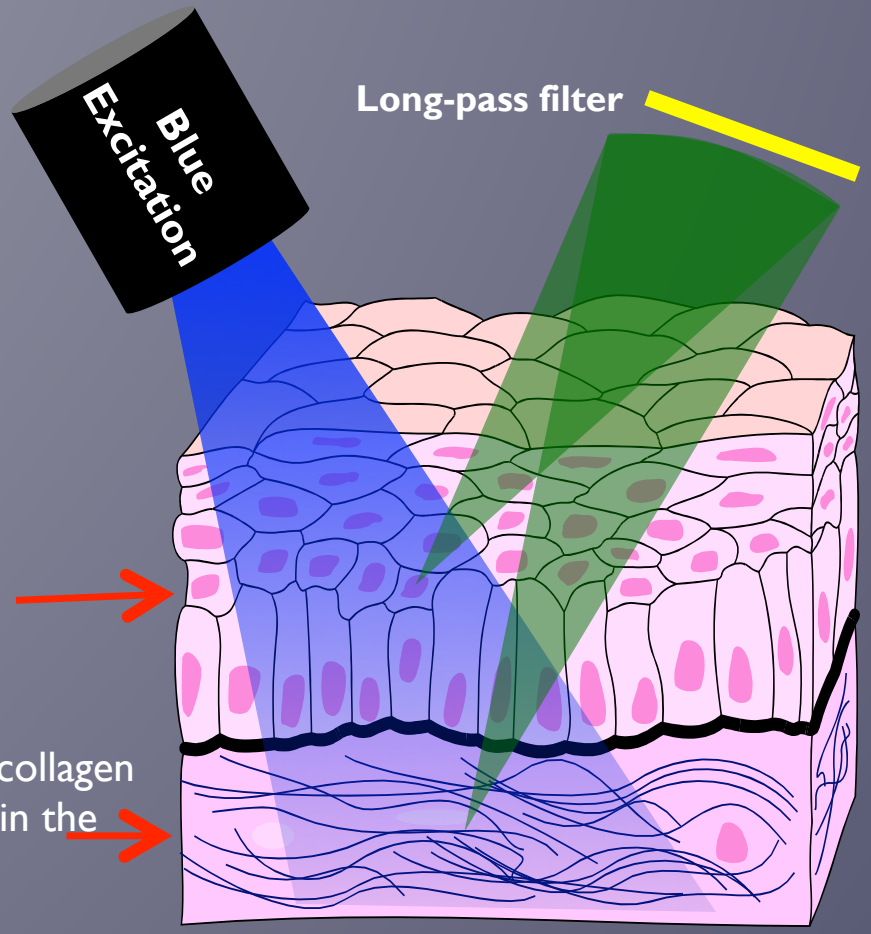
Pierre Lane

Lane *et al.*, **Simple device for the direct visualization of oral-cavity tissue fluorescence.** 2006 11(2):024006. J Biomed Opt.

Fluorescence Visualization (FV)

FVR
(fluorescence visualization retained)

FVL
(fluorescence visualization loss)



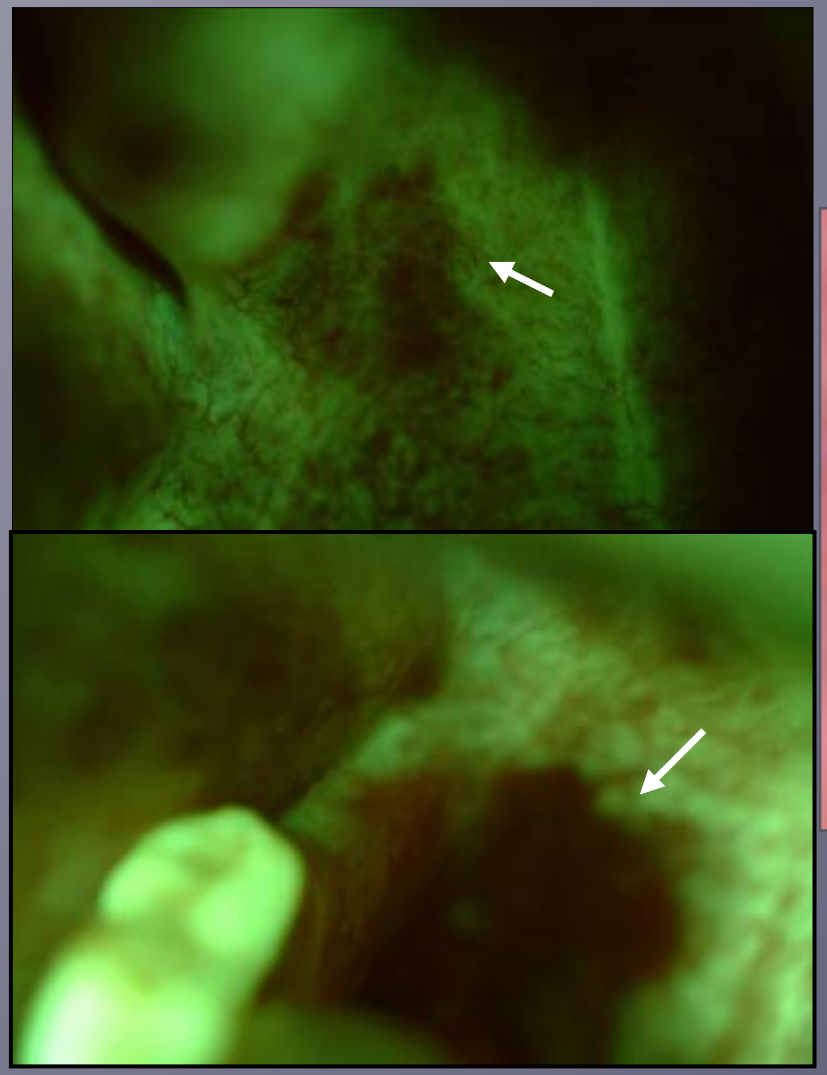
Fluorescence due to FAD/NADH (cellular level)

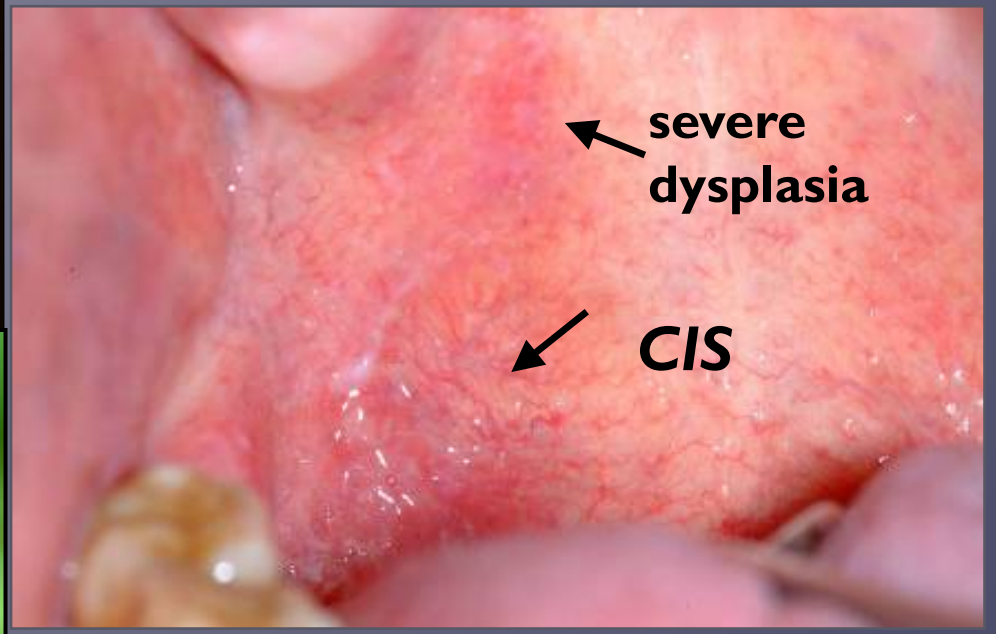
Fluorescence due to collagen cross-links & elastin (in the subtending stroma)

- Epithelial Thickening
- ↑ Nuclear Scattering
- ↑ Metabolic Activity
  (↑ FADH/NAD)
- Decomposition (or restructuring) of the of Collagen Matrix
- ↑ Micro-Vascularization

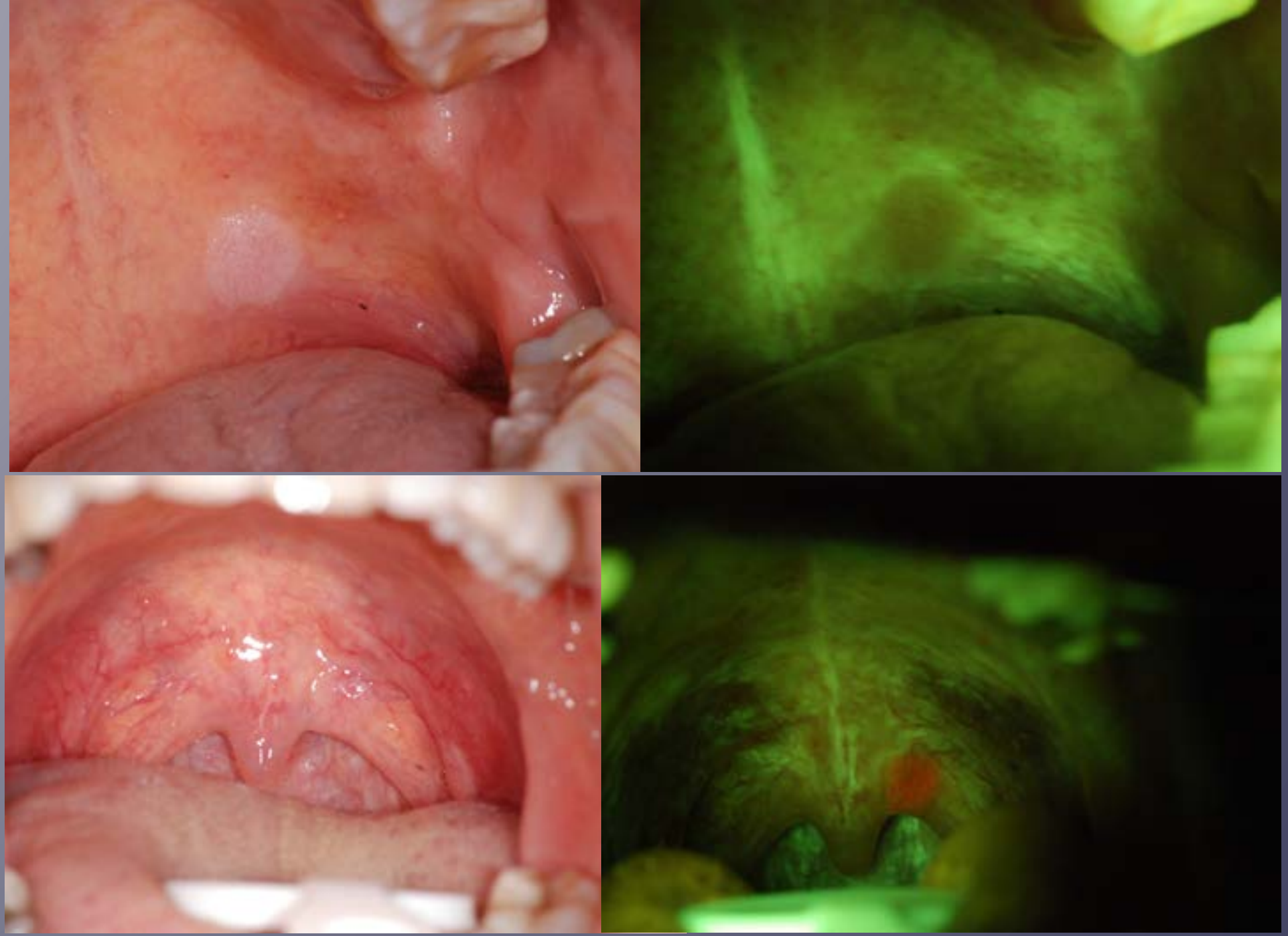
Poh *et al.*, 2009 (book chapter)

Identification of clinically not-apparent change

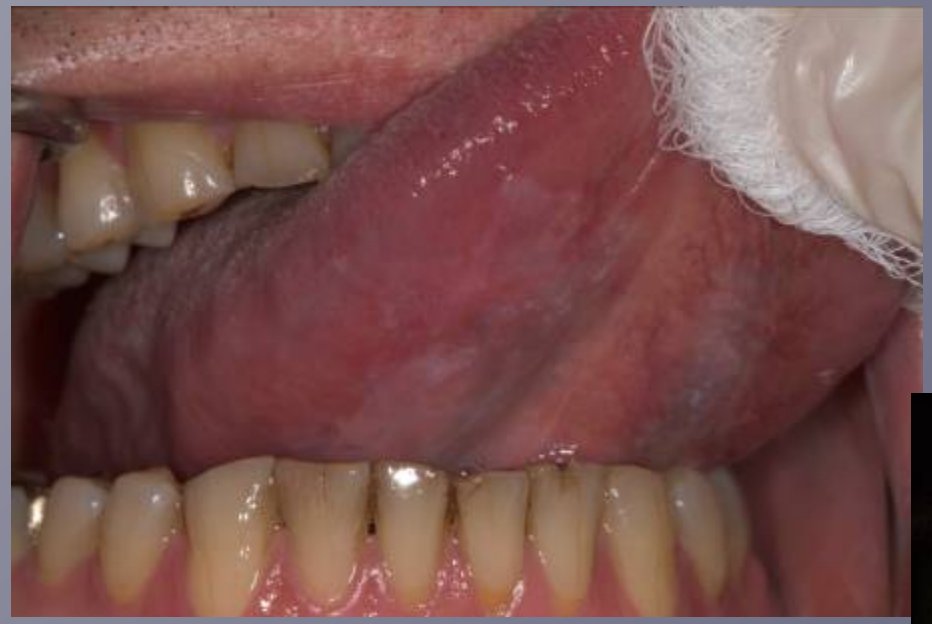


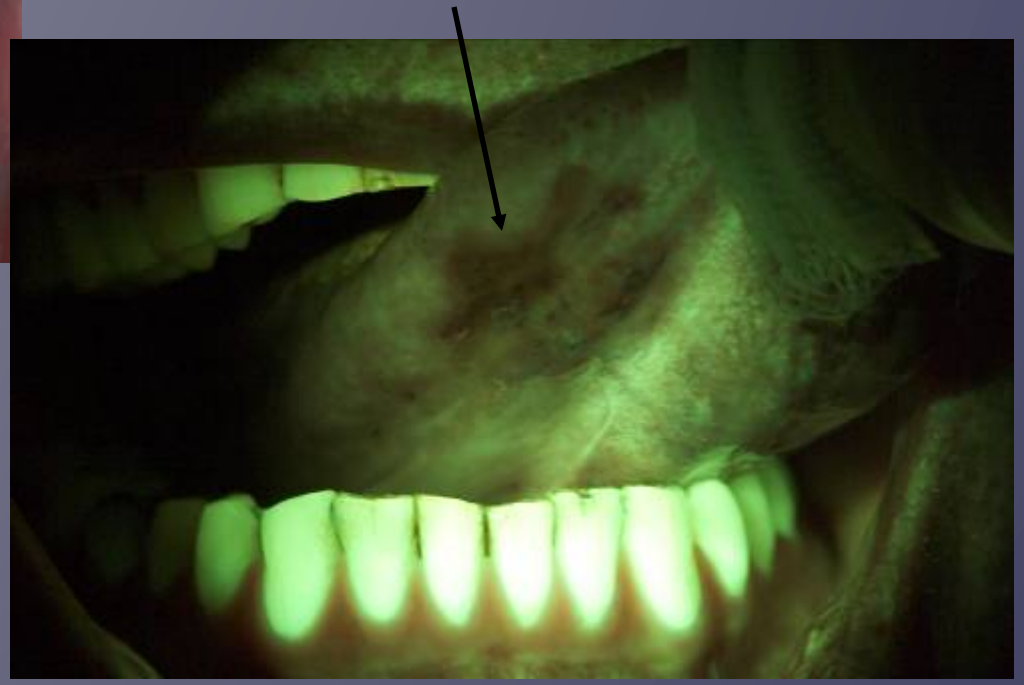


Poh *et al.*, Head and Neck, 2007



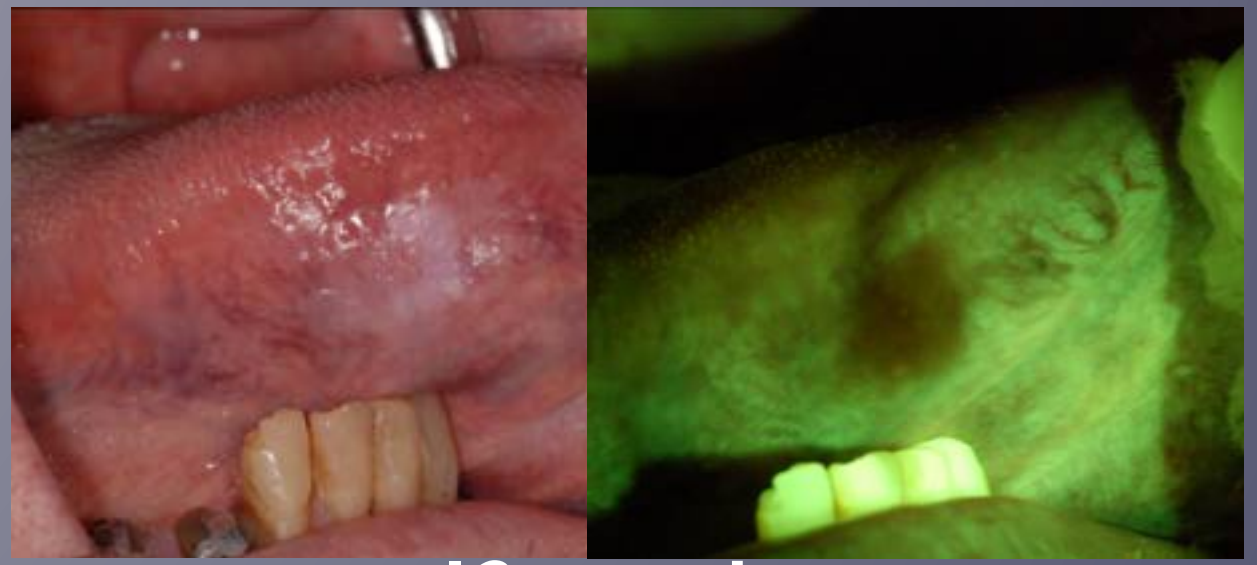
FV helps on the decision of where to biopsy



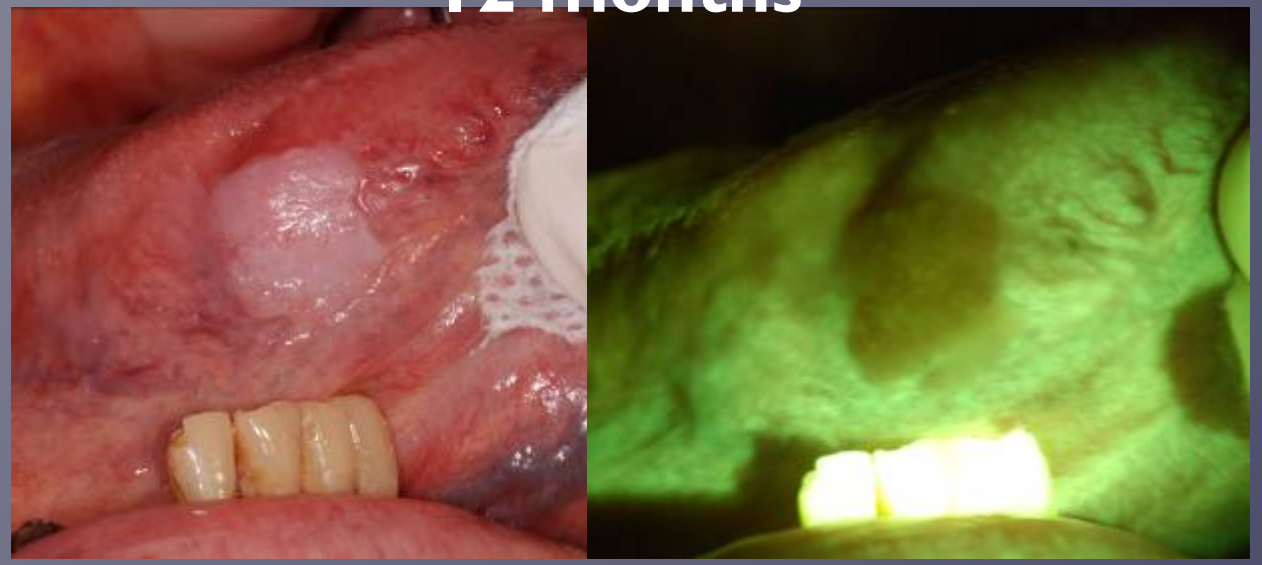


Diffuse non-homogenous leukoplakia at the right ventral tongue

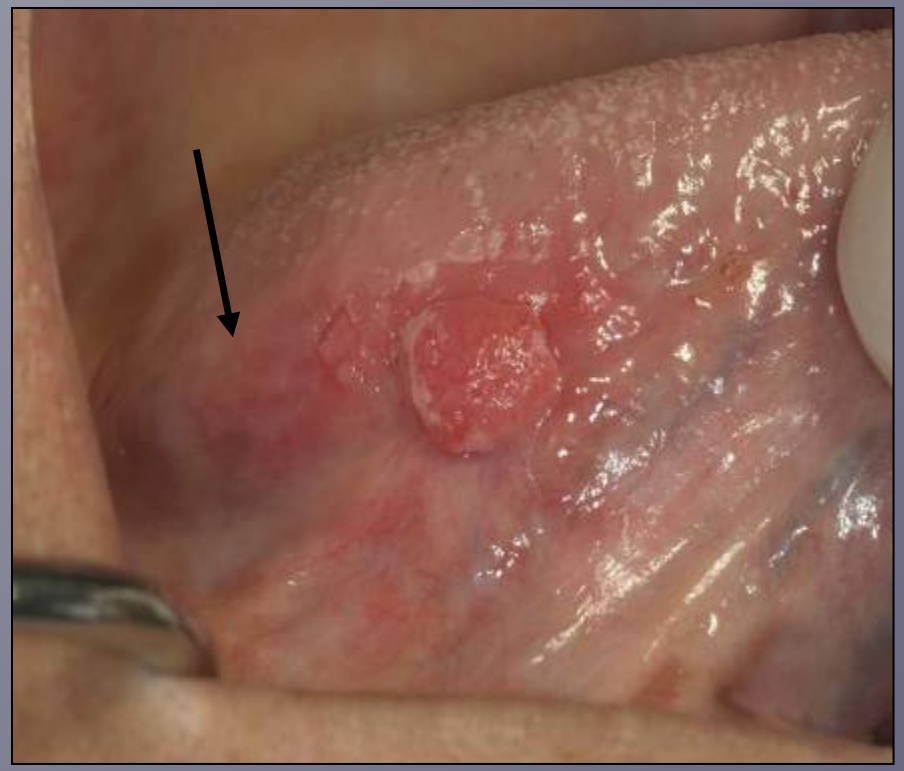
When to biopsy



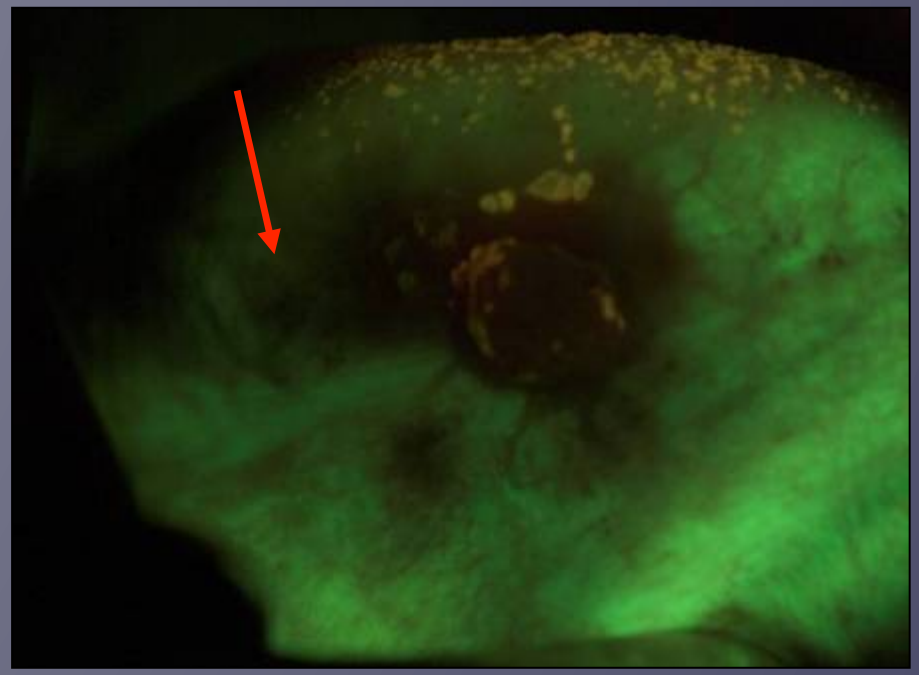
12 months



The extension of the high-grade oral lesion



Clinical white light image –
Invasive cancer and severe dysplasia (arrow)



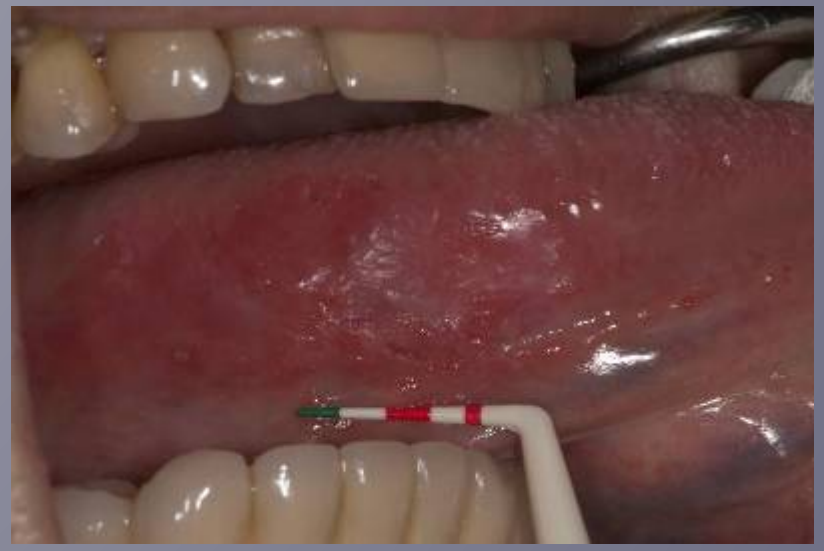
Fluorescence visualization (FV)

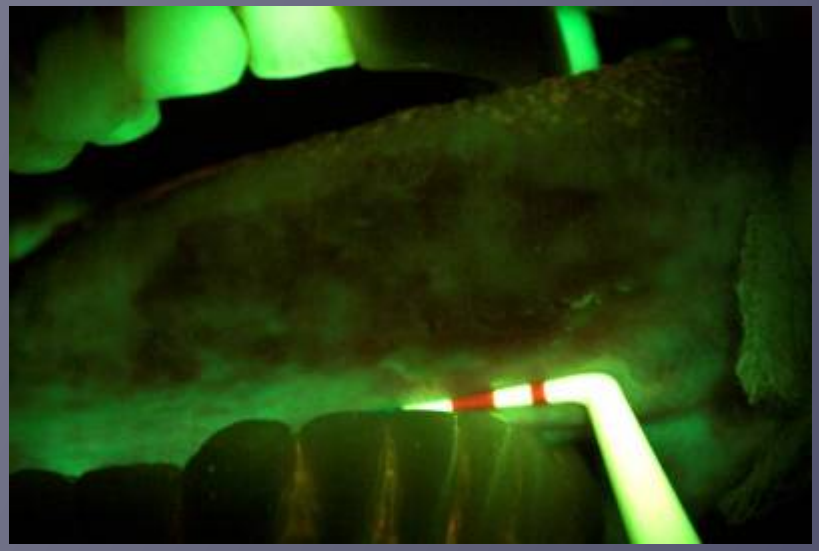
FV in the operating room

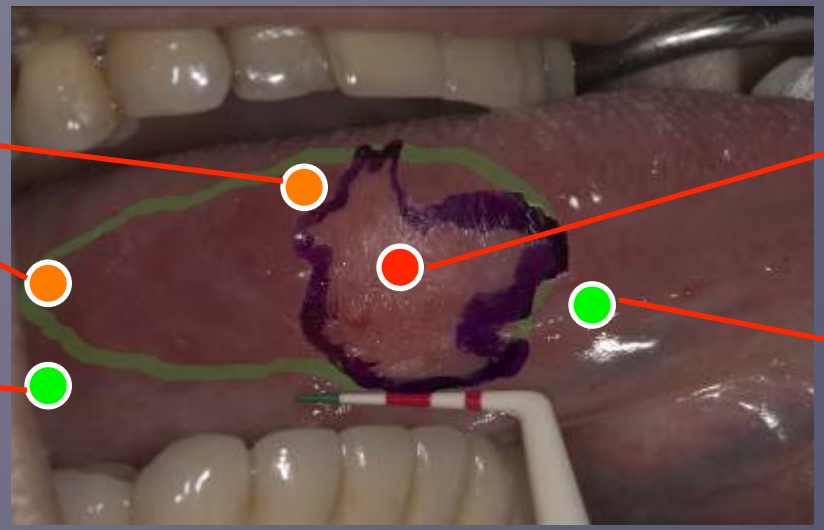
Question 1:

Can we use this tool in the operating room to assist the decision of surgical margin?

FV in the operating room

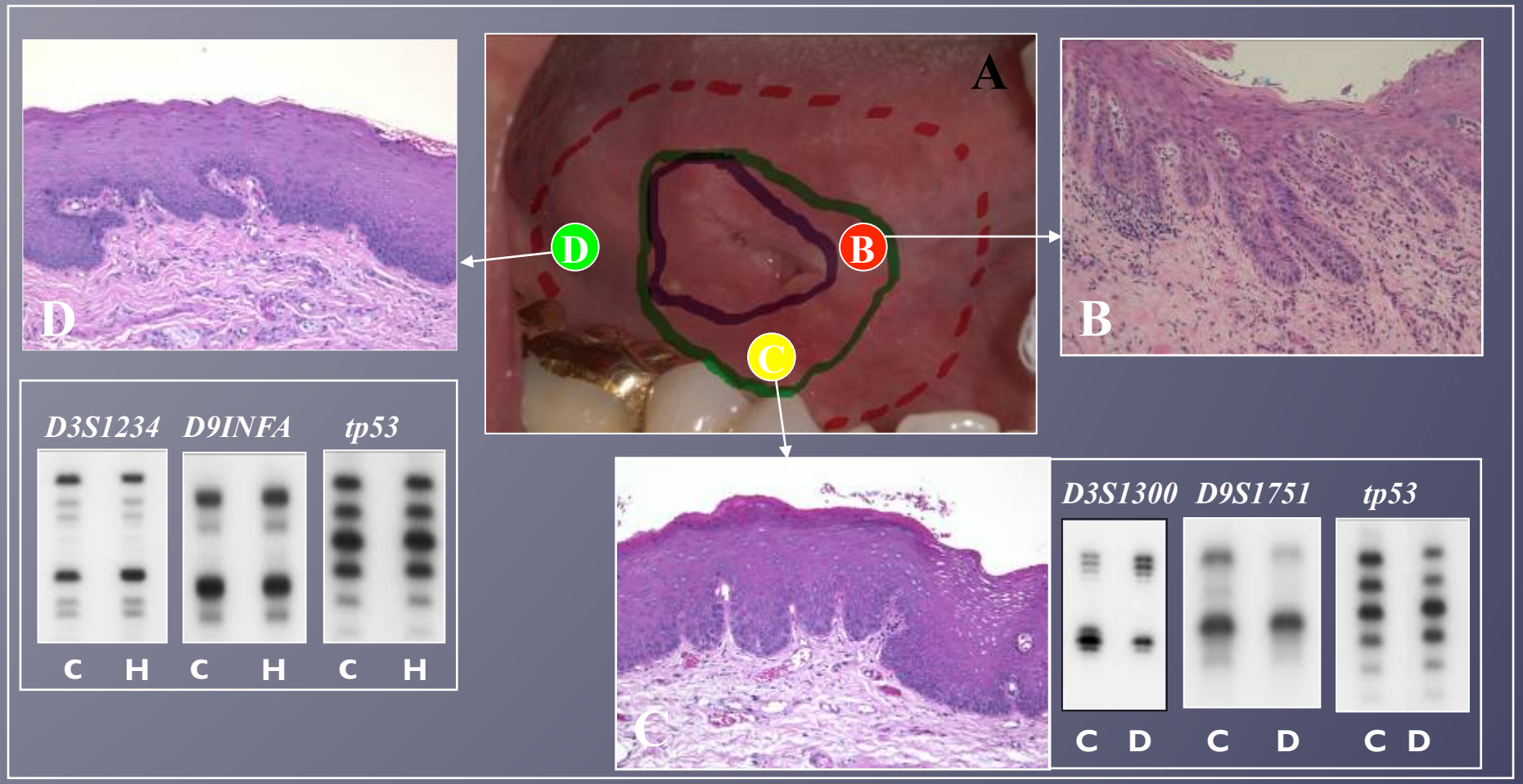






Clin Can Res, 12(22), 6716-22, 2006

- FV can recognize **histologically high-grade and molecularly high-risk areas.**
- 19/20 lesions has FV positive area outside the tumor area and the FV margin is **not evenly around** the tumor area



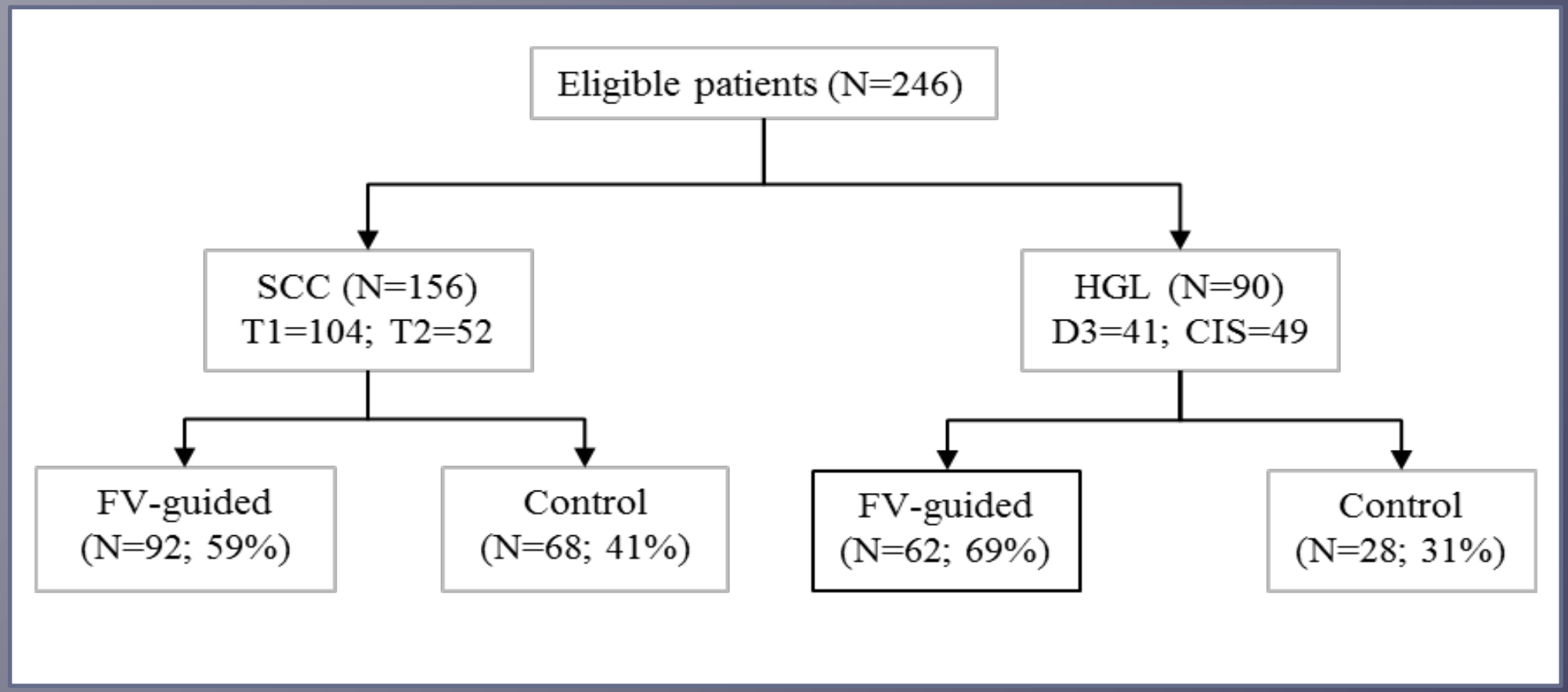
Clin Can Res, 12(22), 6716-22, 2006

FV in the operating room

Question 2:

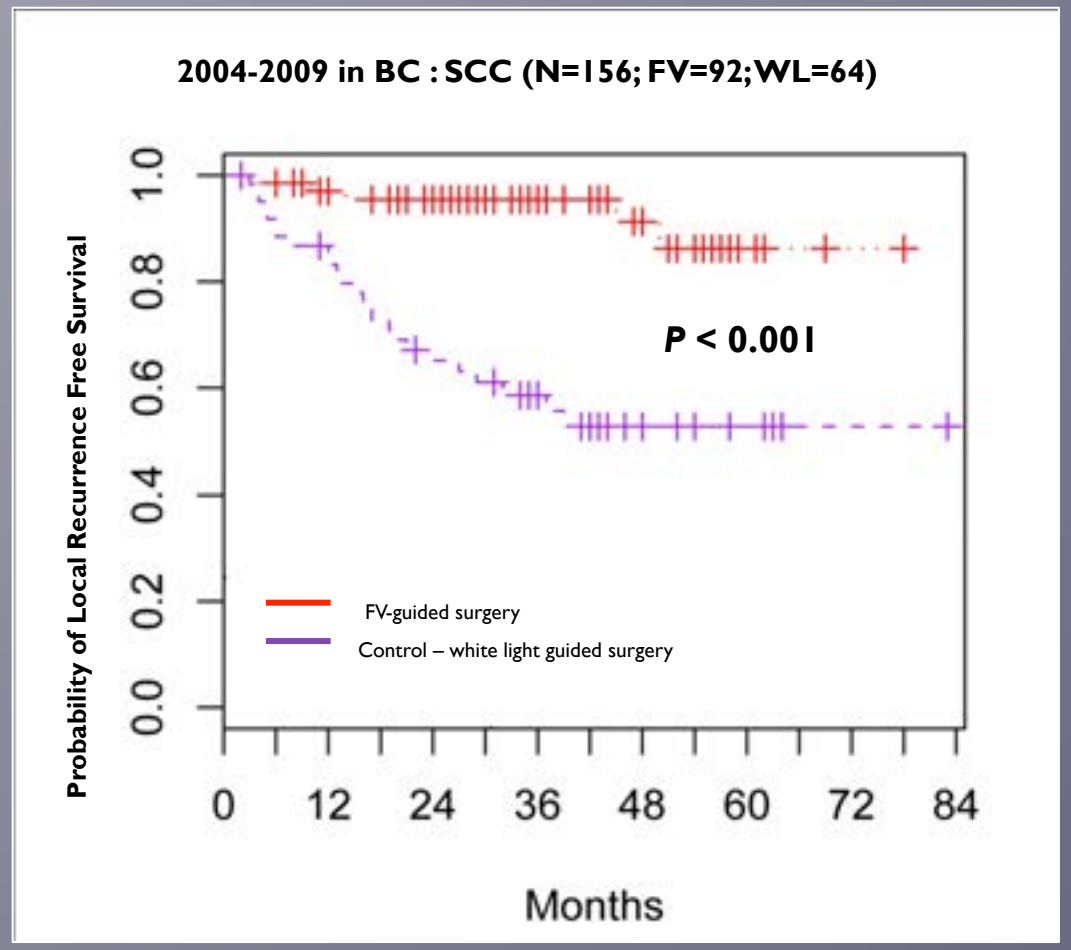
Does the tool really make impact on patient's outcome, i.e., recurrence rate?

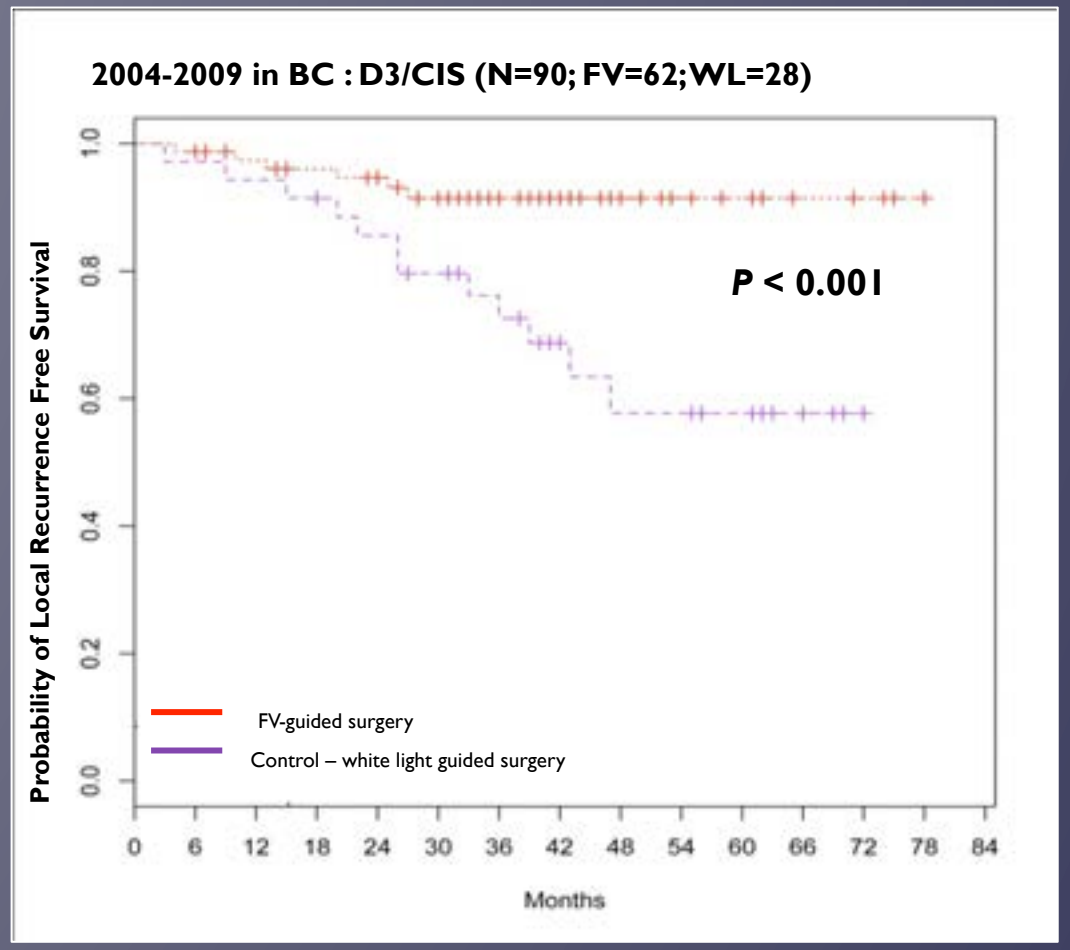
Study Scheme: 2004-2009 British Columbia



Poh et al., JAMA Otolaryngol Head Neck Surg. 2016;142(3):209-216.

FV appears to reduce local recurrence





3-year recurrence rate reduces from 41% to 6.5%.

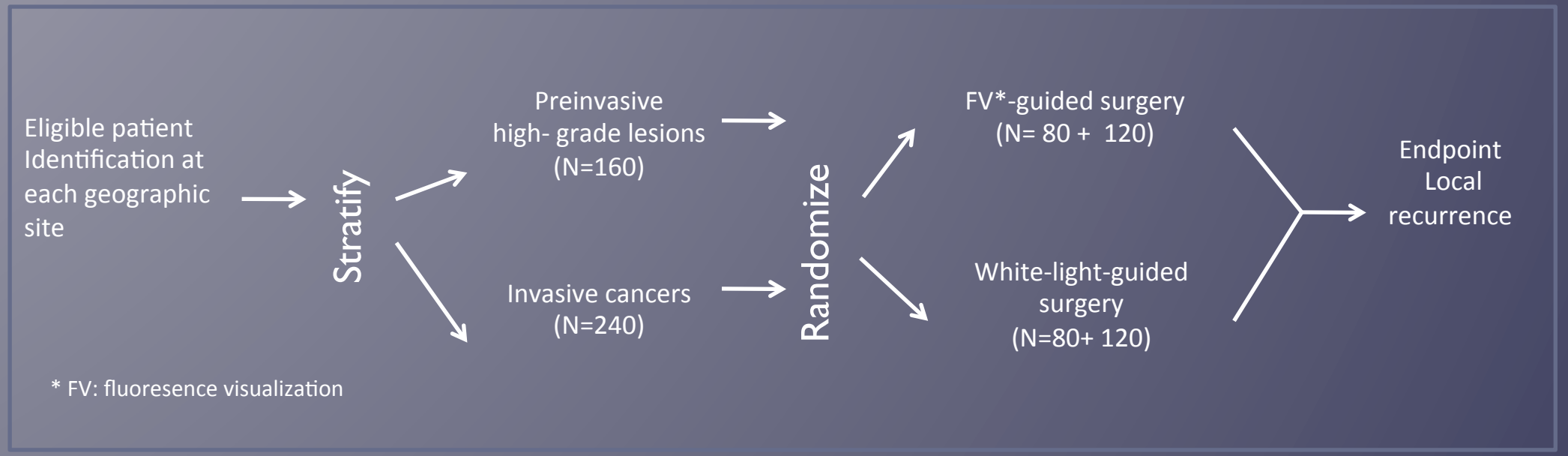
3-year recurrence rate reduces from 39% to 8%

JAMA Otolaryngol Head Neck Surg. 2016;142(3):209-216

COOLS trial-

Canadian **O**ptically-guided approach for **O**ral **L**esions **S**urgical Trial

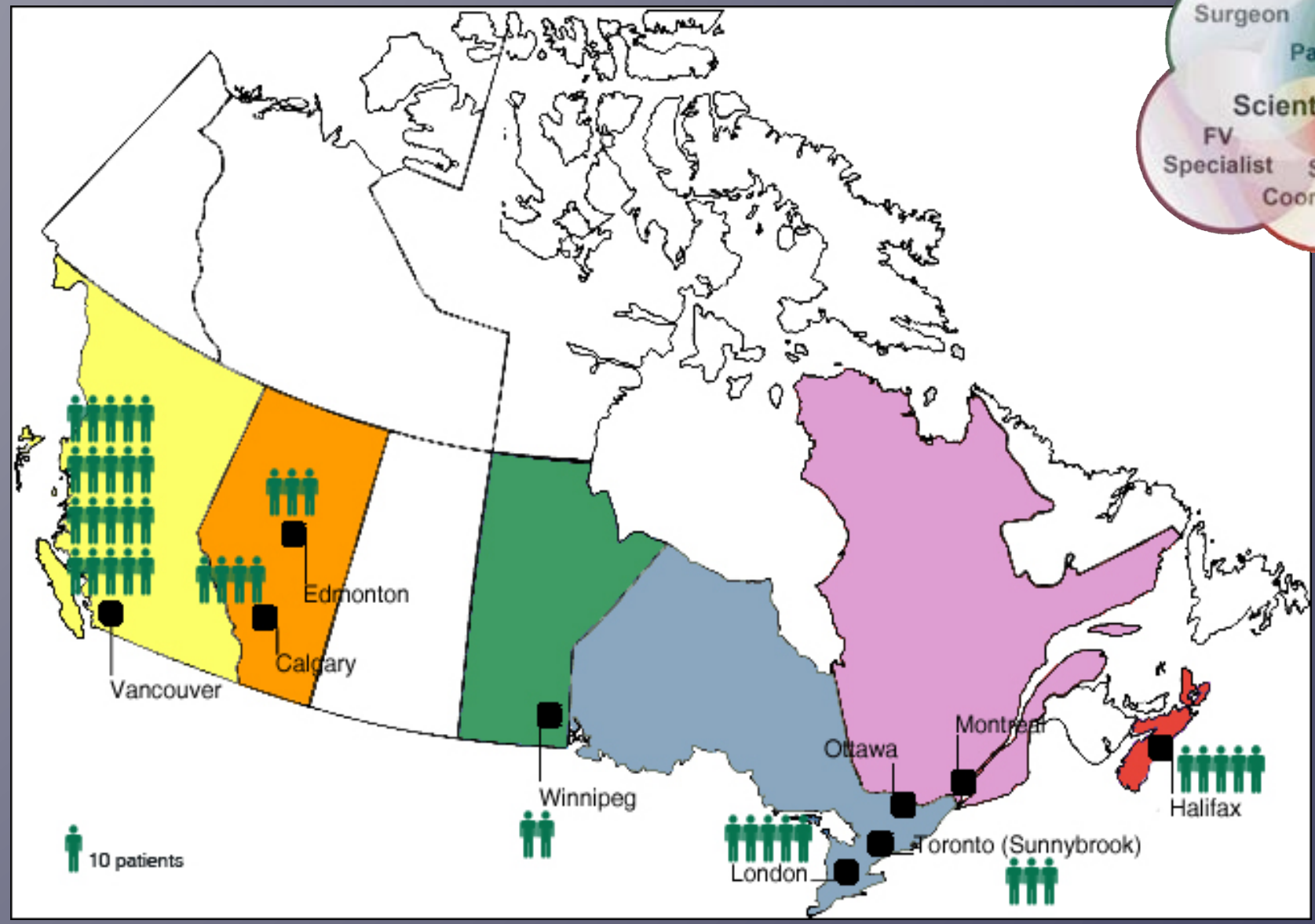
- Phase III randomized controlled trial
- 400 patients: Severe dysplasia/CIS; T1 and T2 oral cancer



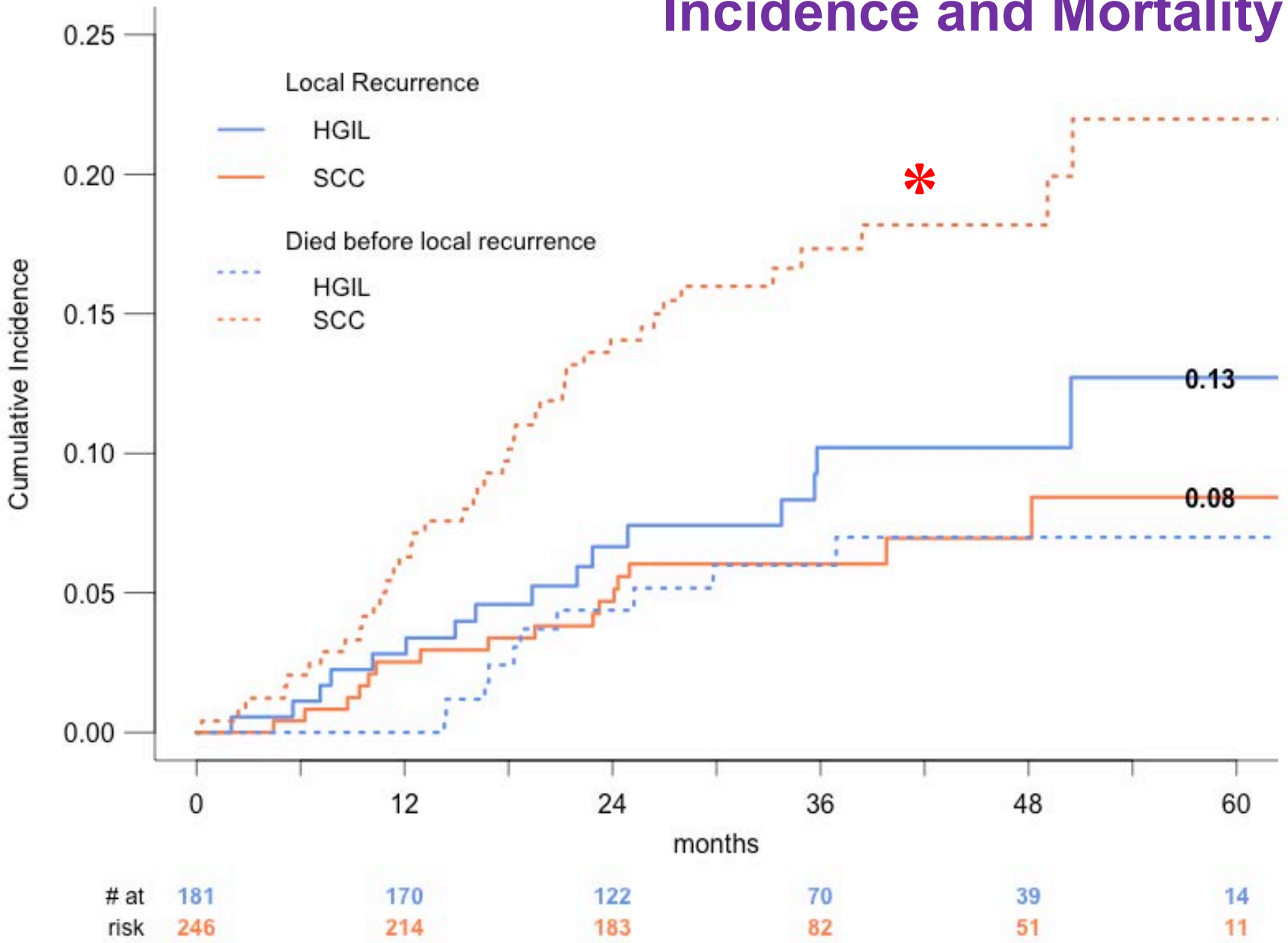
- 4.8 million, 6 – year project (September 1st, 2010) – milestone driven project

Poh et al. BMC Cancer 2011, 11:462

Pan-Canadian Network for Oral Cancer Control

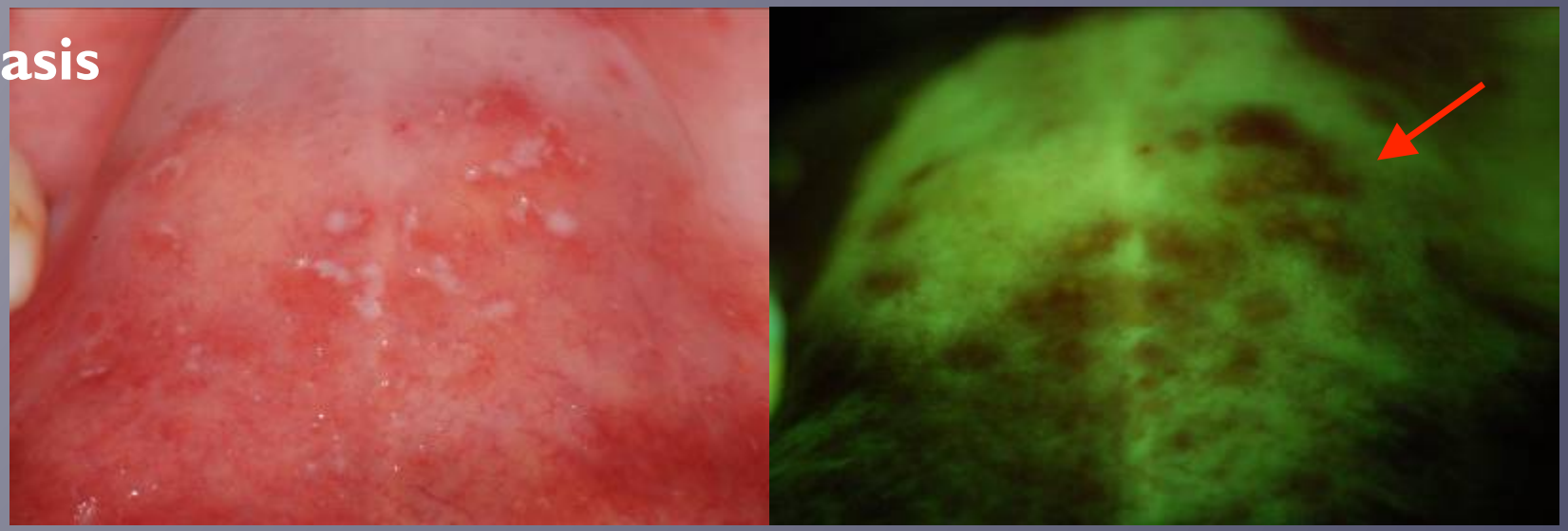


Incidence and Mortality

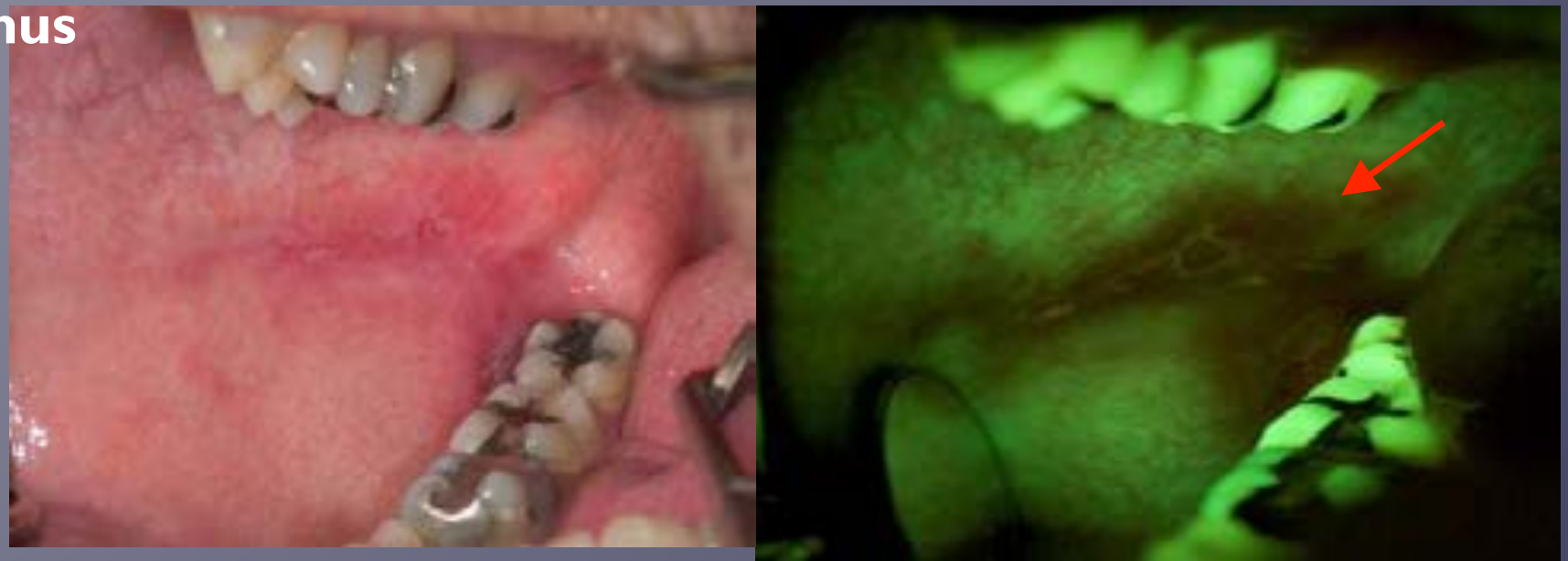


Masking by Infection and Inflammation

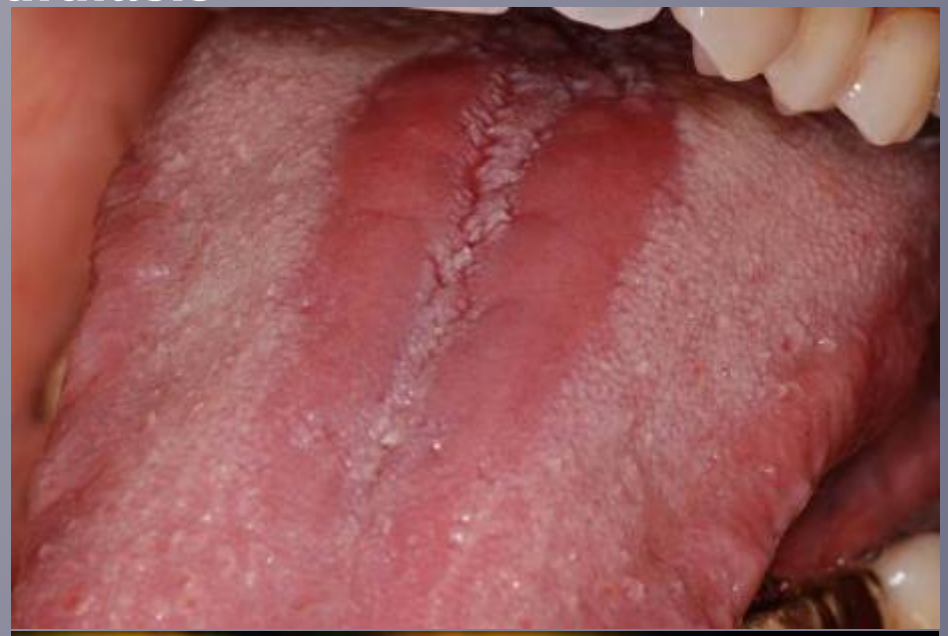
Oral candidiasis

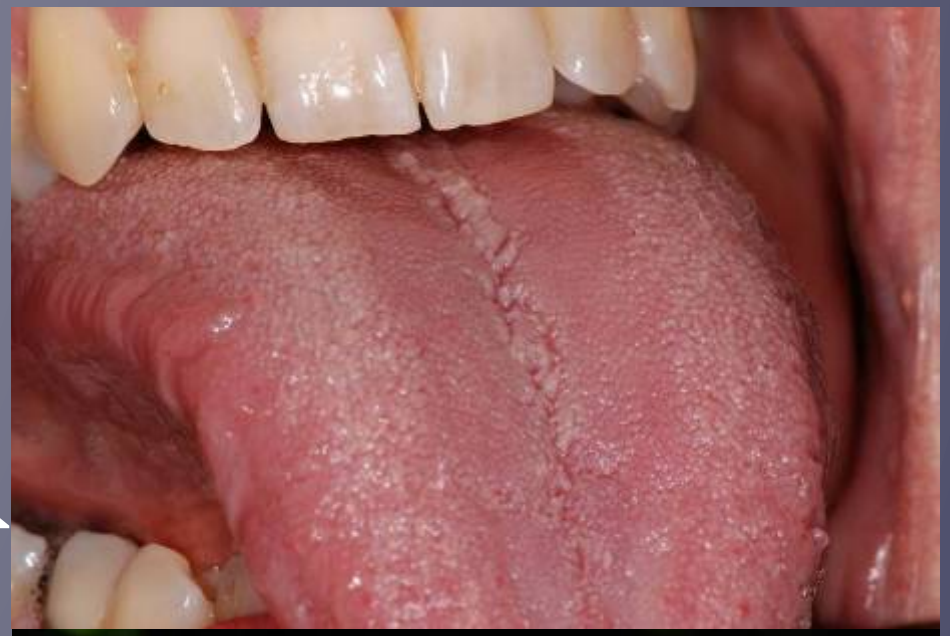


Lichen planus

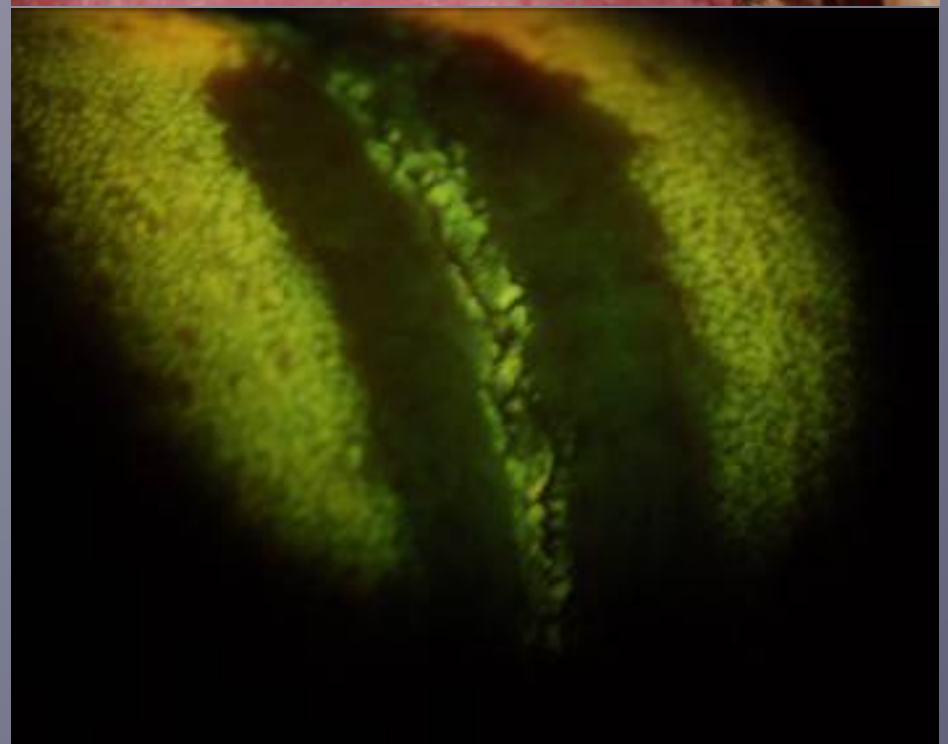


Oral candidiasis



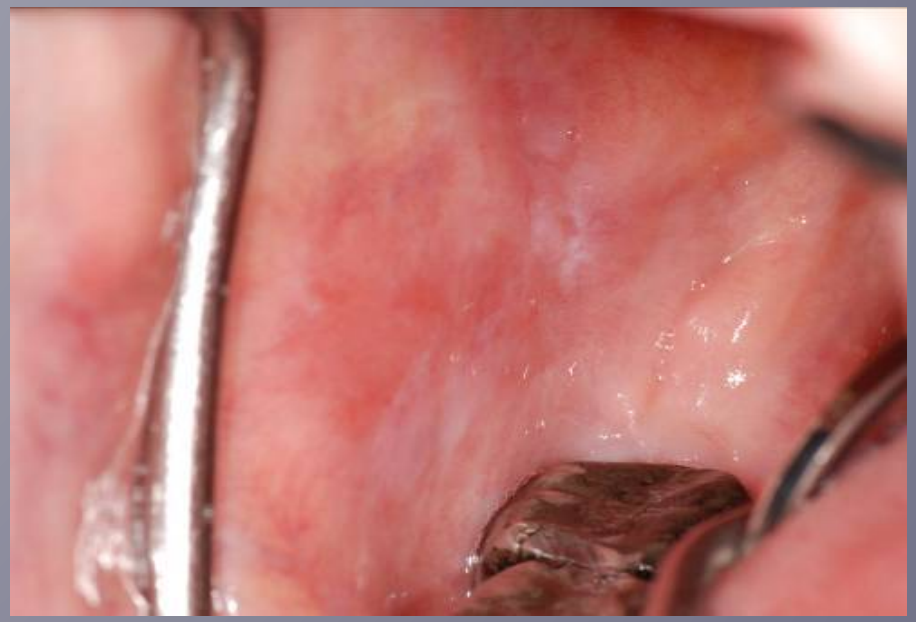


4 weeks

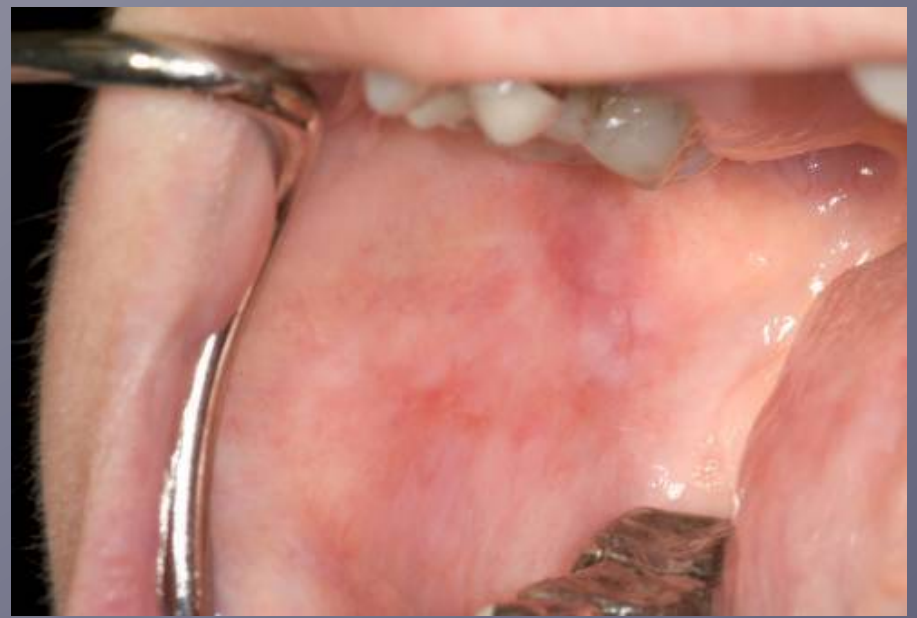


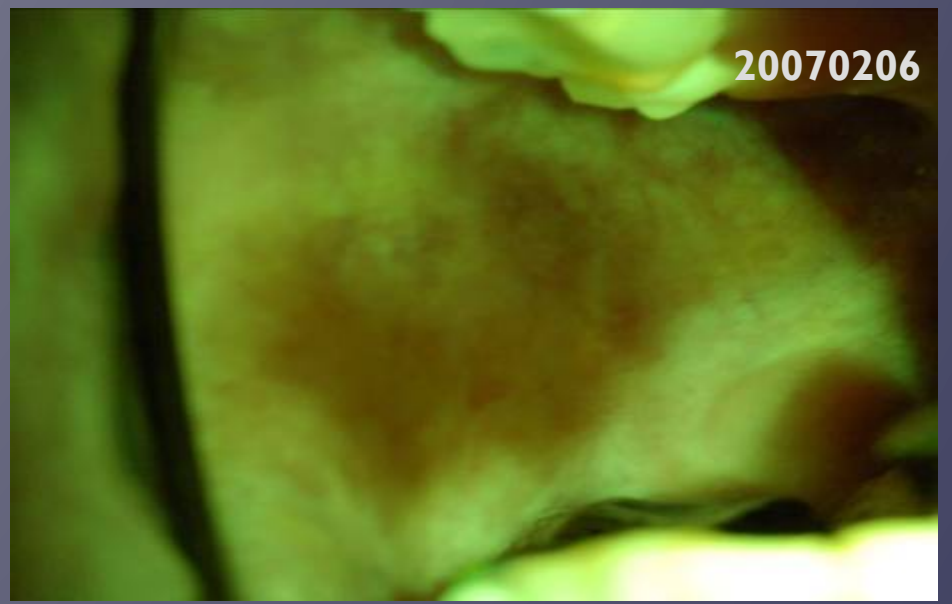
25

Lichen planus



3 months



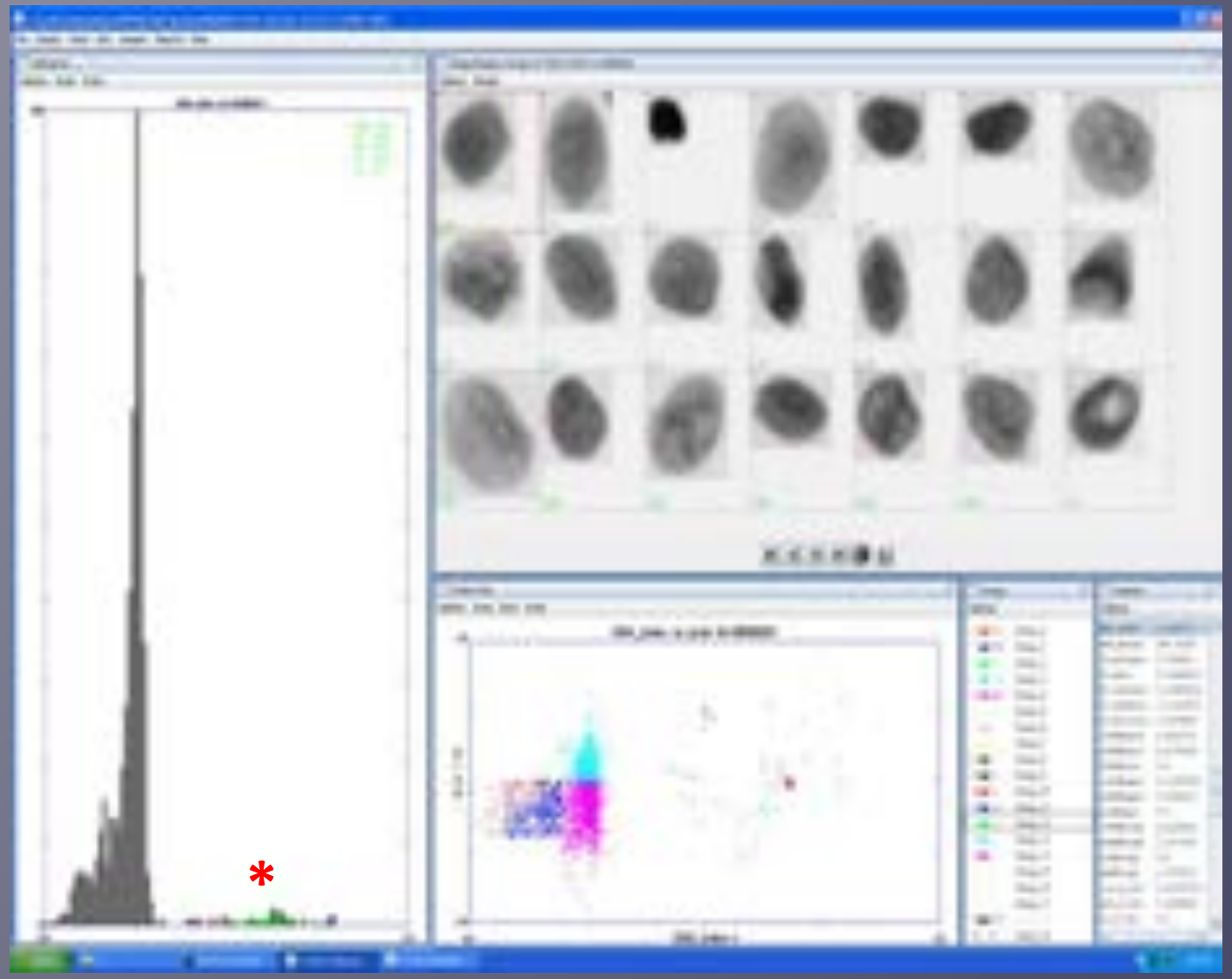


Quantitative Cytology using high-resolution microscopy imaging - cNPS (cytology-Nuclear Phenotype Score)

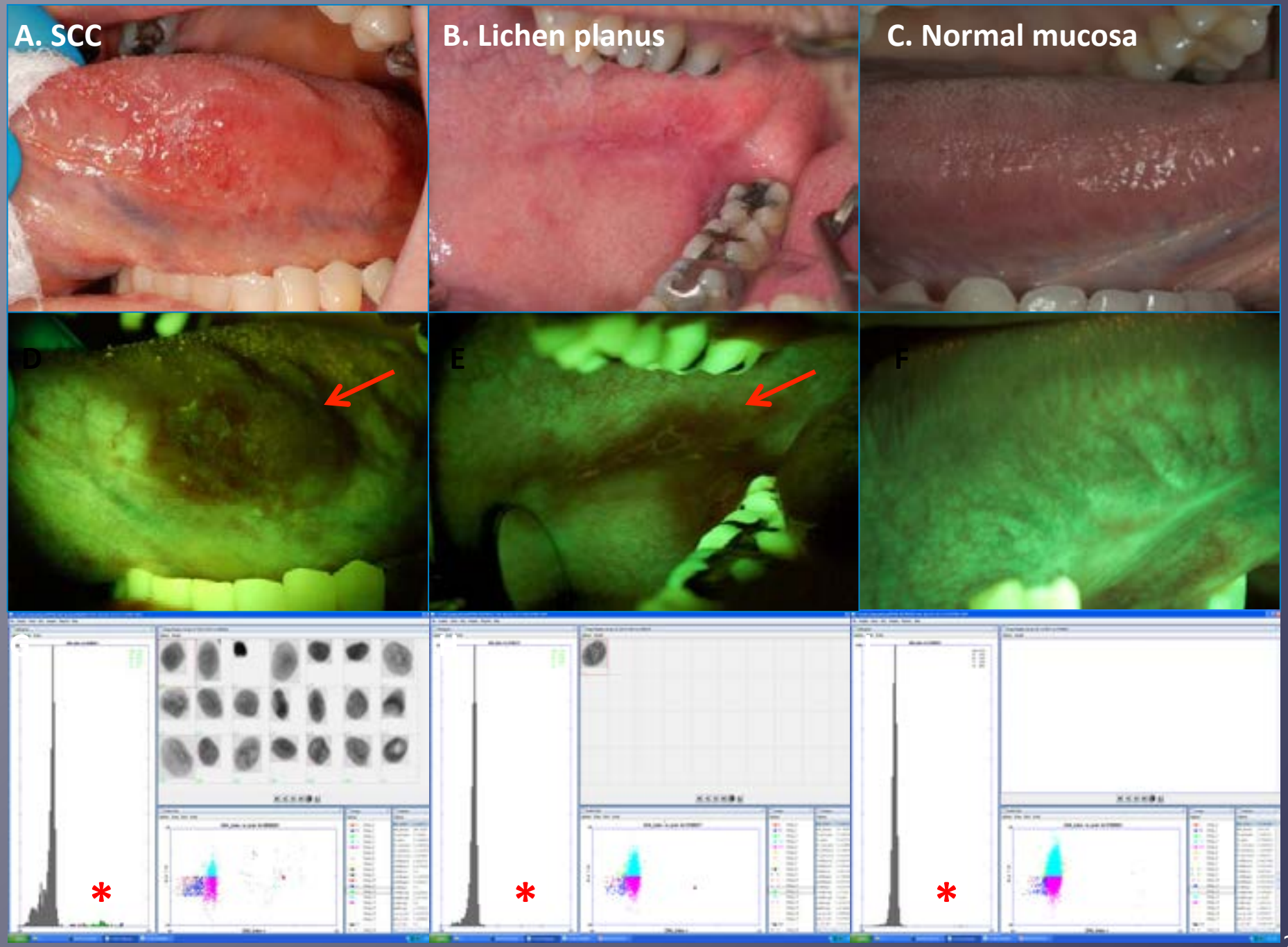
Development of cNPS to <u>automatically</u> capture alterations in

1. DNA content (ploidy)
2. Nuclear morphology features (~110)

Quantitative Cytology using high-resolution microscopy imaging - cNPS (cytology-Nuclear Phenotype Score)



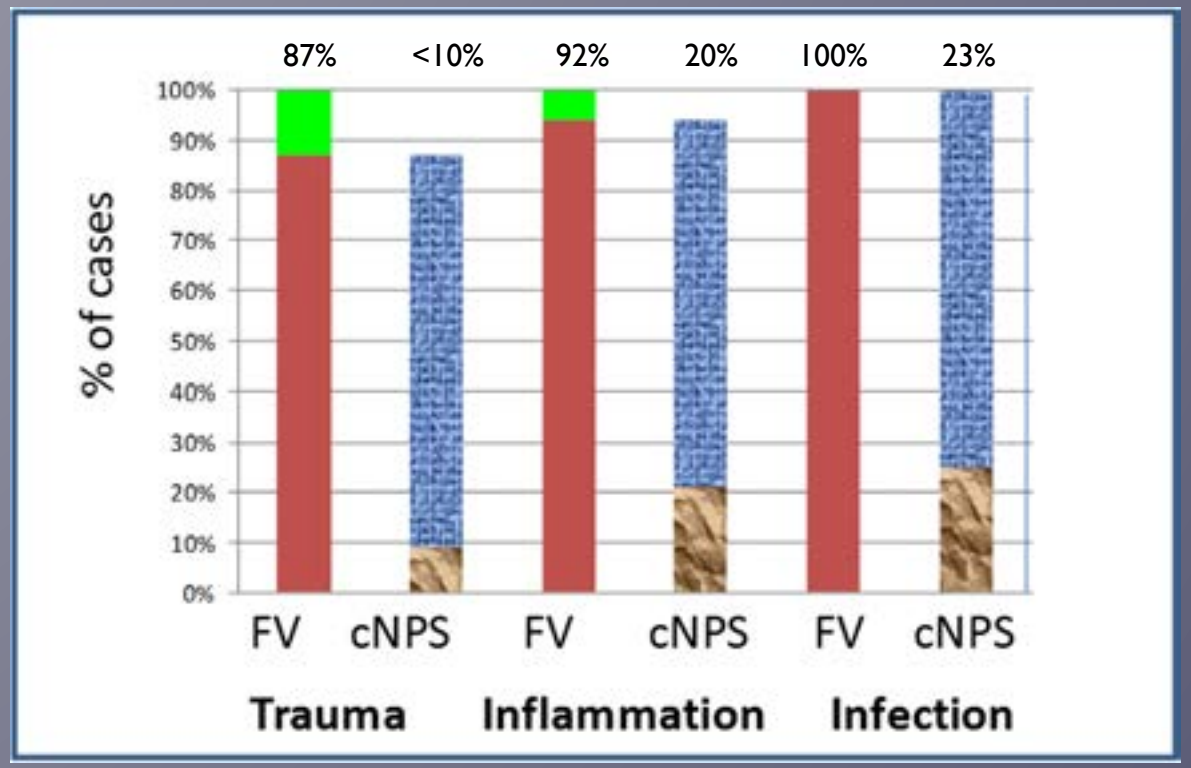
Quantitative cytology



Two-step screening

Step 1: Clinical white light and/or FV (VELScope®)

Step 2: Quantitative Cytology



FV retained (FVR)

FV loss (FVL)

cNPS- /FVL

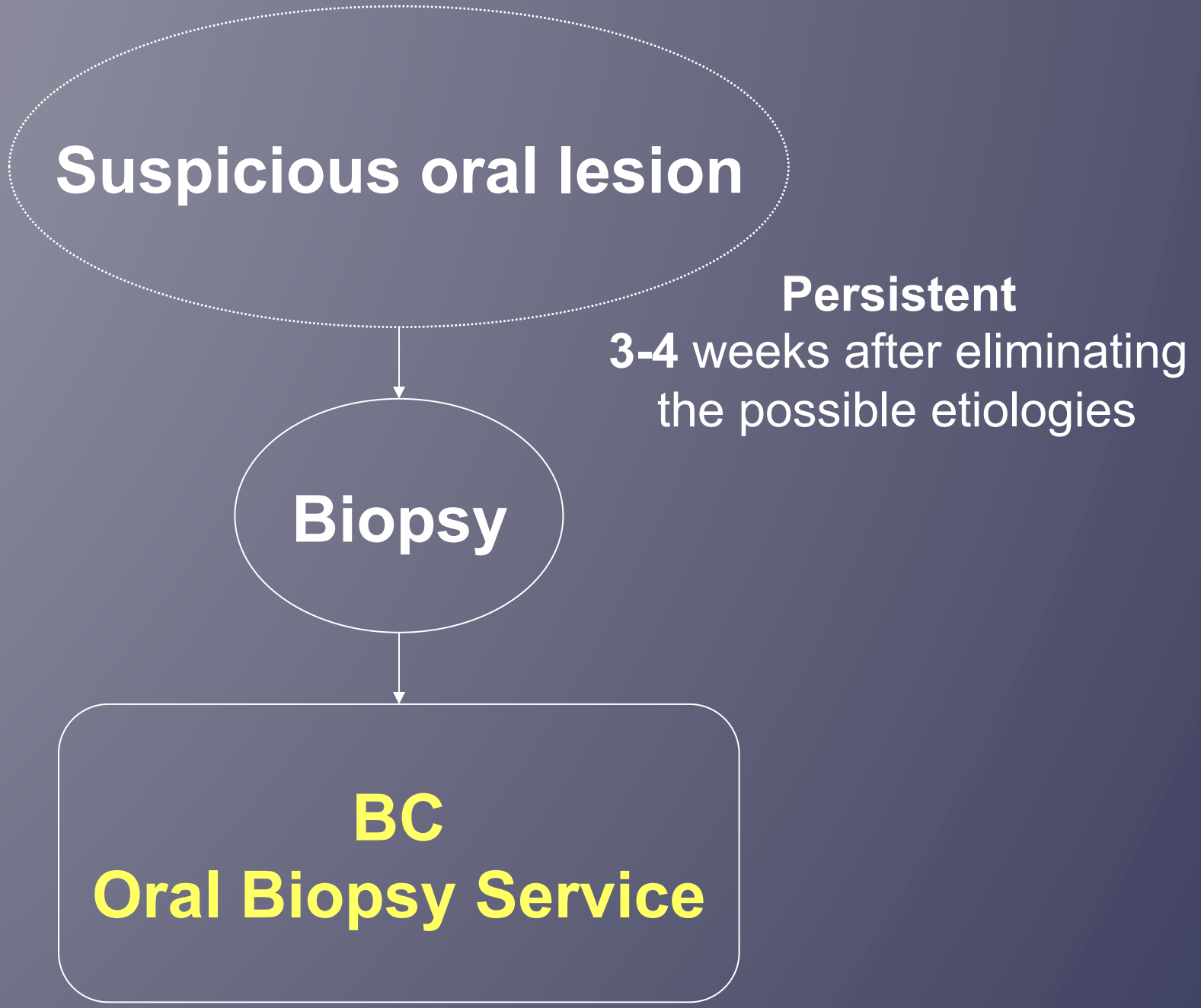
cNPS+/FVL

N=68 N=28 N=12

Suspicious oral lesion

Persistent
3-4 weeks after eliminating the possible etiologies

Biopsy


Suspicious oral lesion
Persistent
3-4 weeks after eliminating the possible etiologies
Biopsy
BC
Oral Biopsy Service

Infobahn Oral Biopsy Service (https://iobs@dentistry.ubc.ca)

- ✓ Get pathology report online
- ✓ Accurate description and diagnosis
- ✓ Manage patients and biopsy history

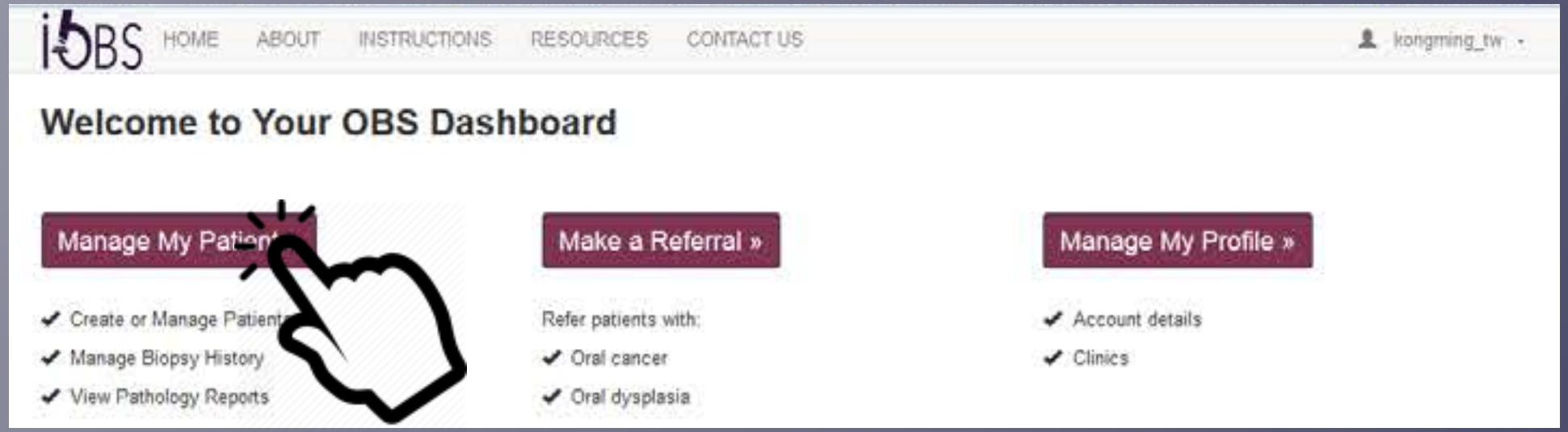
UBC DENTISTRY

Vancouver CoastalHealth
Promoting wellness. Ensuring care.

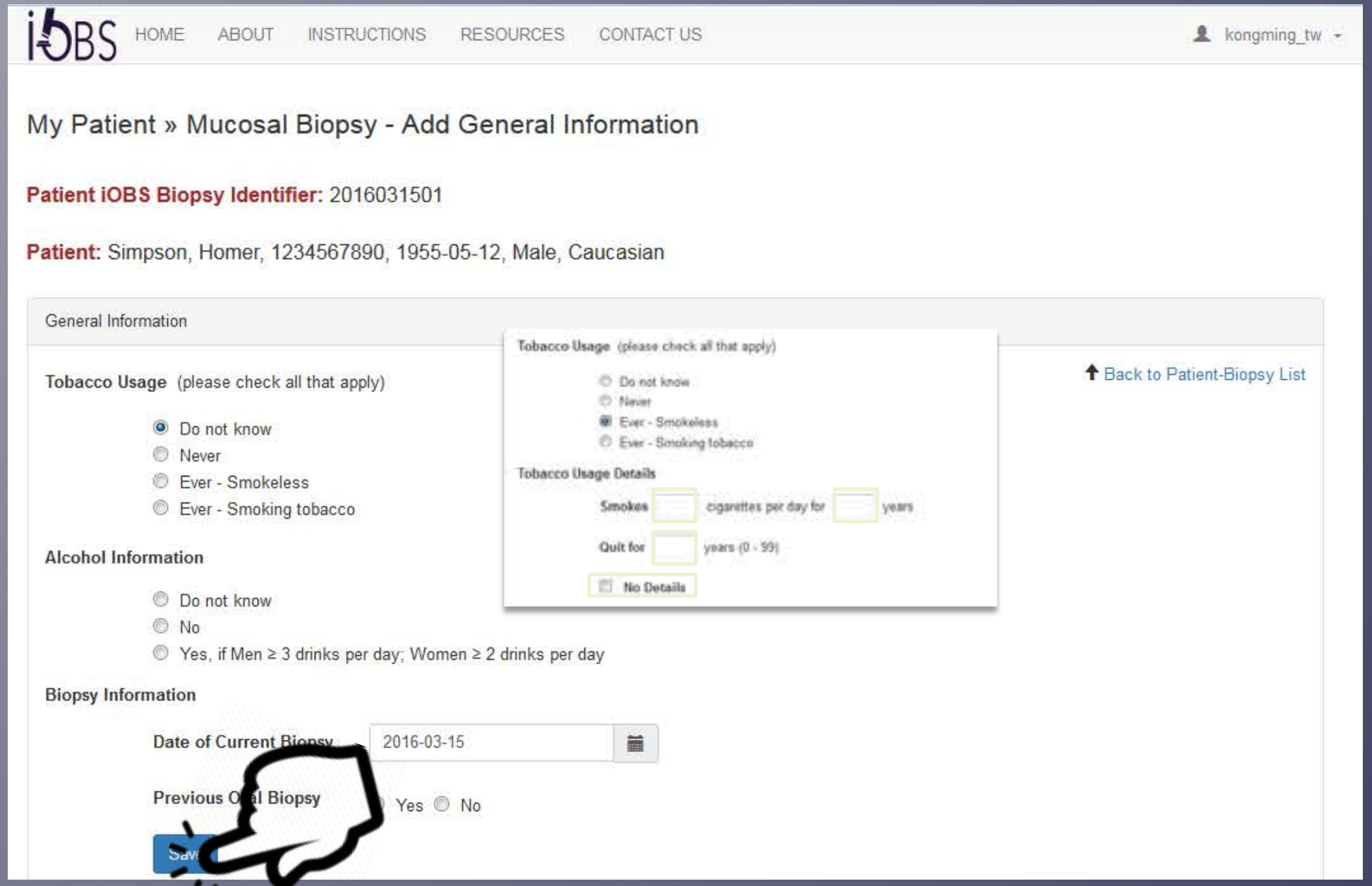
CANADIAN PARTNERSHIP AGAINST CANCER
PARTENARIAT CANADIEN CONTRE LE CANCER

BC Cancer Agency
CARE + RESEARCH

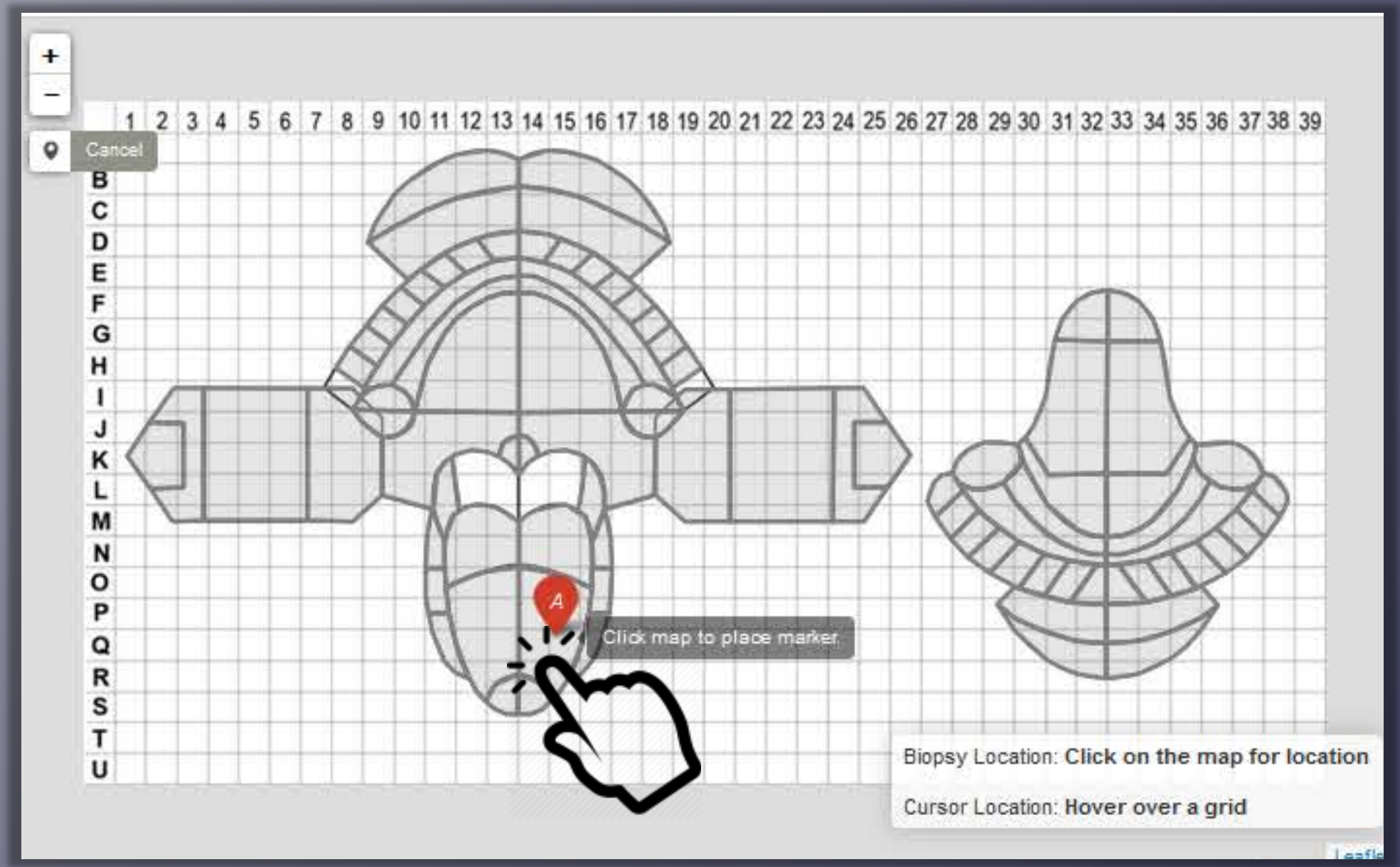
MANAGE PATIENTS



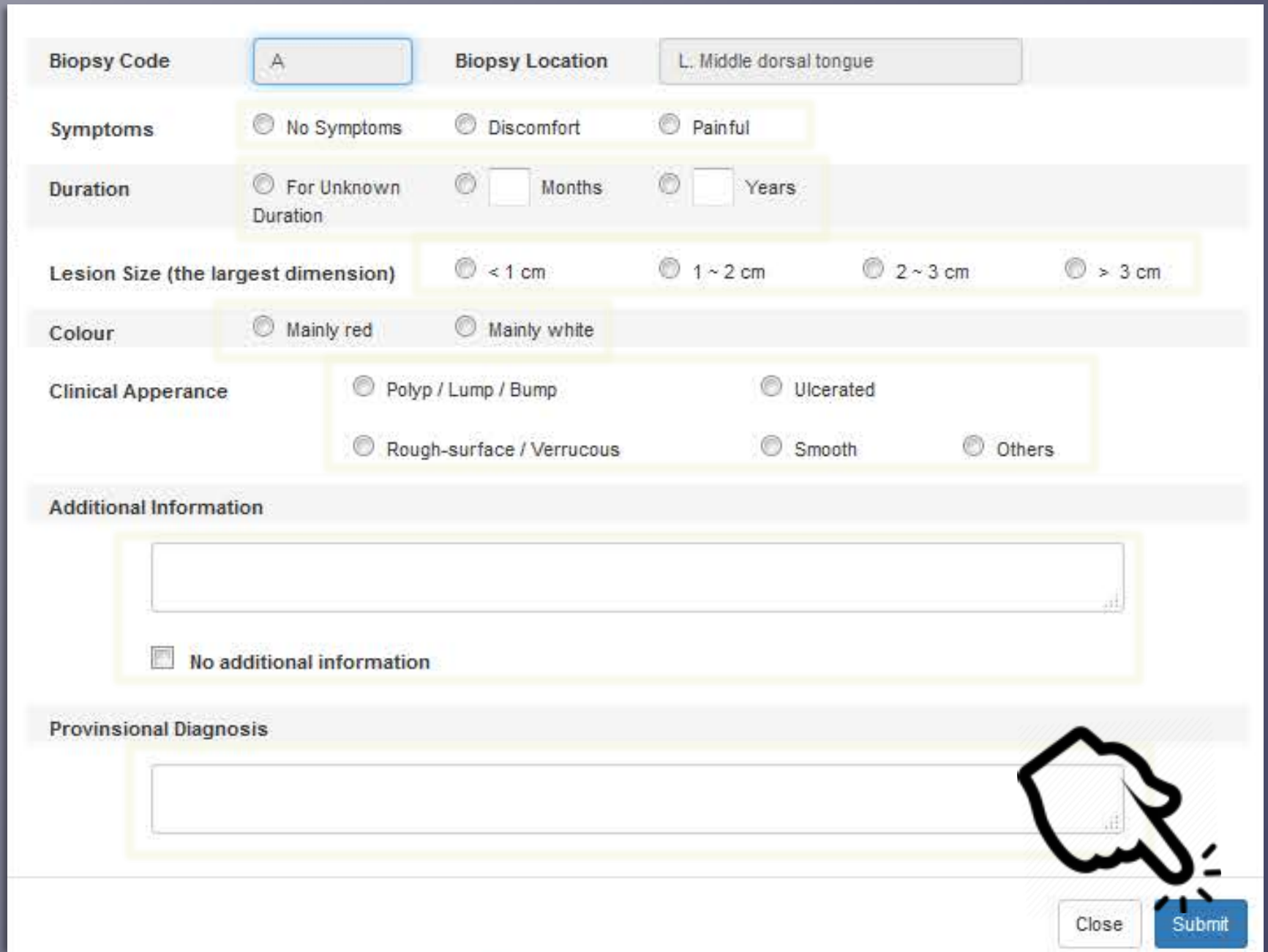
ORAL MUCOSAL BIOPSY



ORAL MUCOSAL BIOPSY



ORAL MUCOSAL BIOPSY



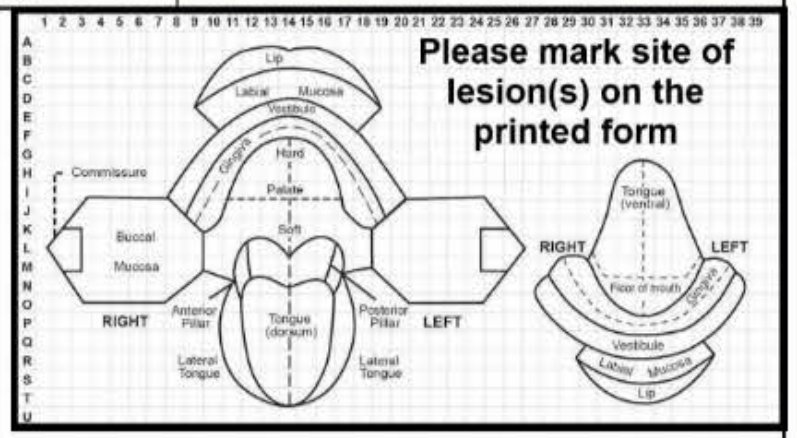
BC ORAL BIOPSY SERVICE
Oral Mucosal Biopsy

Biopsy Date: 09/10/2014

PATIENT	aaa, bbb **PHN:** N/A; **DOB:** 11/10/2010; Female; Asian
HABIT	**Tobacco:** Smoking, Current, 20 cigarette(s)/day, 1 year(s); **Alcohol:** No; **Marijuana:** Do not wish to answer
PREVIOUS ORAL BIOPSY	No
CURRENT BIOPSY	**Photo Attached:** Yes (e-mail)

Bx A: Clinical Information: Incisional; 20mm x 12mm; Right Lateral Tongue; Asymptomatic; White, 60 month (s)
D/D: lichen planus, r/o dysplasia

Bx B: Clinical Information: Incisional; 8mm x 5mm; Left Buccal Mucosa; Asymptomatic; Ulcerated, 4 week (s)
D/D: lichen planus



CLINICIAN	Dr. F. Catherine Poh **Signature** _____

Pathology Report Sent To: *(Office 1)* 675 West 10th Avenue, Vancouver, BC, V5Z1Z3

*Please **submit PRINTED FORM WITH SPECIMEN** to the BC Oral Biopsy Service Vancouver General Hospital, Room 1400 JPPN1, 910 West 10th Avenue, Vancouver BC, V5Z 1M9.*

Submit Edit

SEARCH THROUGH YOUR PATIENTS

Show All entries

Search by any of the following fields:

Clinic Postal Code	Last Name	First Name	Middle Name	PHN	Date of Birth	Sex	Ethnicity	Last Update	
A1C 0V1	Simpson	Homer		1234567890	1955-05-12	M	Caucasian	2016-03-15	Edit Patient
A1C 0V1	Simpson	Marge		9999999999	1955-10-01	F	Caucasian	2016-03-15	Edit Patient
A1C 0V1	Simpson	Lisa		8888888888	2009-05-08	F	Caucasian	2016-03-15	Edit Patient
A1C 0V1	Simpson	Bart		No PHN	1989-12-17	M	Caucasian	2016-03-15	Edit Patient
A1C 0V1	Simpson	Maggie		6666666666	1987-04-19	F	Caucasian	2016-03-15	Edit Patient
F4M 1L7	Simpson	Homer		1234567890	1955-05-12	M	Caucasian	2016-03-15	Edit Patient
F4M 1L7	Simpson	Marge		9999999999	1955-10-01	F	Caucasian	2016-03-15	Edit Patient
F4M 1L7	Simpson	Lisa		8888888888	2009-05-08	F	Caucasian	2016-03-15	Edit Patient
F4M 1L7	Simpson	Bart		No PHN	1989-12-17	M	Caucasian	2016-03-15	Edit Patient
F4M 1L7	Simpson	Maggie		6666666666	1987-04-19	F	Caucasian	2016-03-15	Edit Patient
T7E 5I3	Simpson	Homer		1234567890	1955-05-12	M	Caucasian	2016-03-15	Edit Patient
T7E 5I3	Simpson	Marge		9999999999	1955-10-01	F	Caucasian	2016-03-15	Edit Patient
T7E 5I3	Simpson	Lisa		8888888888	2009-05-08	F	Caucasian	2016-03-15	Edit Patient
T7E 5I3	Simpson	Bart		No PHN	1989-12-17	M	Caucasian	2016-03-15	Edit Patient
T7E 5I3	Simpson	Maggie		6666666666	1987-04-19	F	Caucasian	2016-03-15	Edit Patient

ACCESS PATHOLOGY REPORT

Gold standard for risk assessment

Presence and degree of dysplasia

What is dysplasia?

I. At cellular level:

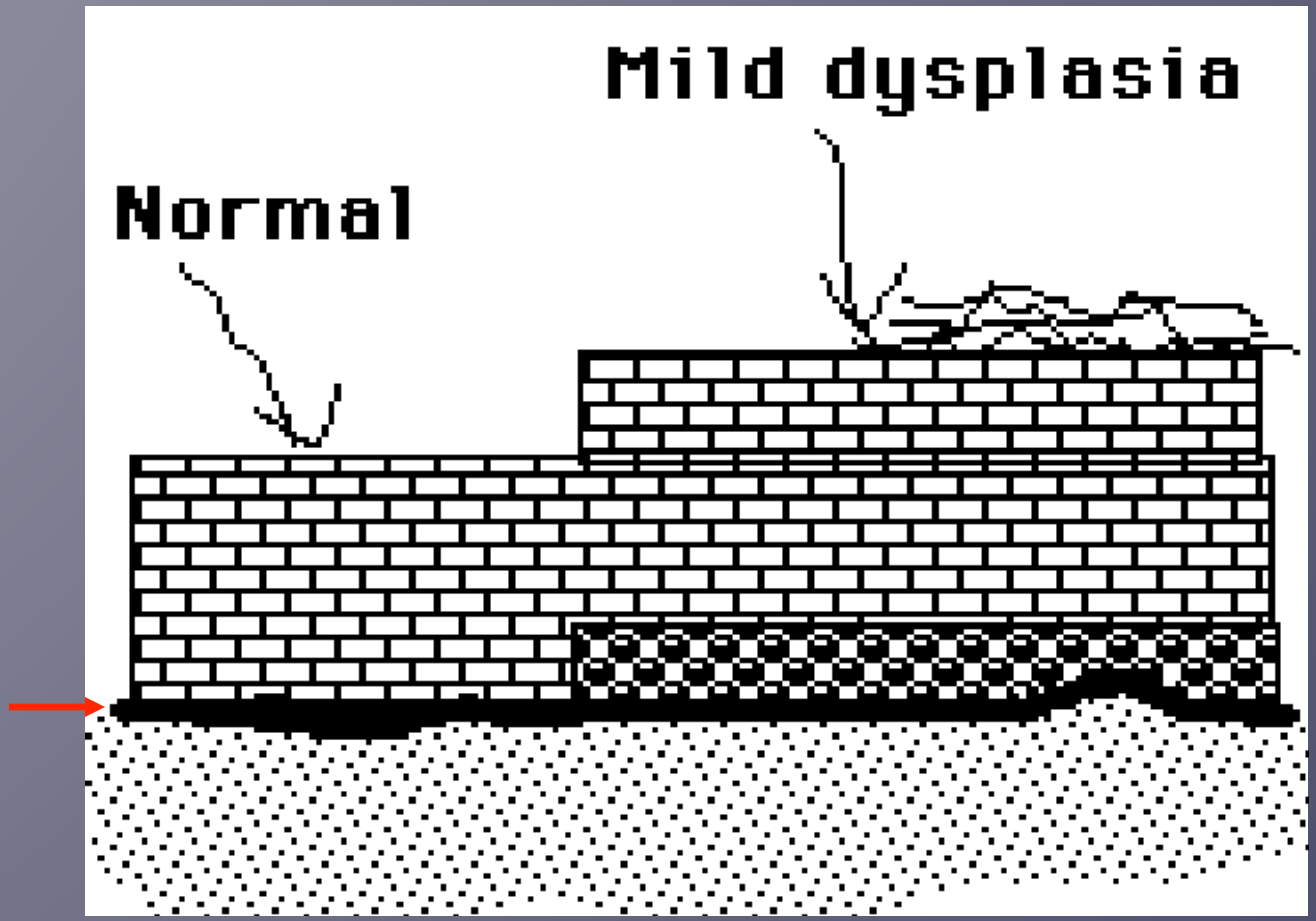
Criteria often used for dysplasia (WHO):

a. Irregular stratification or loss of polarity of the cells in the epithelium.
b. Increased mitoses
c. Nuclear hyperchromatism.
d. Increased nuclear/cytoplasmic ratio.
e. Polymorphism of cells.
f. Abnormal keratinization...

II. At architectural level:

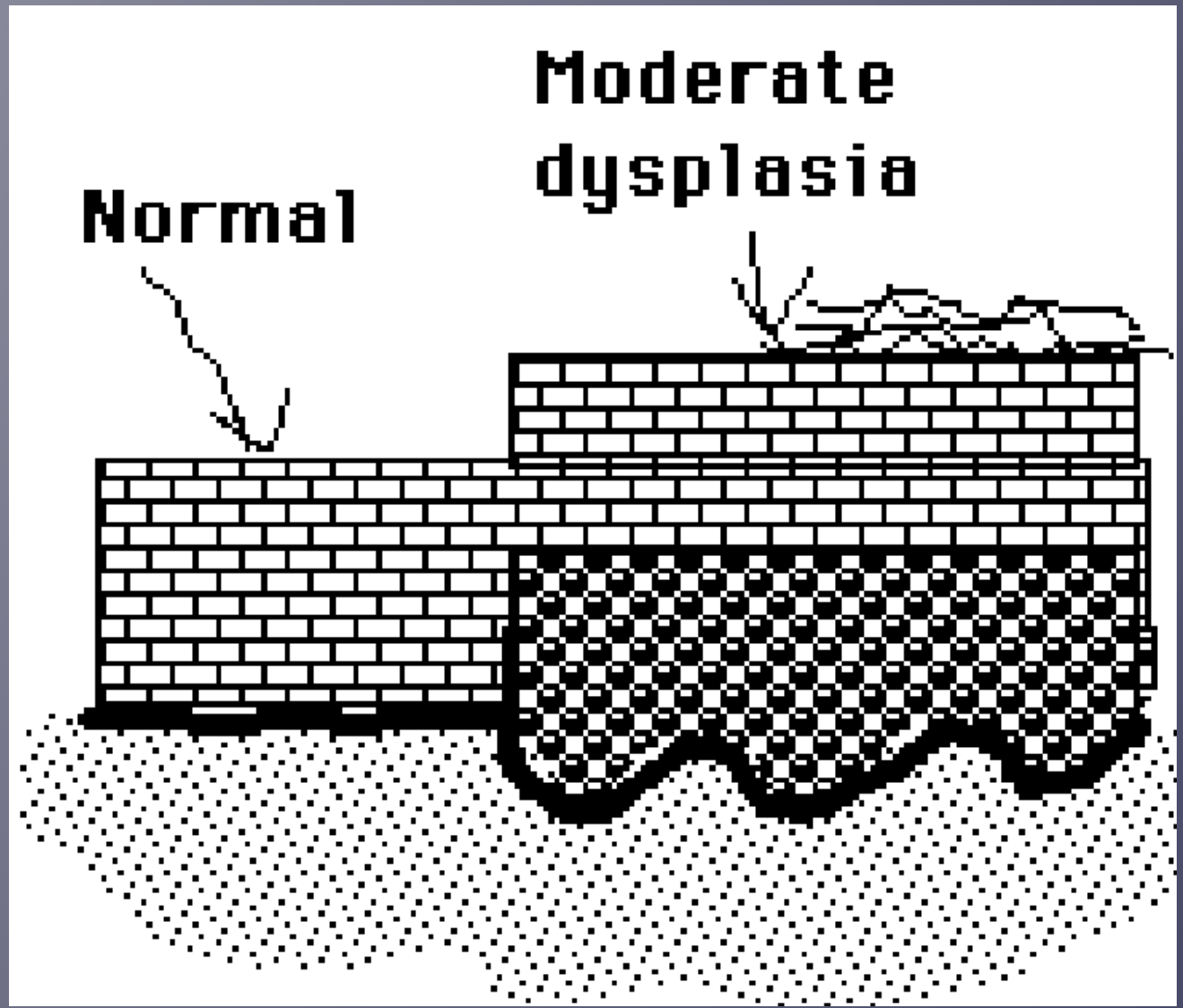
Mild dysplasia

Dysplastic cells involving basal and parabasal cells



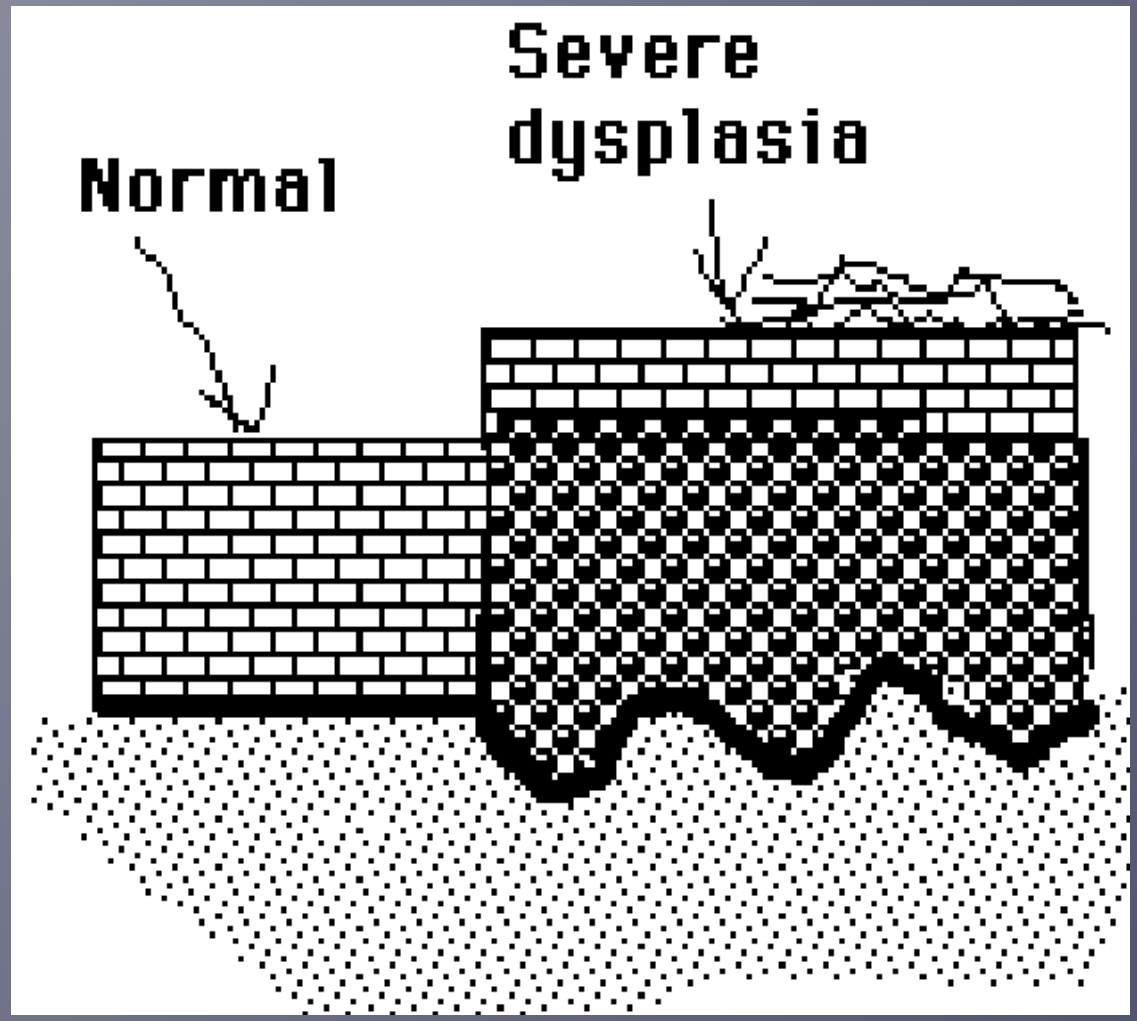
Moderate dysplasia

Dysplastic cells involving the lower half of the epithelial cells



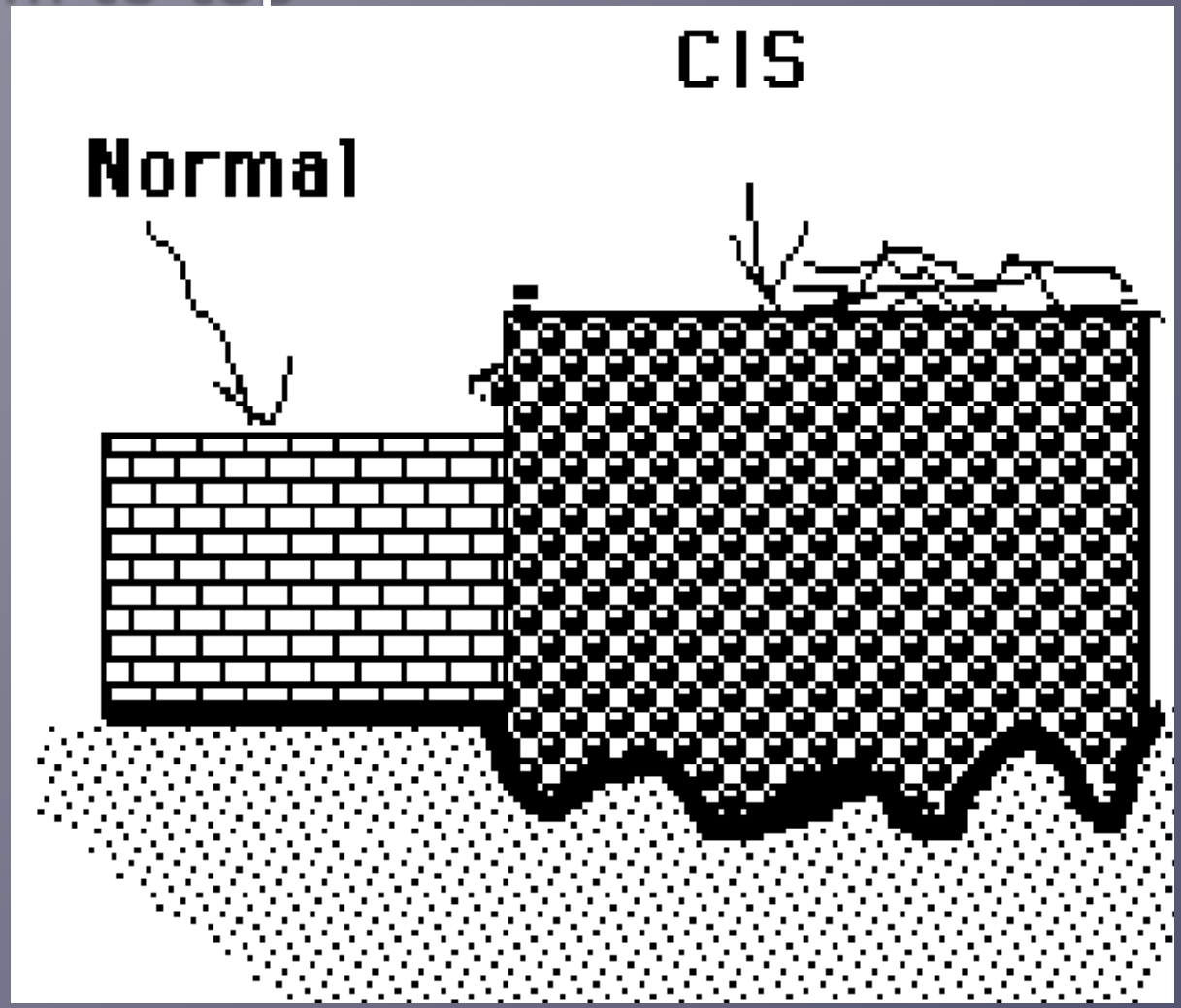
Severe dysplasia

Dysplastic cells involving the lower 2/3 of the epithelial cells



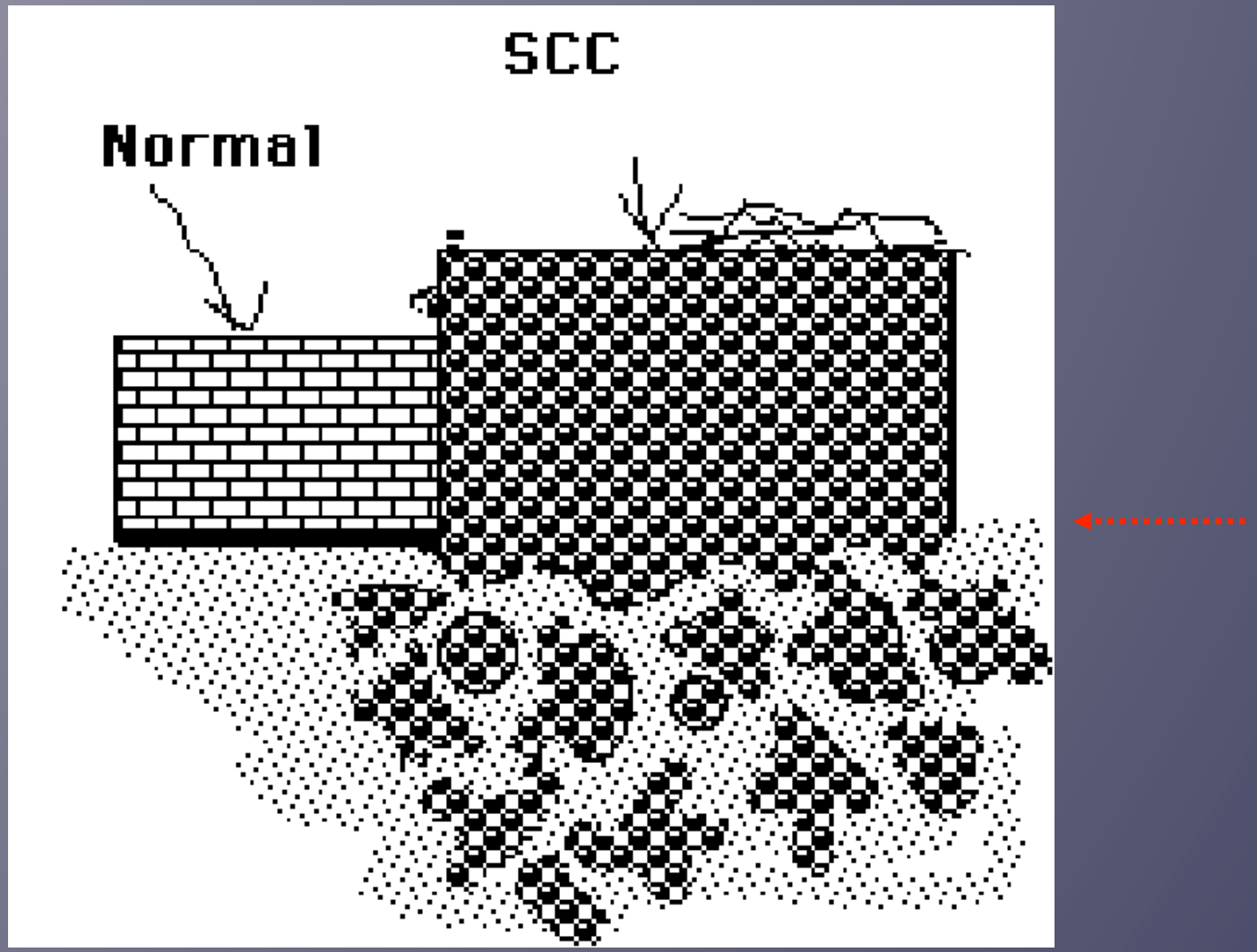
Carcinoma *in situ* (*CIS*)

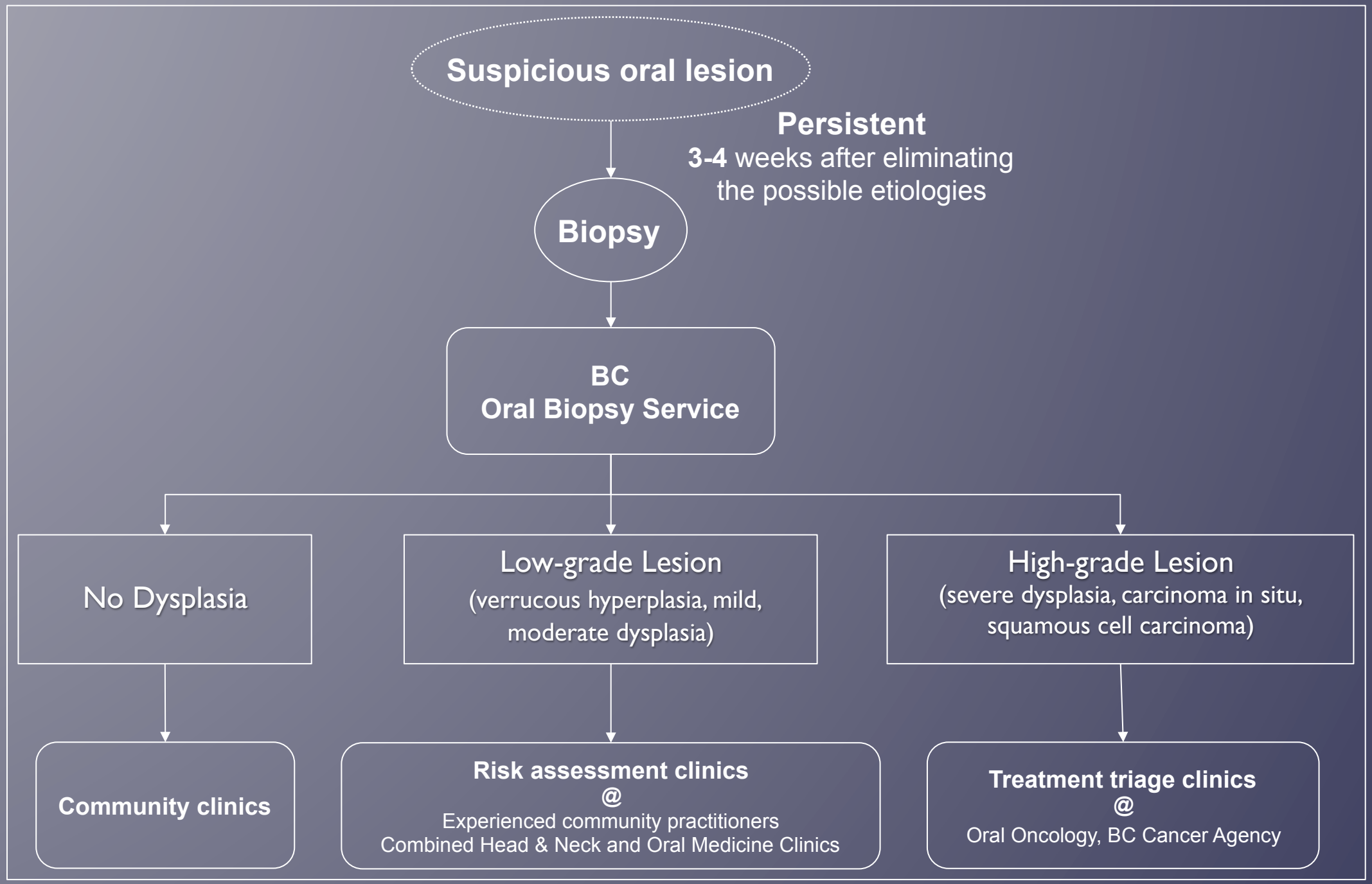
Dysplastic cells involving all the epithelial layers from bottom to top

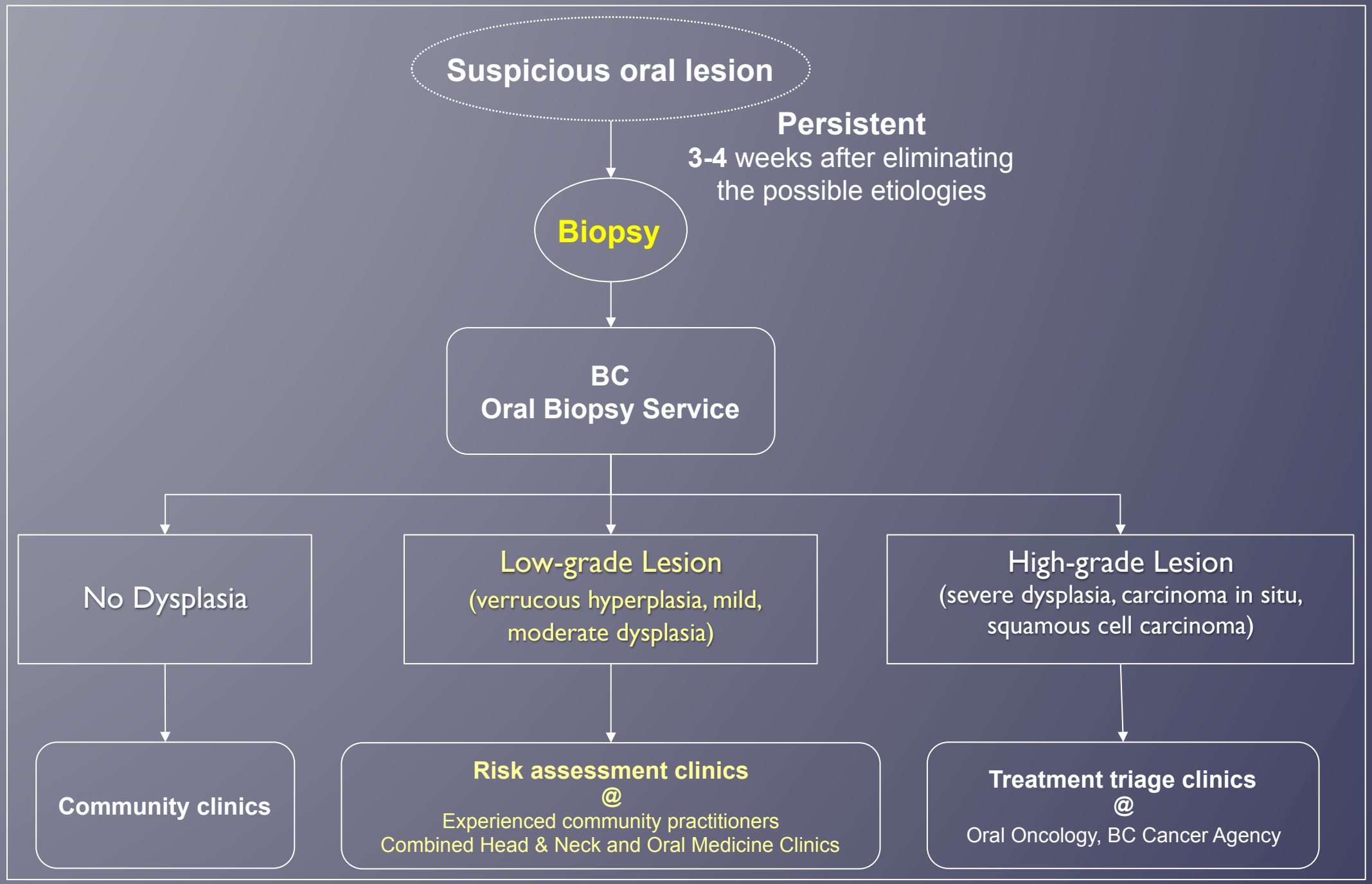


Invasive squamous cell carcinoma

Basement membrane is disrupted by the dysplastic cells




Suspicious oral lesion
Persistent
3-4 weeks after eliminating the possible etiologies
Biopsy
BC Oral Biopsy Service
No Dysplasia
Low-grade Lesion
(verrucous hyperplasia, mild, moderate dysplasia)
High-grade Lesion
(severe dysplasia, carcinoma in situ, squamous cell carcinoma)
Community clinics
Risk assessment clinics
@
Experienced community practitioners
Combined Head & Neck and Oral Medicine Clinics
Treatment triage clinics
@
Oral Oncology, BC Cancer Agency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@
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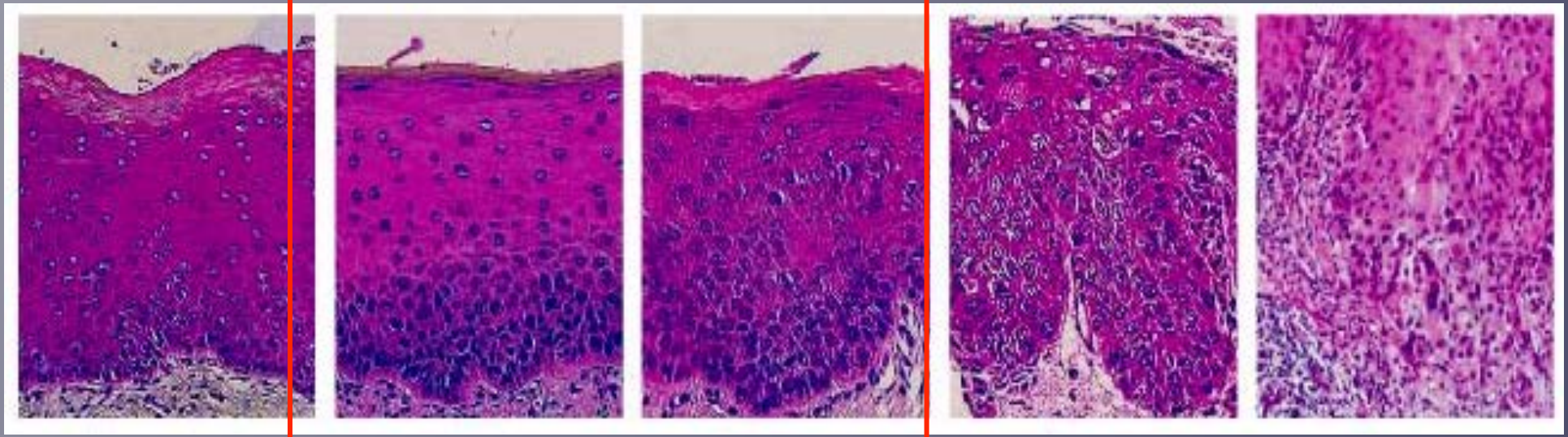
Treatment triage clinics
@
Oral Oncology, BC Cancer Agency

Histological progression model of oral lesions



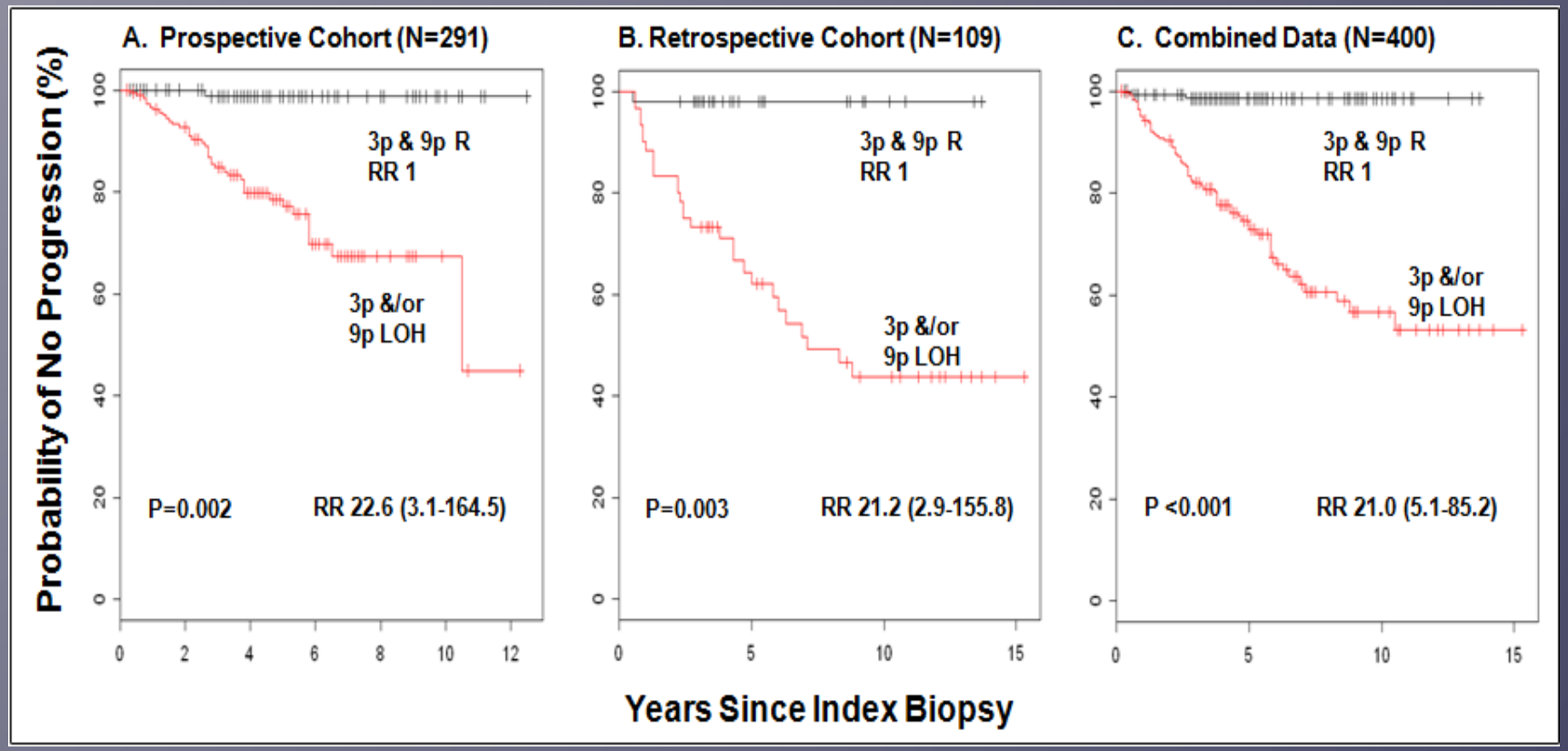
Hyperplasia → Mild Dysplasia → Moderate Dysplasia → Severe Dysplasia/CIS → Invasive SCC

Low grade dysplasia

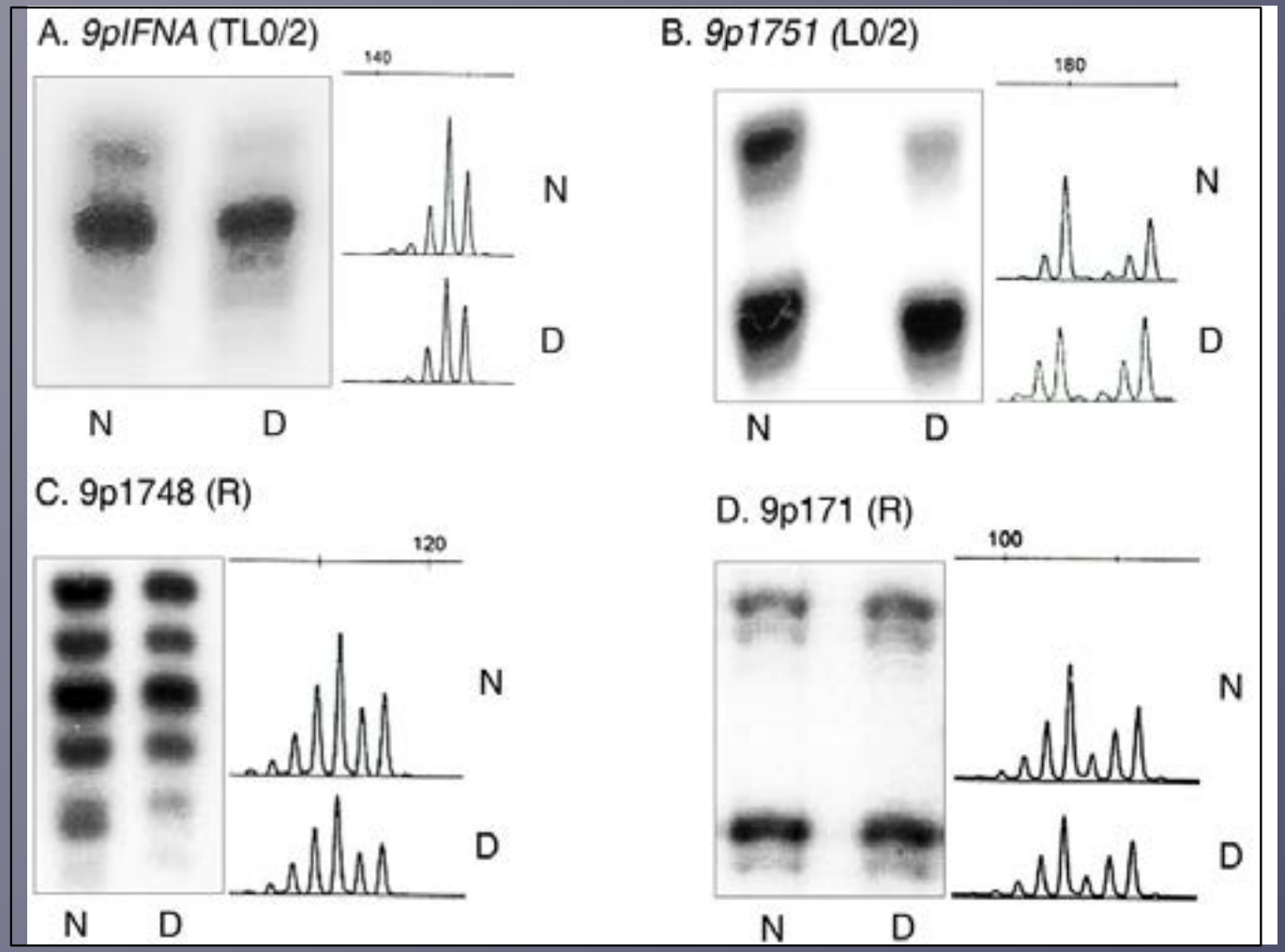
High risk? Low risk?

Loss of Heterozygosity (LOH) to Predict Malignant Risk for Oral Premalignant Lesions

- Published retrospective (2000) and prospective (2012) studies using LOH at 3p14 and/or 9p21 to predict risk of progression (25-35% in 5 years)



Loss of heterozygosity at 9p21

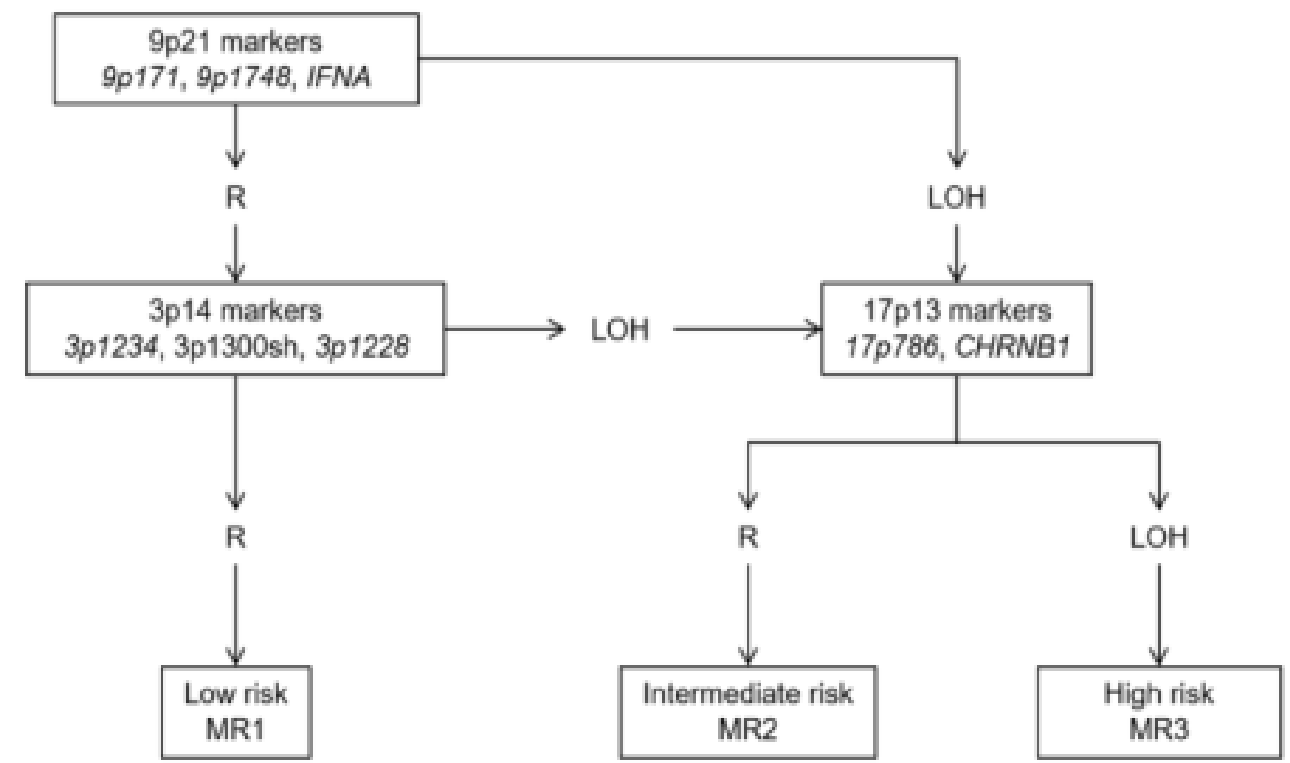


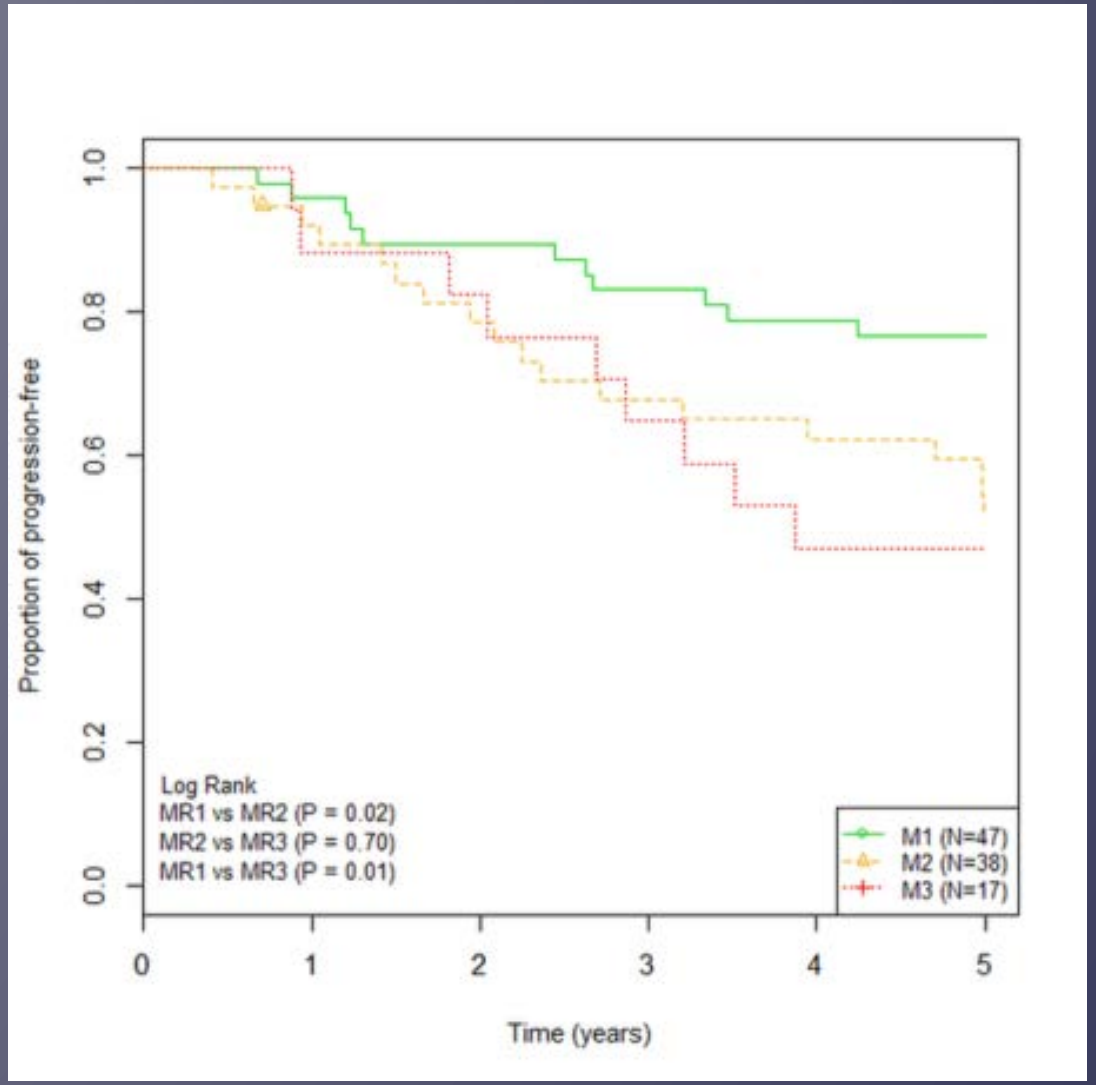
Collaborate with Cancer Genomic Lab, BCCA

Funded by Genome BC

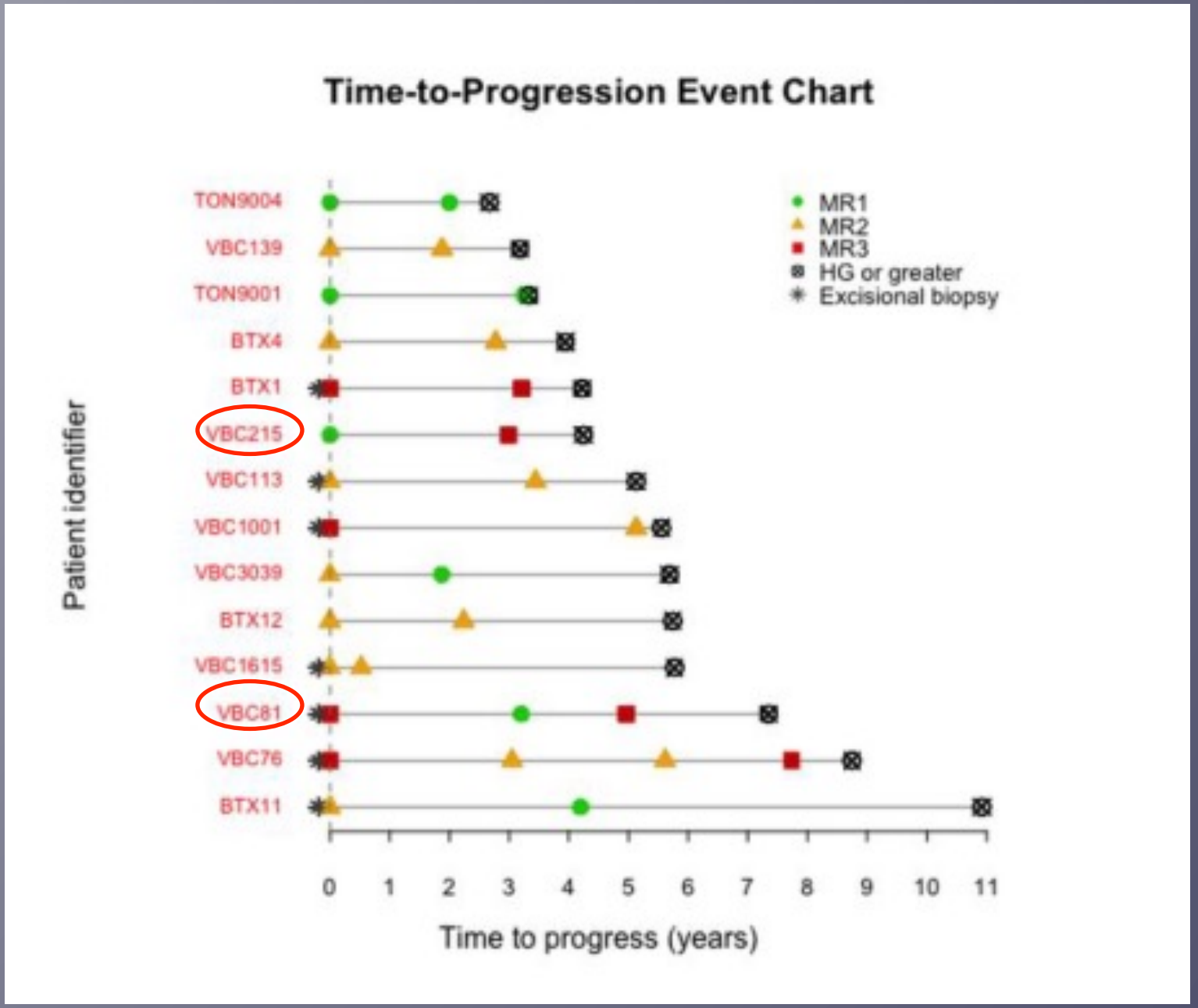
Genome BritishColumbia

An actionable test using loss of heterozygosity in identifying high-risk oral premalignant lesions. Liu *et al.*, (2018)





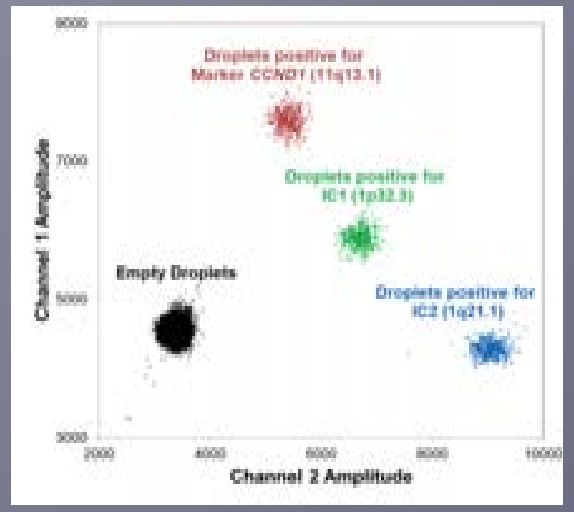
High-risk profile of tongue and MR3 (LOH at 9p21 and/or 3p14, and 17p13) was significantly associated with progression (HR, 6.7; 95% CI, 2.6-17.6) with a **specificity of 98.4% at identifying progressors.**

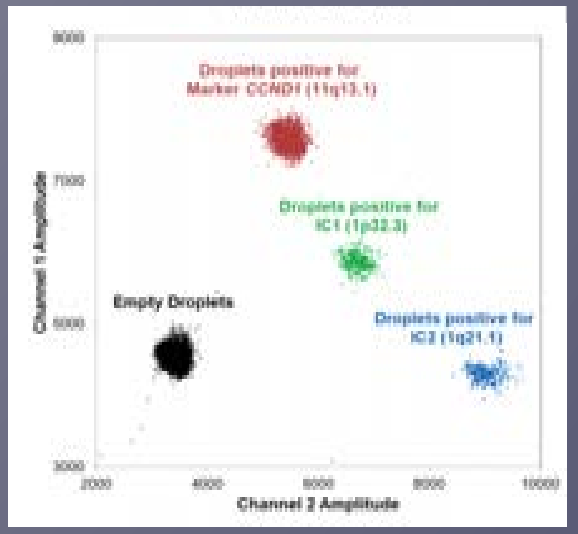


Liu *et al.*, 126 (1), 54–62(2018)

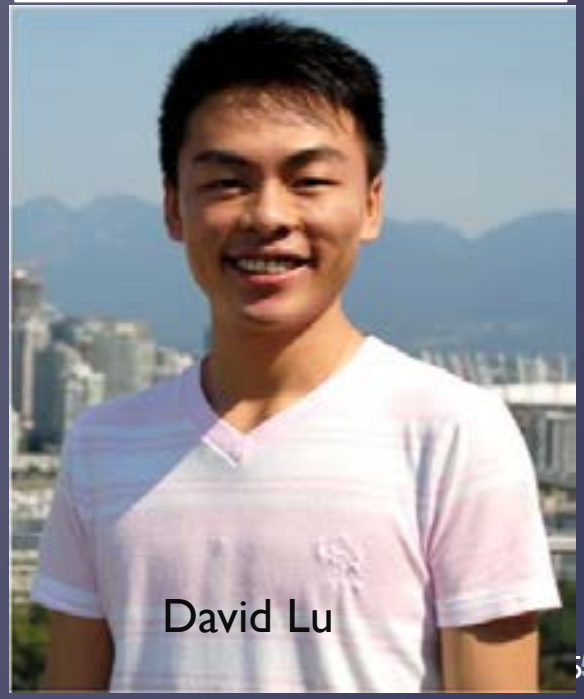
ddPCR platform-

- Using internal control – no need for control samples
- Can detect homozygous deletion
- Can be used to test brushing samples – non invasive approach

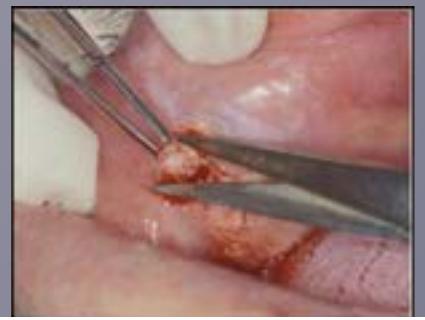


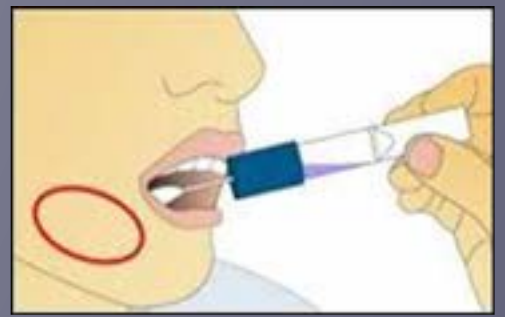


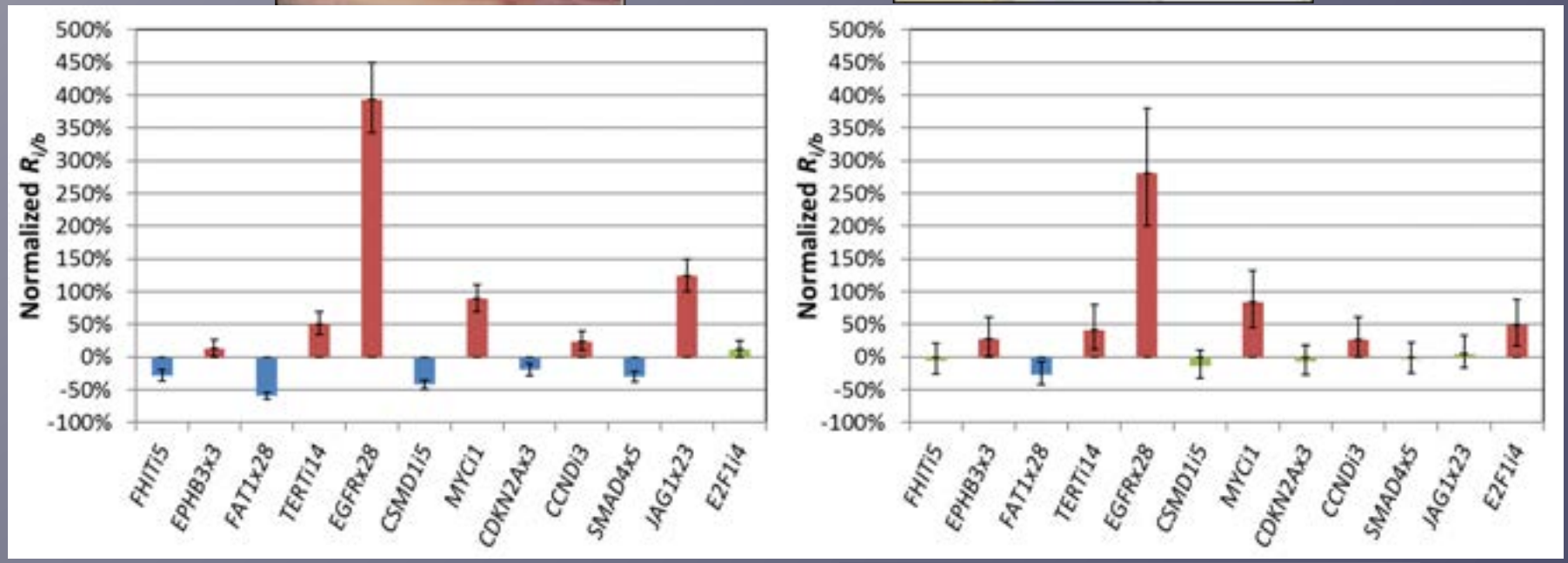

Curtis Hughesman


David Lu

ddPCR platform- non-invasive approach







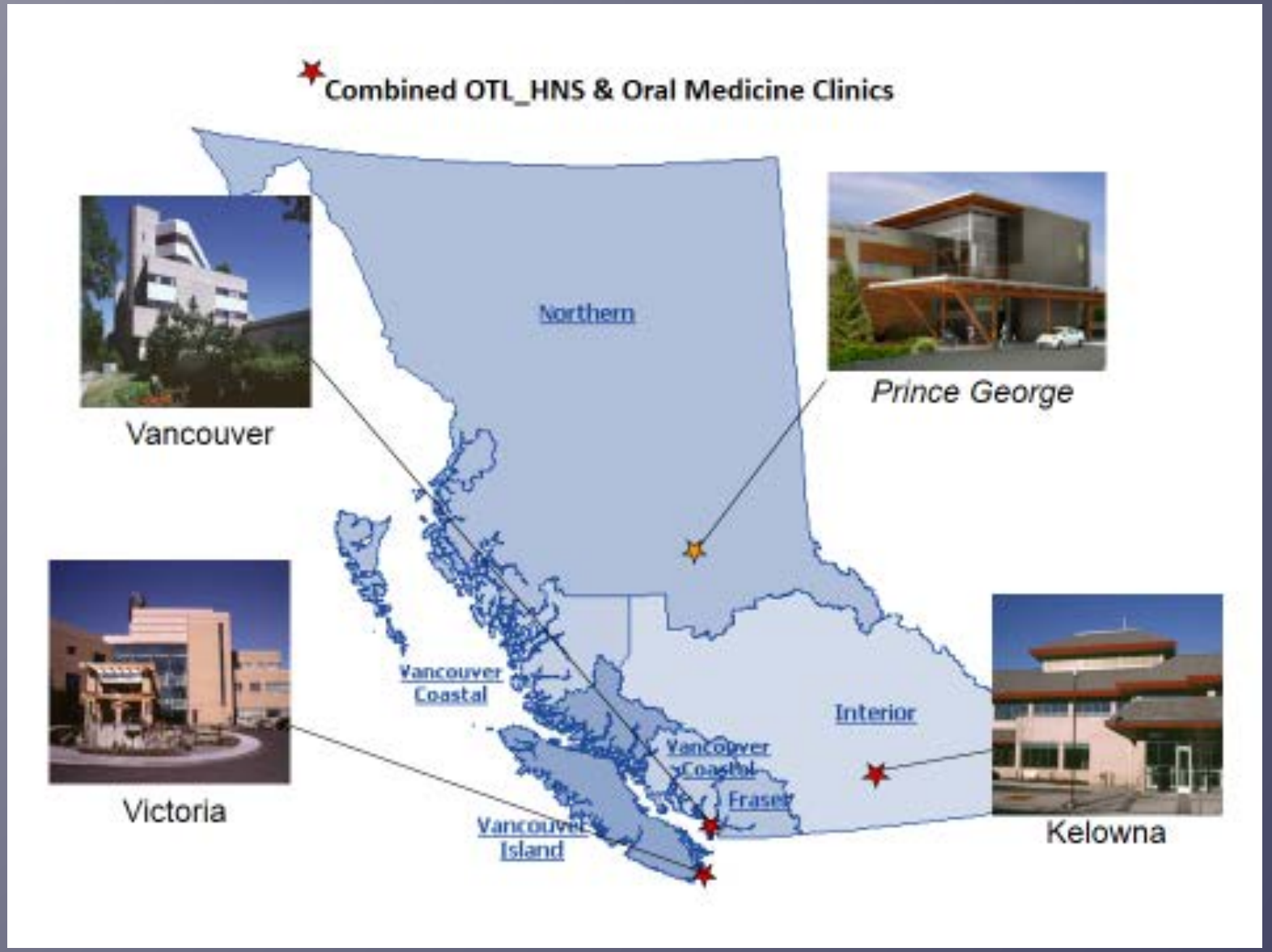
Gains: 3q, 5p, 7p, 8q, 11q, 20p
Loss: 3p, 4q, 8p, 9p, 18q

Gains: 3q, 5p, 7p, 8q, 11q, 20q
Loss: 4q

iTOP Clinic
Combined Otolaryngology Head & Neck Surgery & Oral Medicine Clinics

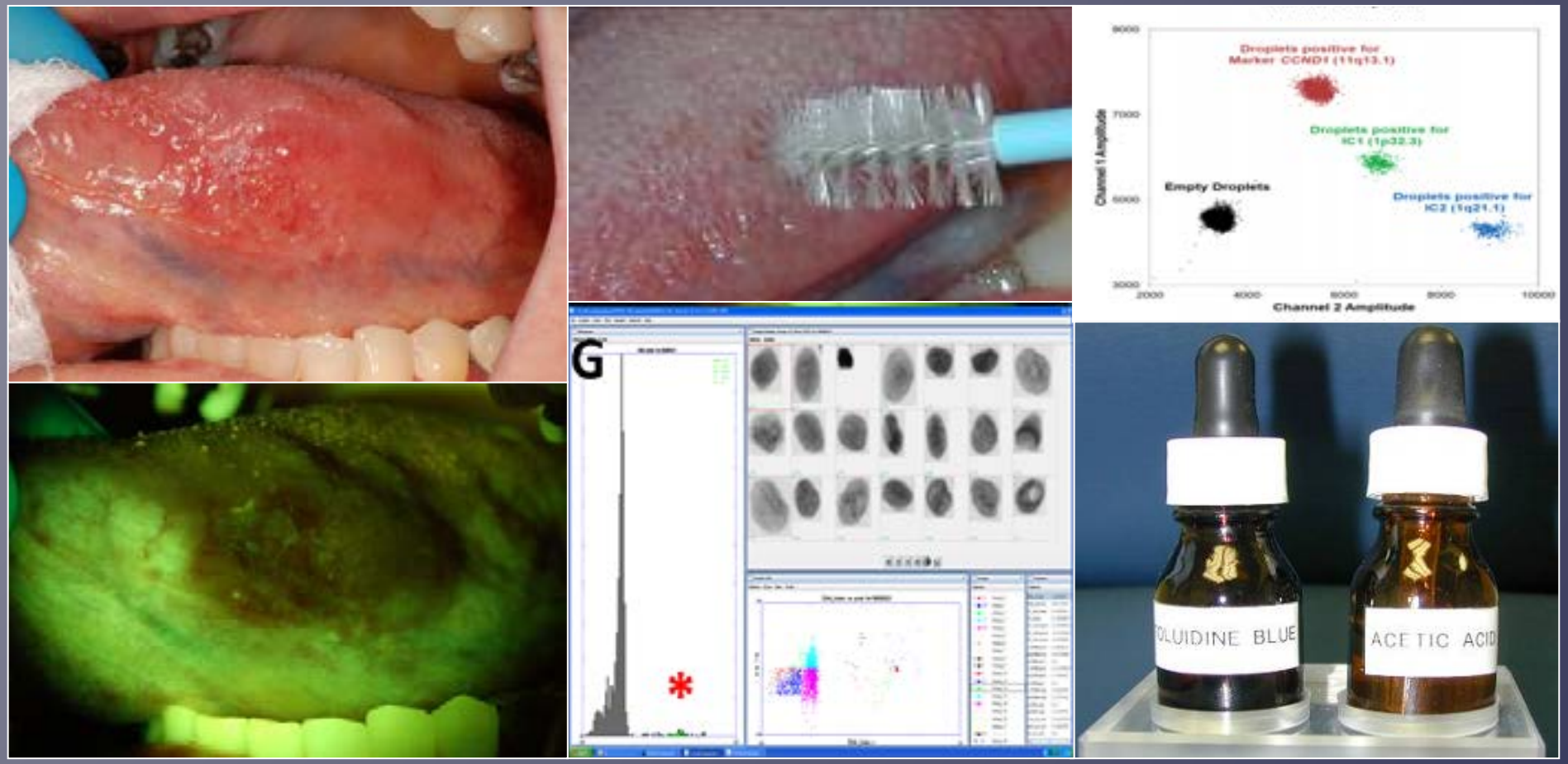
4.8 million

944.735 km²



iTOP clinic

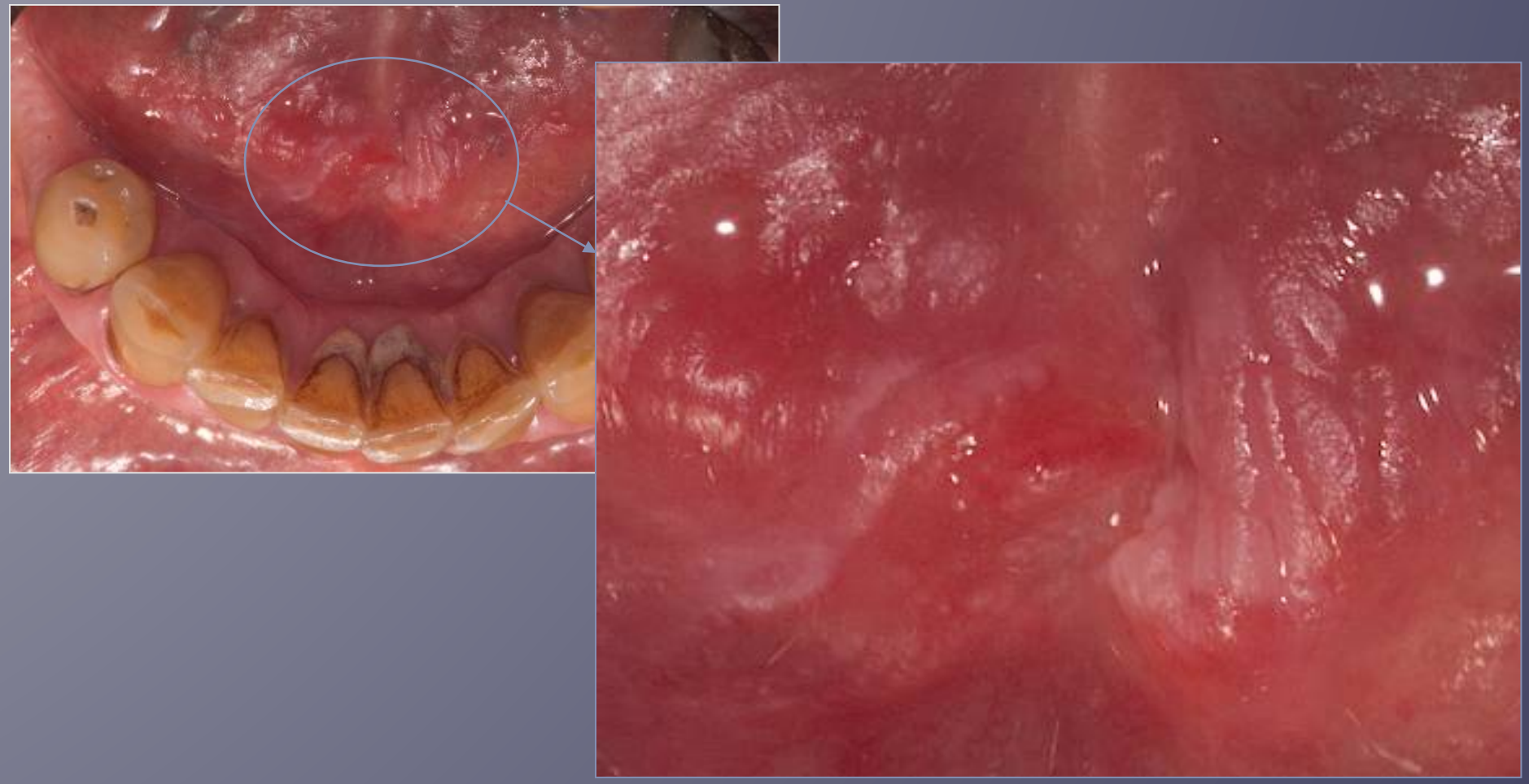
- *in vivo* Optical Devices
- Quantitative Cytology using Nuclear Phenotype Score
- Molecular tests



A good picture is better than a thousand words!

High resolution digital clinical images

High resolution digital clinical images



Toluidine Blue

Toluidine blue (TB) is a metachromatic, acidophilic stain (Tolonium Chloride) and has higher affinity to nucleic acid.

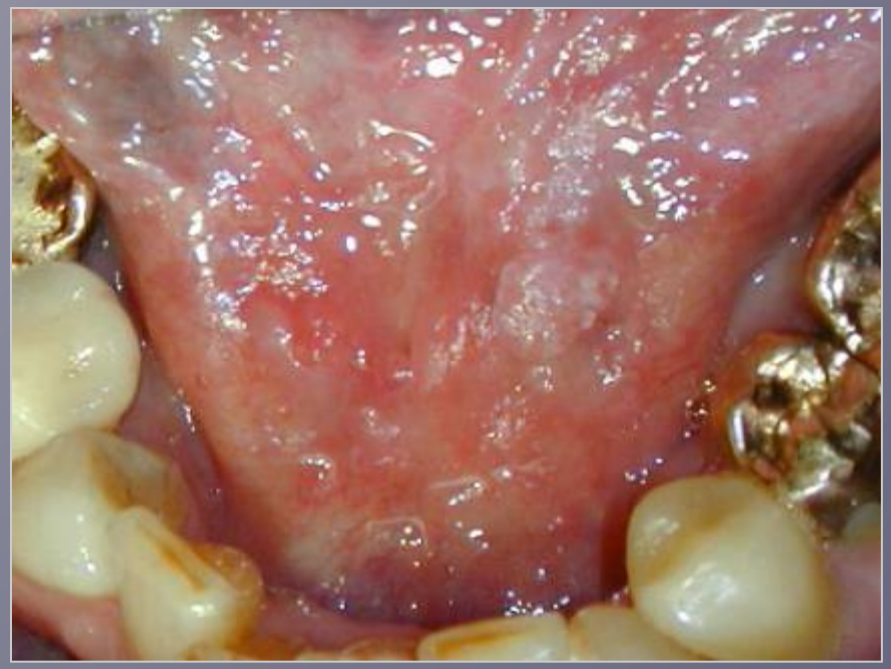
Possible mechanisms:

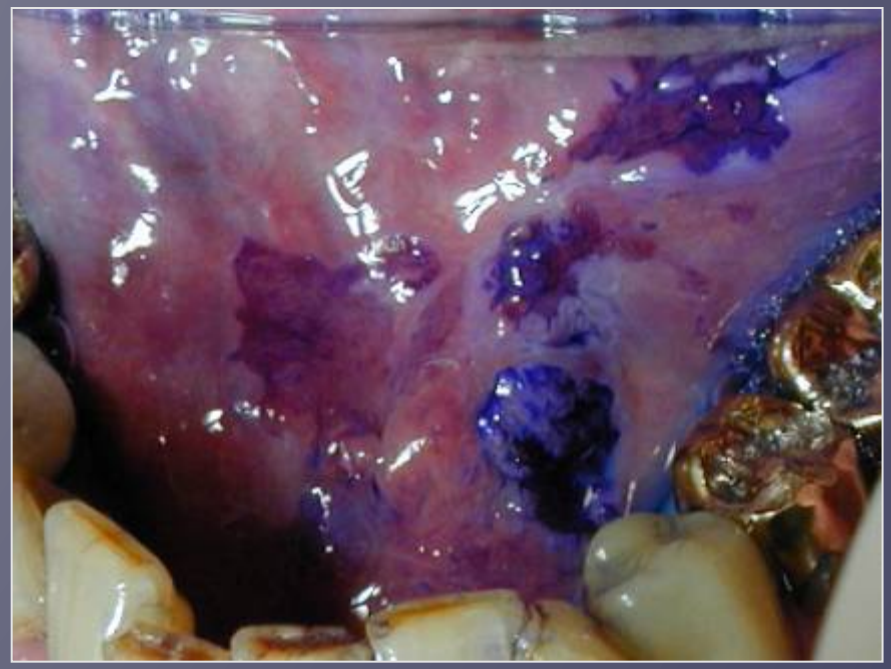
- **↑ DNA &/or RNA and/or**
- **Defective intercellular barrier**

→ the dye to reach deeper cell layers with higher DNA and RNA content

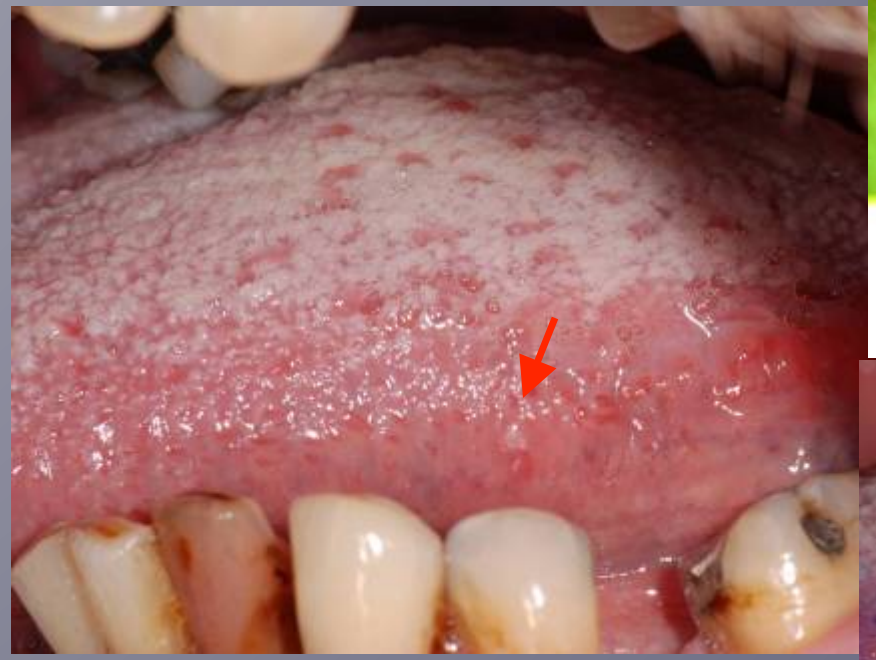
Toluidine Blue

Where is the lesion and where to biopsy?

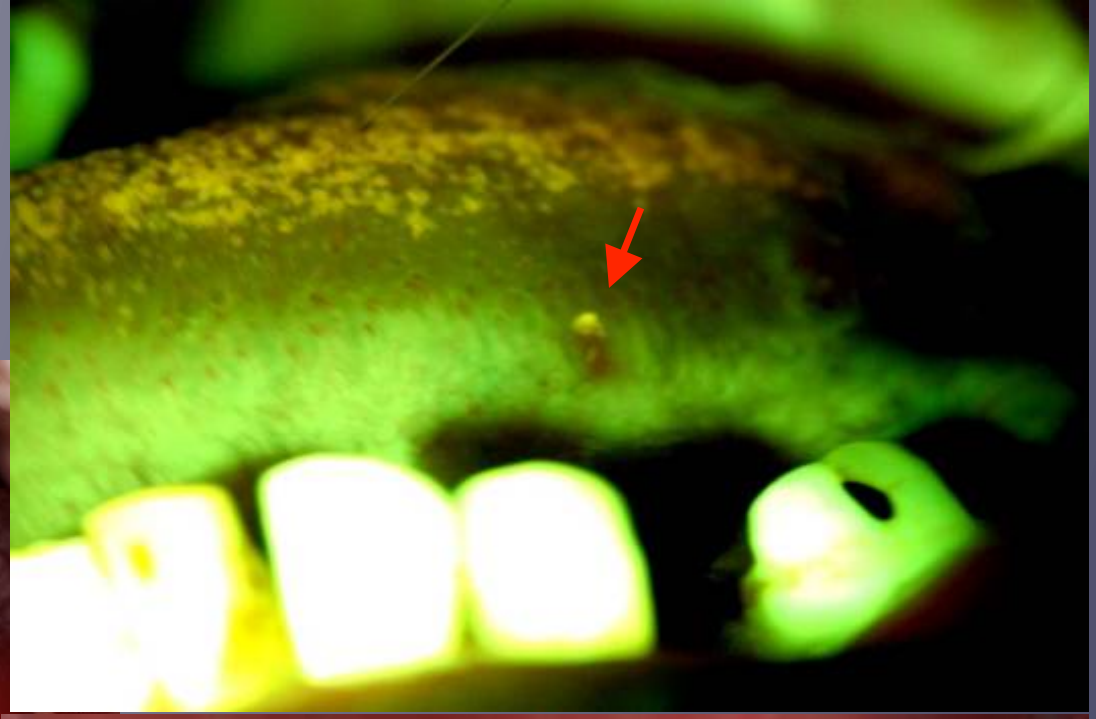




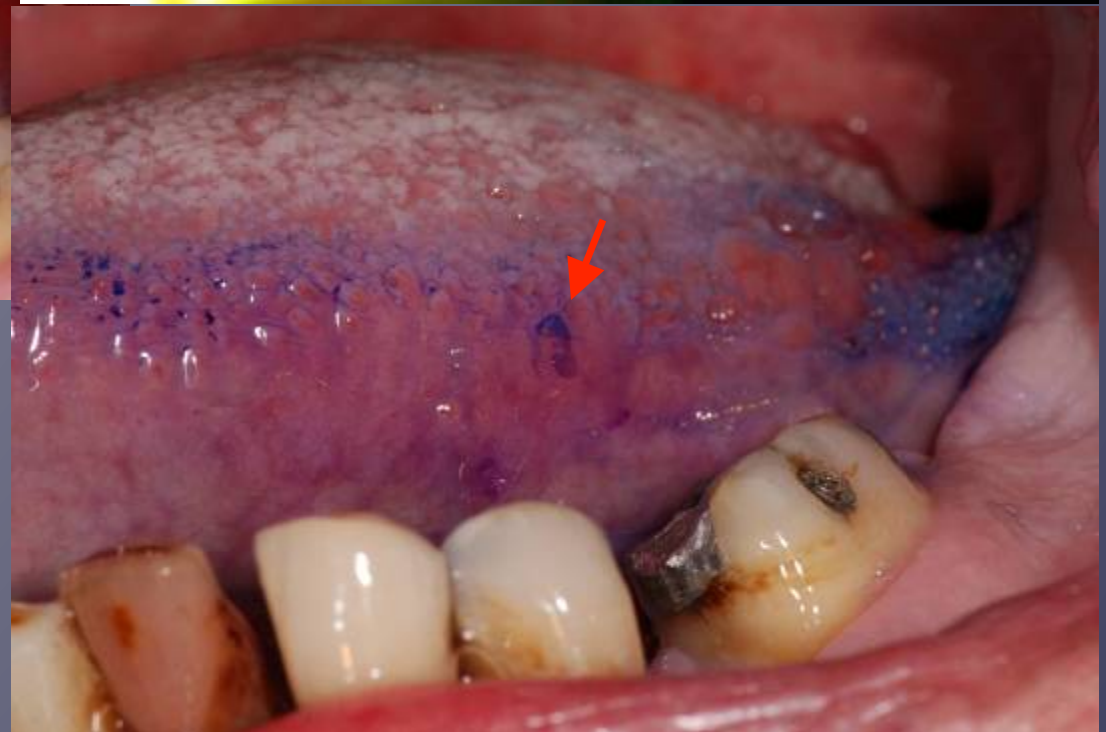
55 y/o M, smoker, HCV + (#4278);
Smoking tobacco since age 13,
40 pack year smoking history.



Carcinoma *in situ*



FV



TB

How to manage these at-risk oral lesions

Manage these at-risk oral lesions:

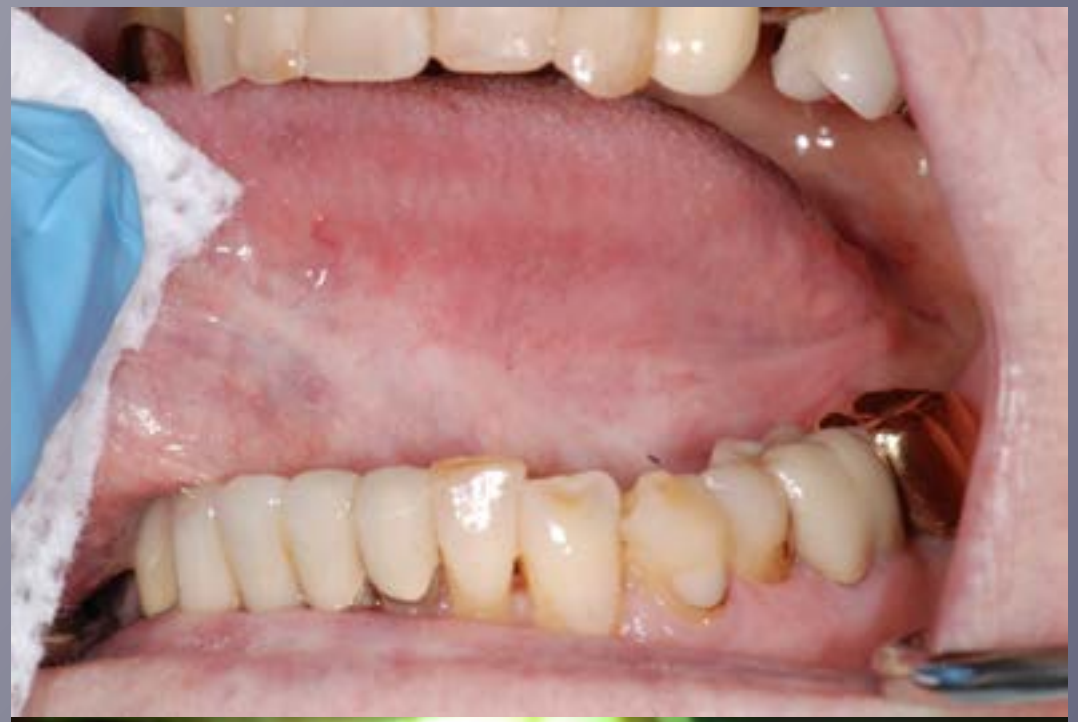
1. Cryotherapy
2. Topical Photodynamic Therapy

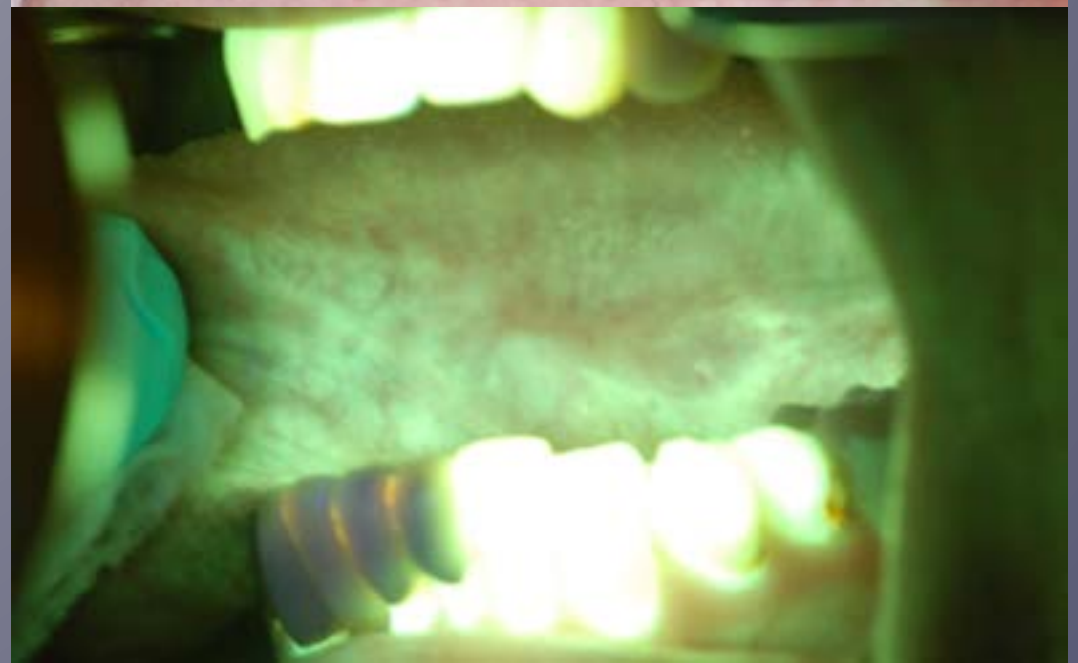
84 F NS

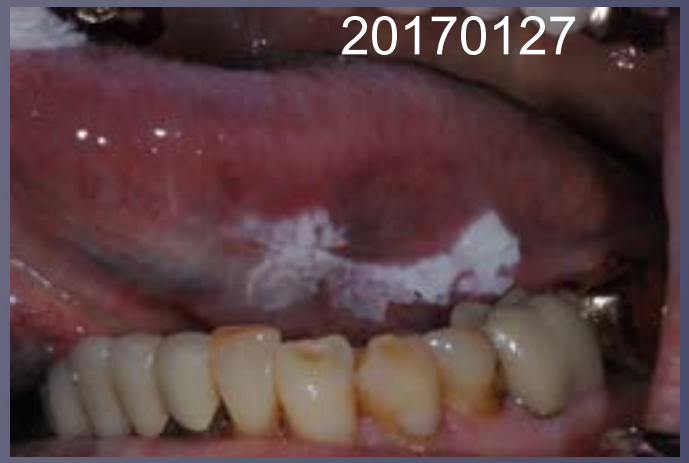
3 months

Cryotherapy using liquid nitrogen

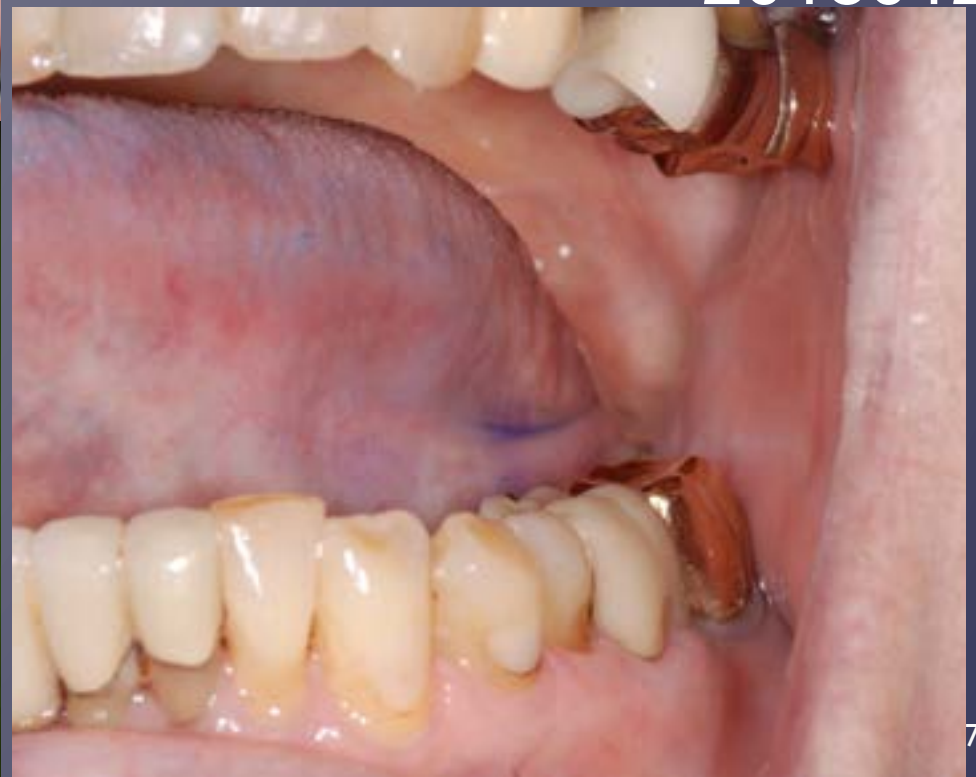
20170420



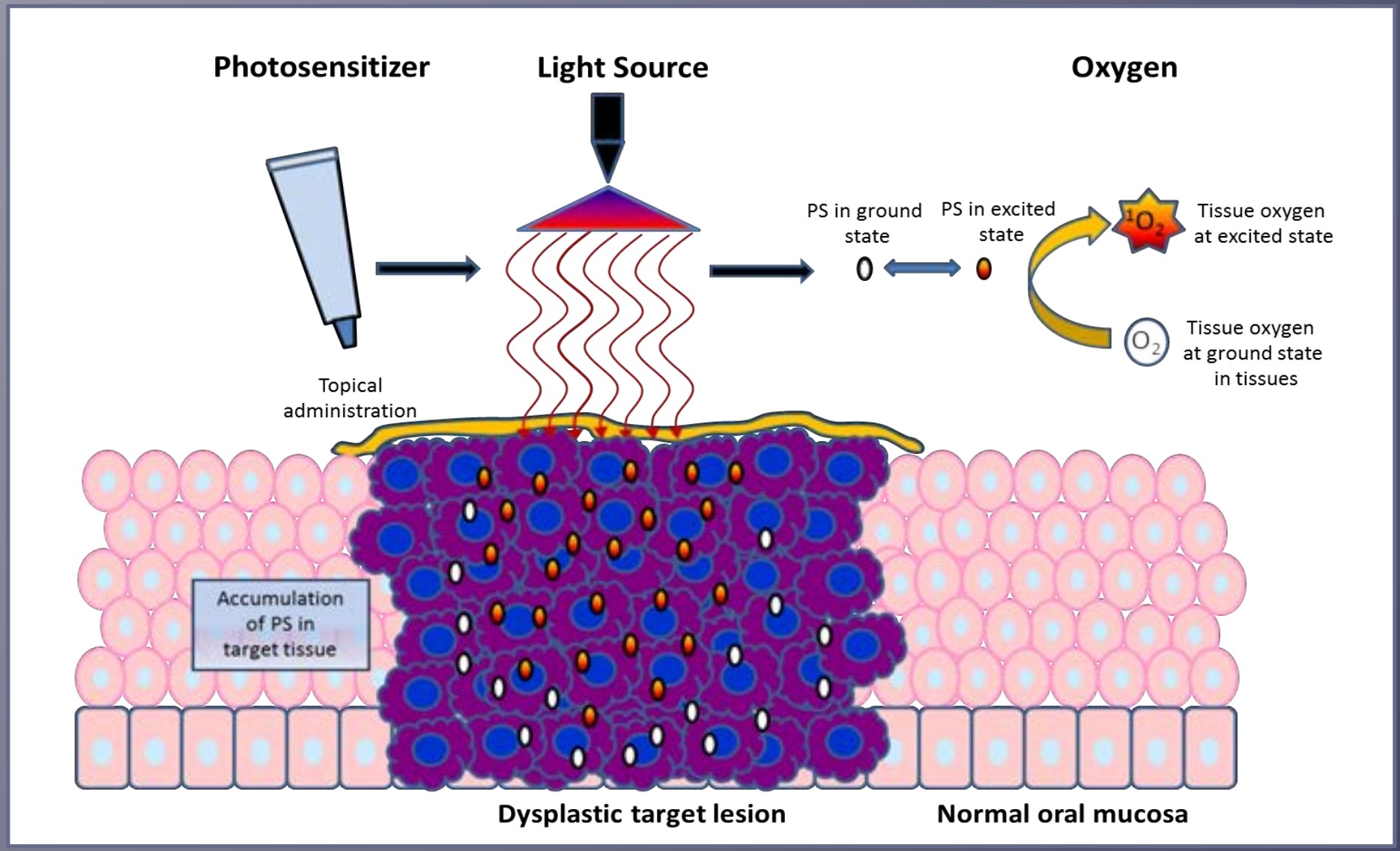




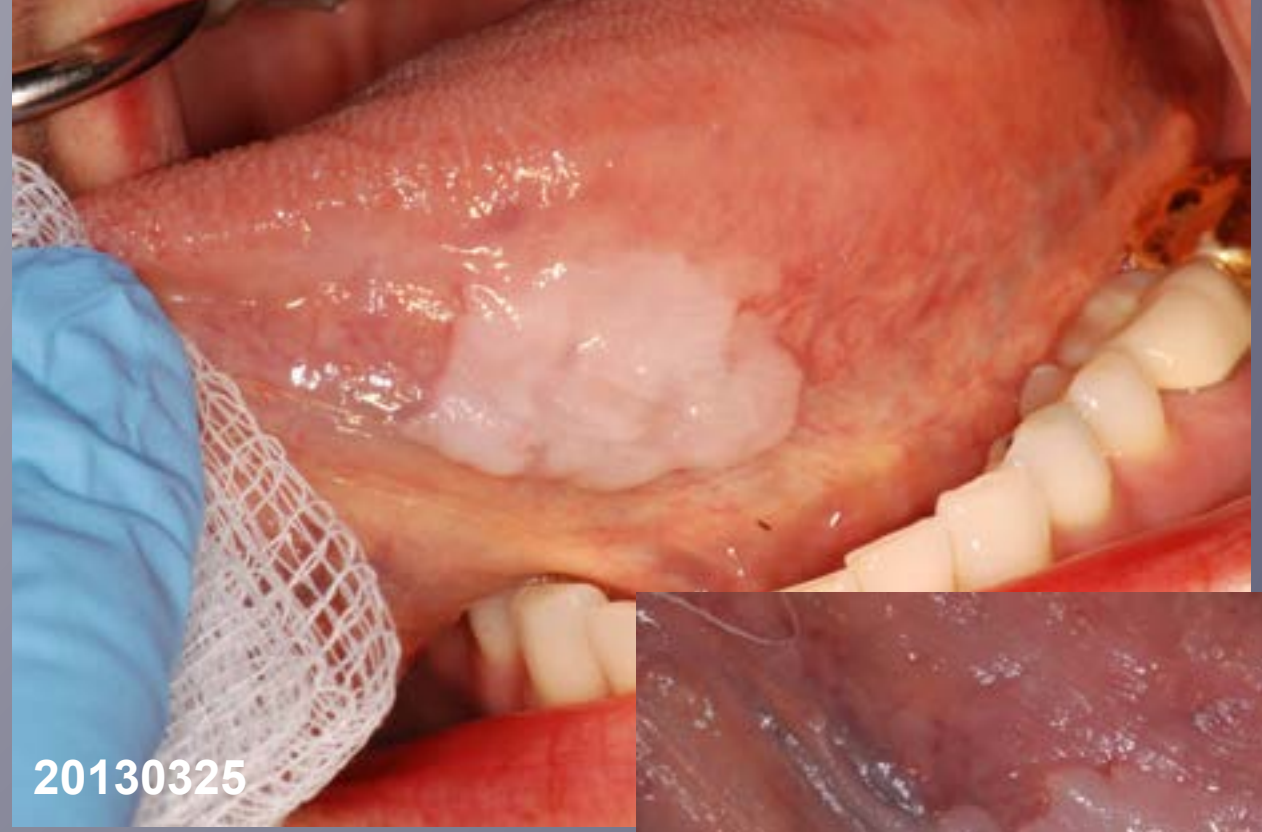
20180127



Topical Photodynamic Therapy using 20% 5-ALA (5-Aminolevulinic Acid)

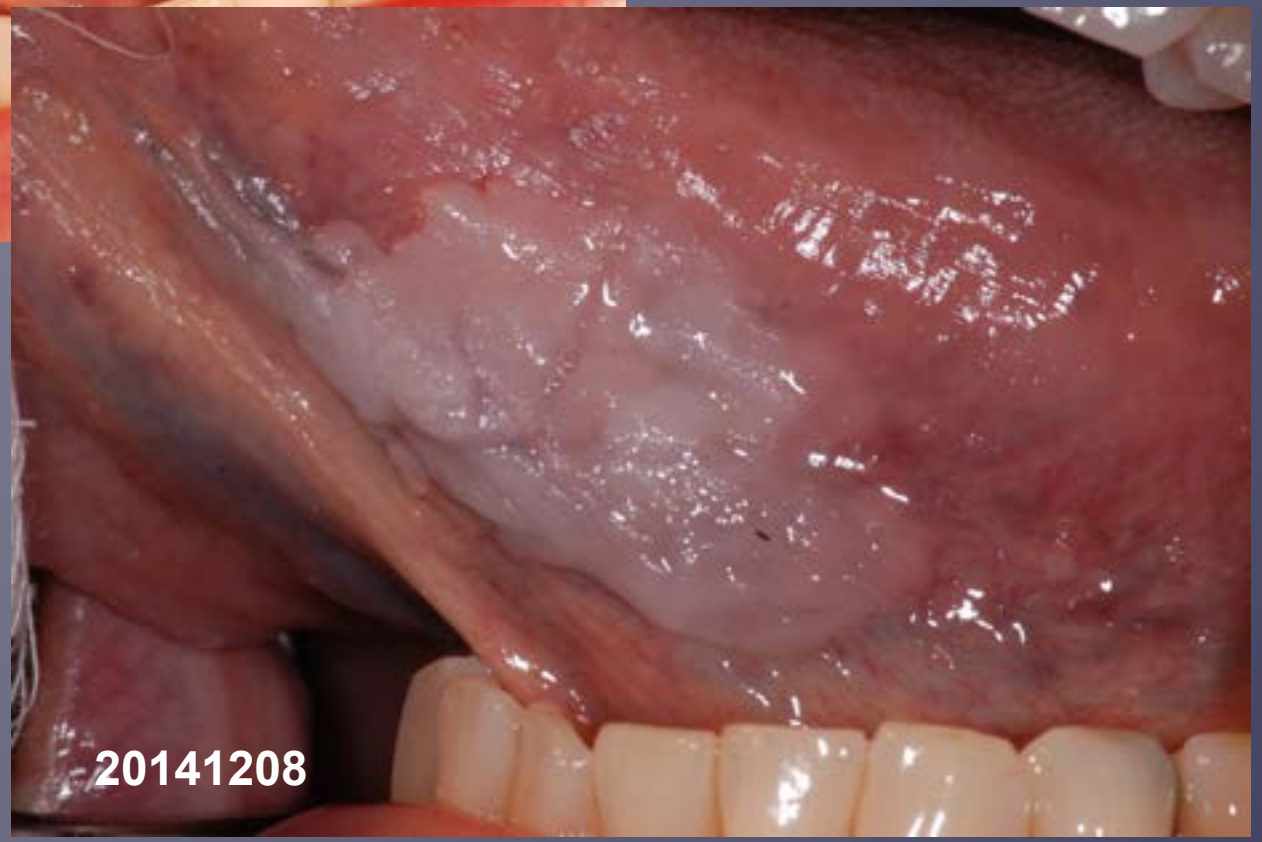


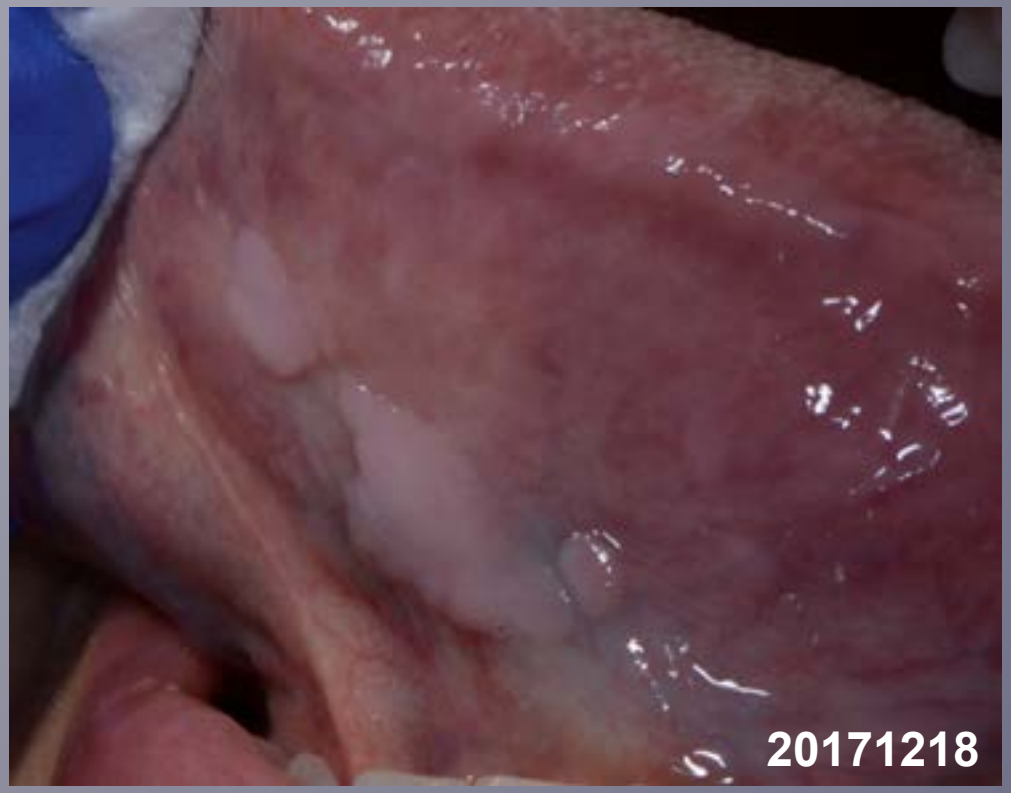
Sainin and Poh (2013) **Photodynamic therapy: a review and its prospective role in the management of oral potentially malignant disorders.**

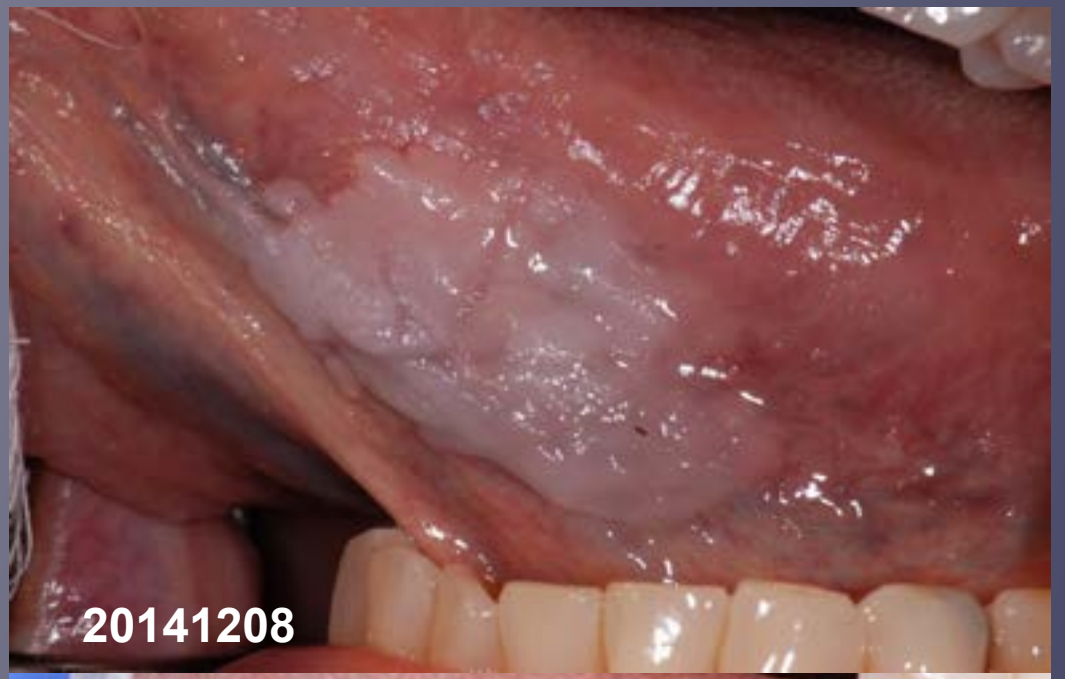


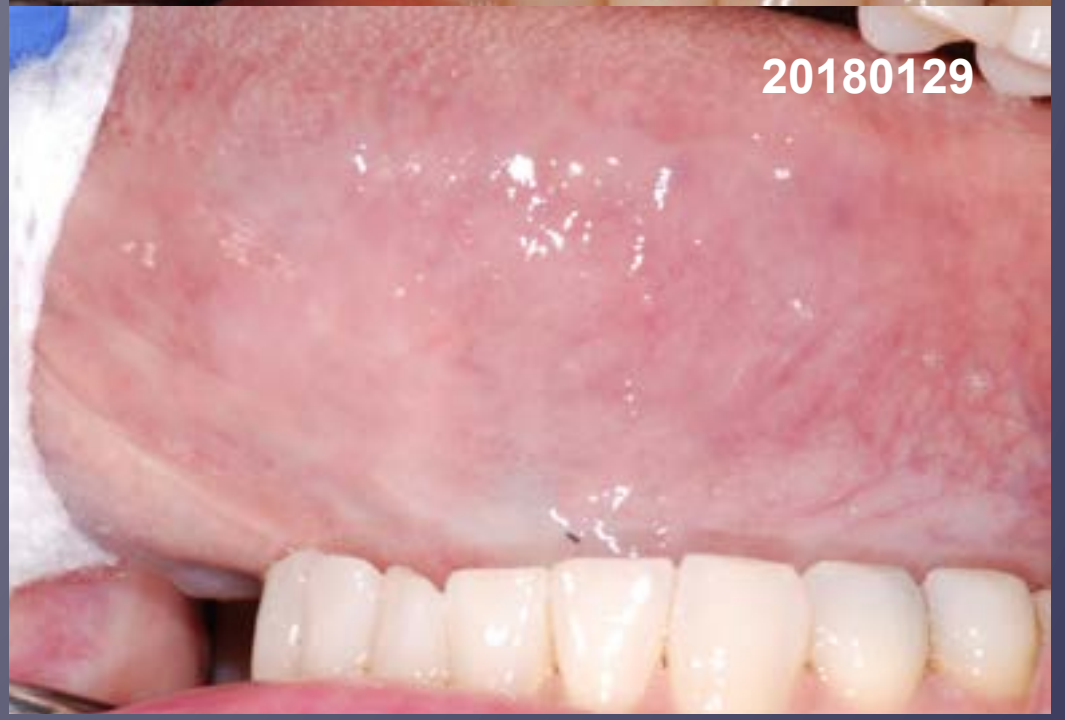
58F NS
Family cancer history

18 months





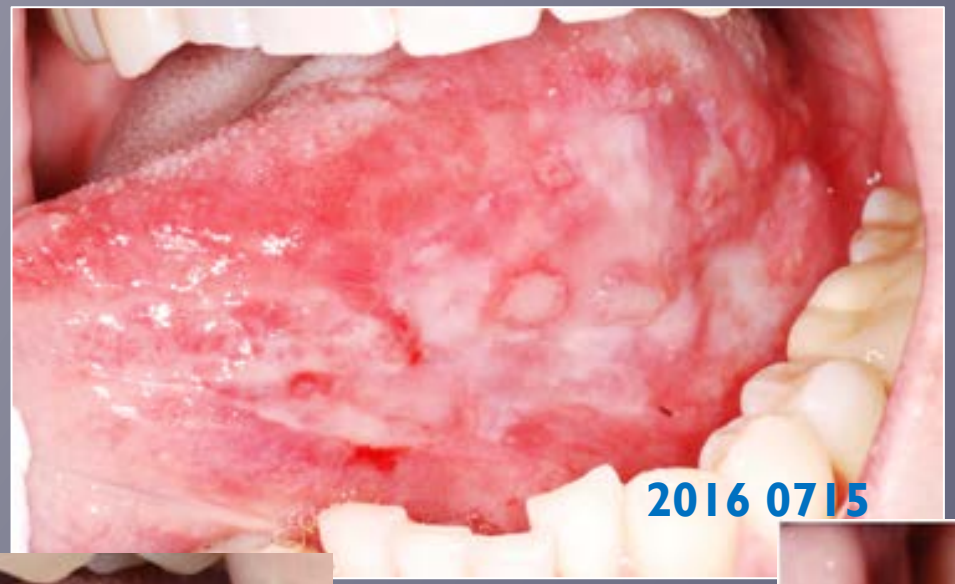




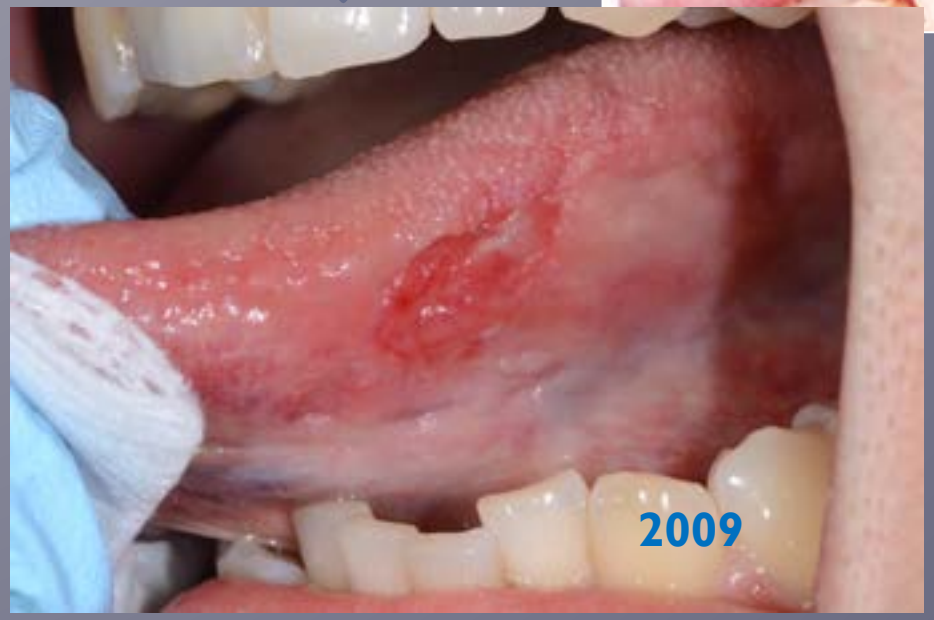
3rd Topical photo dynamic therapy using 20% 5-ALA

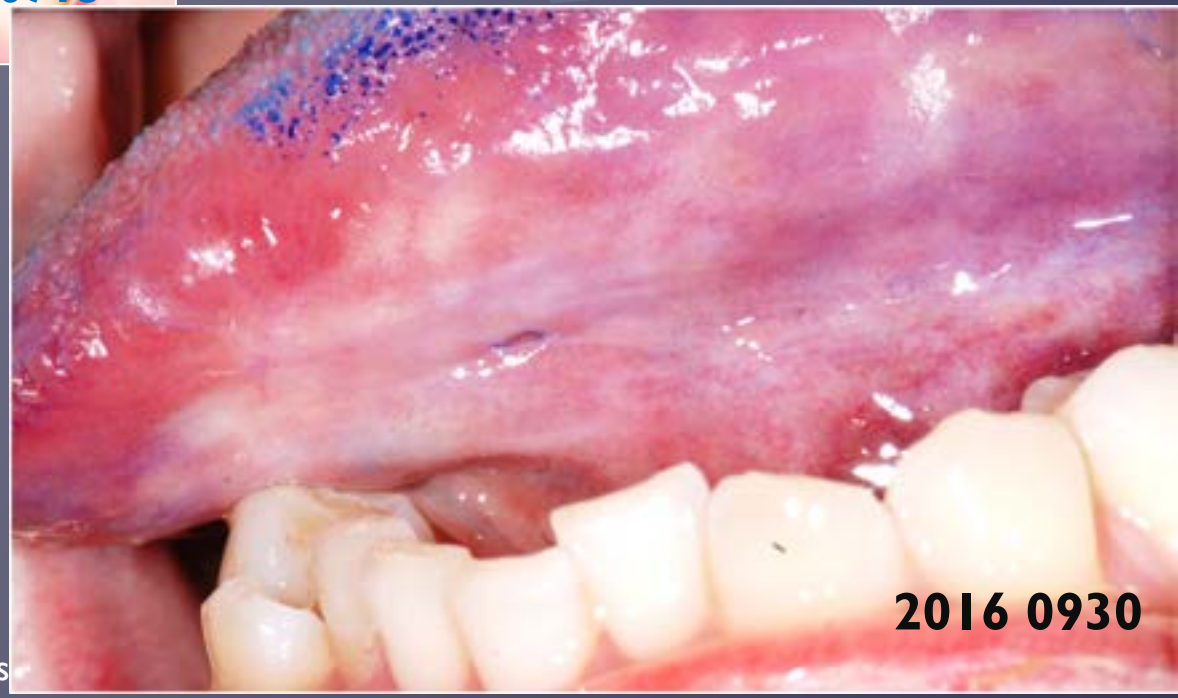
Topical Photodynamic Therapy using 20% 5-ALA (Aminolevulinic Acid)

31 F Nonsmoker, moderate dysplasia follow up for 7 years



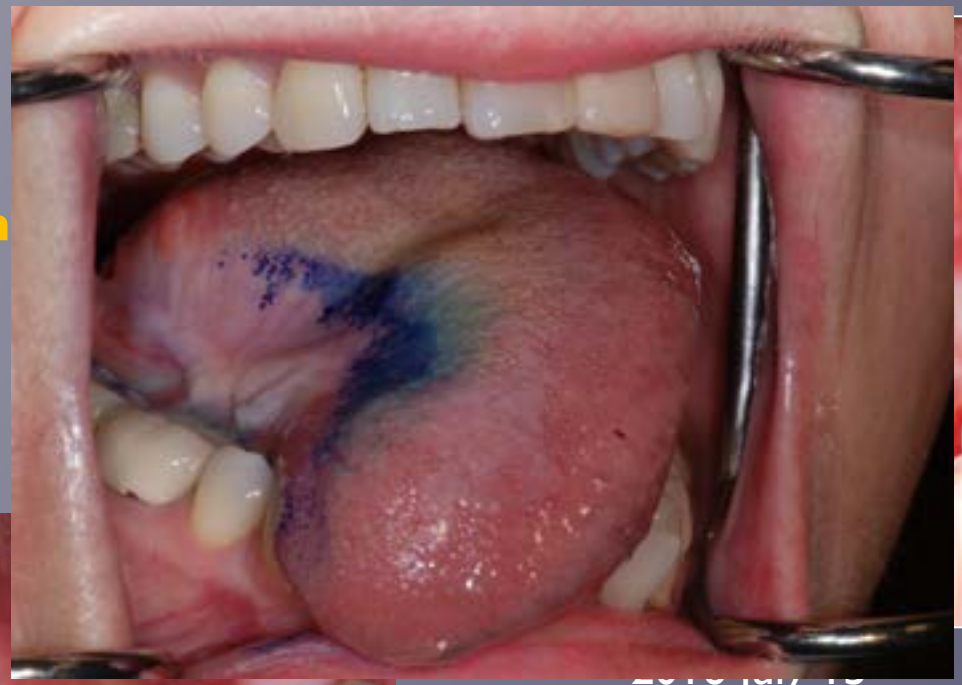
PDT x 2

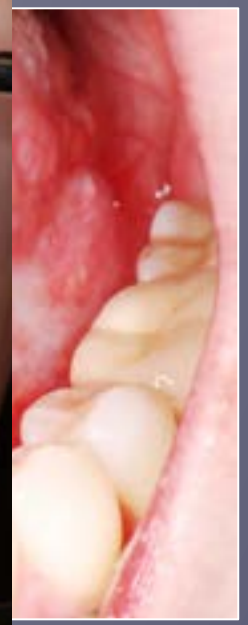


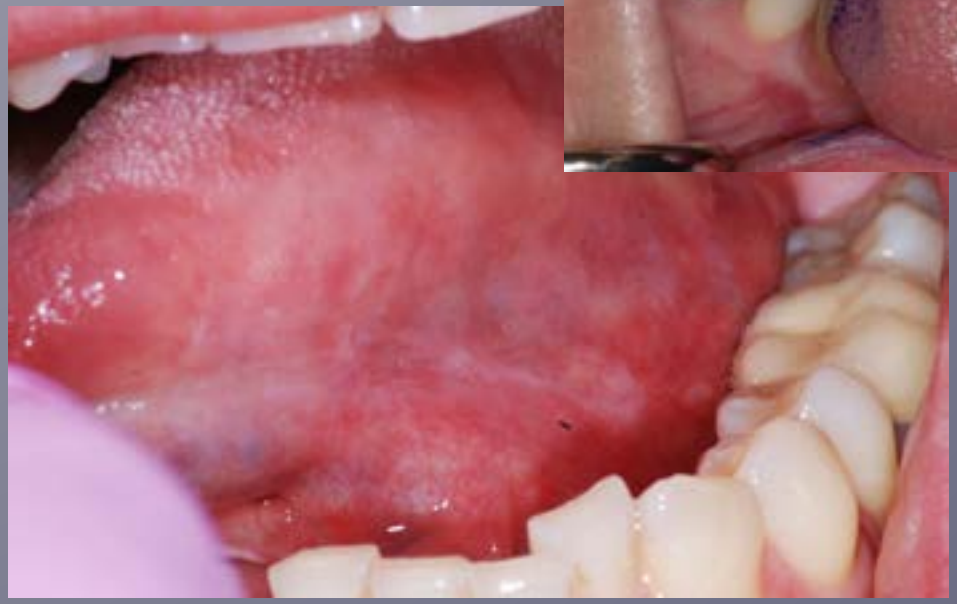


Clinical Trials of Effective Topical Treatments

Topical Photodynam Therapy

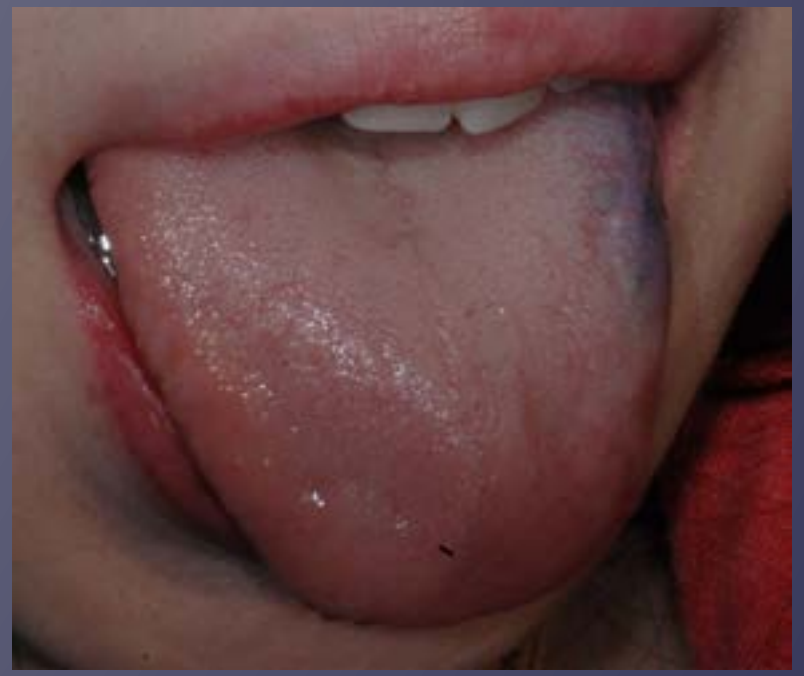






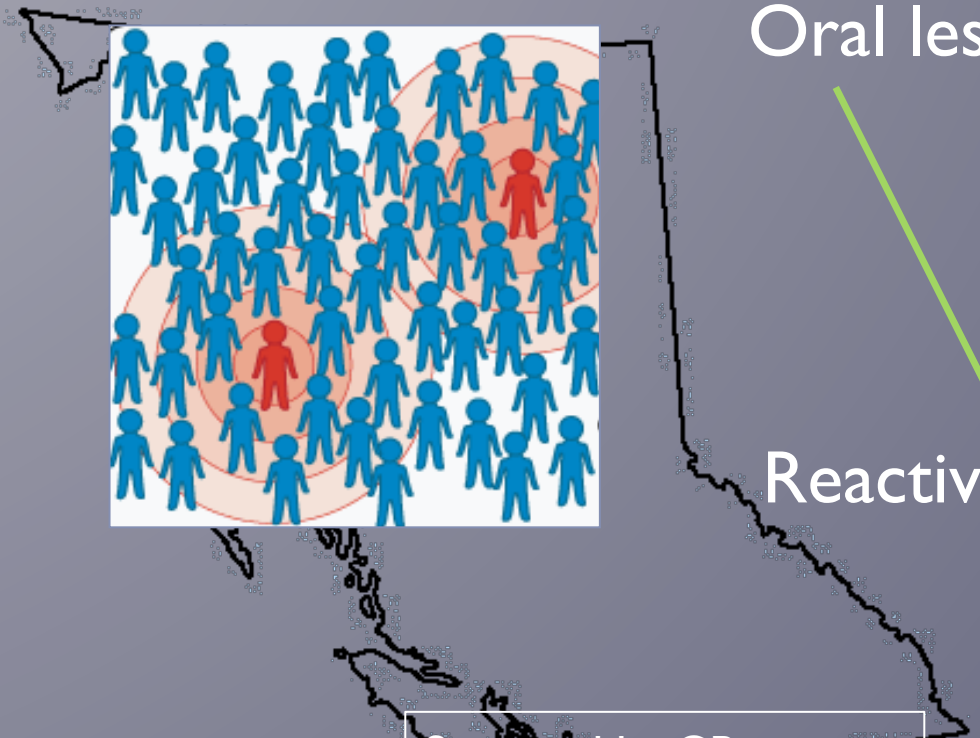
2017 March 24

32 F Nonsmoker



2017 March 24

A PATIENT'S JOURNEY



Oral lesion ? Precancer ? Cancer

Reactive lesion

Cryotherapy
Topical photodynamic therapy

Screened by GPs or dentists, using conventional white-light (VELScope exam)

QC brushing
automatic cytology to sieve off trauma, inflammation, infection

Specialists for assessment & biopsy

REGISTRY (iOBS)
of all mucosal biopsies
Patient information, pathology, molecular information (**LOH**, etc)

Acknowledgement

Collaborators

COOLS study group
Dr. Don Anderson
Dr. Ken Berean
Dr. Penny Brasher
Dr. Scott Durham
Dr. Cathie Garnis
Dr. Martial Guillaud
Dr. Cheryl Ho
Dr. Steven Jones
Dr. Aly Karsan
Dr. Pierre Lane
Dr. Calum MacAulay
Dr. Samson Ng
Dr. Stuart Peacock
Dr. Eitan Prisman
(Dr. Michele Williams)
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OC Discovery & Translational Lab

Dr. Sarah Zhu
Cindy Cui
Alisa Kami
Tony Han
Jessica Chen
Curtis Hughesman
Maria Lopes
David Lu
Kelly Liu
Katya Parfenova

All patients & families

Michael Smith Foundation for Health Research

Canadian Cancer Society / Société canadienne du cancer

UBC DENTISTRY

THE UNIVERSITY OF BRITISH COLUMBIA

BC Cancer Foundation
Supporting research & care at BC Cancer Agency

BC Cancer Agency
CARE & RESEARCH
An agency of the Provincial Health Services Authority

CIHR IRSC

NATIONAL INSTITUTES OF HEALTH

The Terry Fox Research Institute
L'Institut de recherche Terry Fox

Genome BritishColumbia