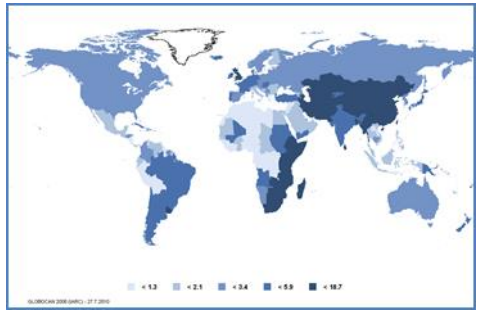
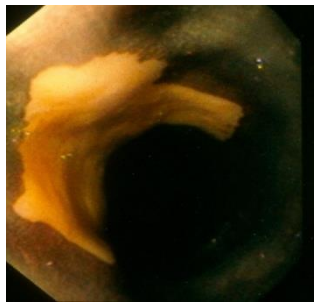
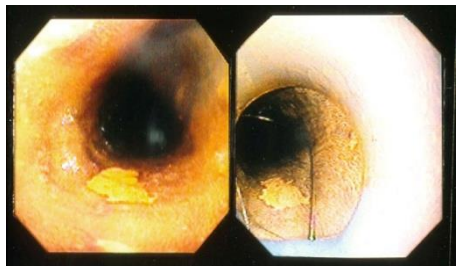
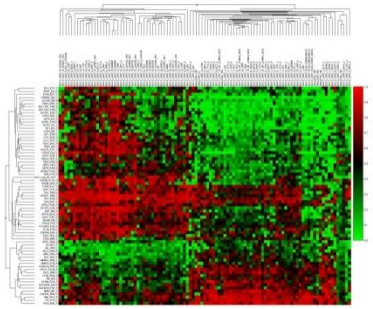


Early Detection and Treatment of ESCC Overview

Sandy Dawsey
NCI

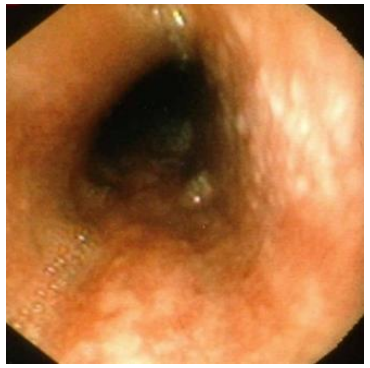






ESCC Survival

5-year survival (US)	19%
5-year survival (Iran)	3%



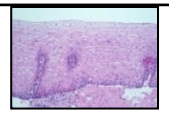
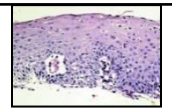
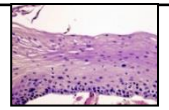
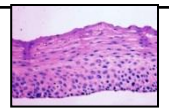
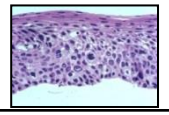
> 90% 5-year survival < 10%

- Late Sx → late Dx → Poor survival
- Need early detection and treatment
- Need to screen asxic adults in HR pops

Components of a Successful Early Detection and Treatment Program

ID of precursor lesions
Primary screen
Endoscopic localization
Staging
Therapy

Identification of ESCC Precursor Lesions

Diagnosis		Cumulative Incidence (OR) 3.5 yrs	13.5 yrs
Normal		2% (1.0)	8% (1.0)
Esophagitis		0% (---)	6% (0.8)
Mild Dysplasia		5% (2.2)	24% (2.9)
Moderate Dysplasia		27% (15.8)	50% (9.8)
Severe Dysplasia		67% (67.6)	74% (31.3)

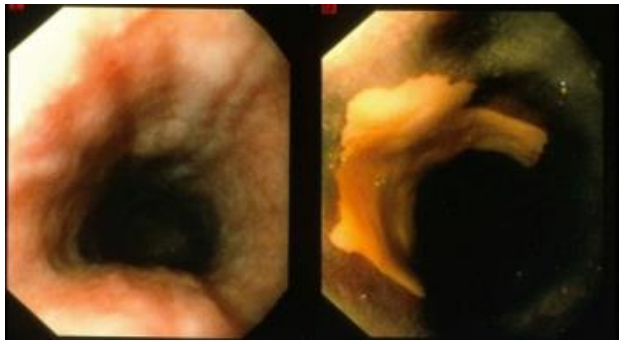
- Moderate and severe dysplasia are the clinically important precursor lesions

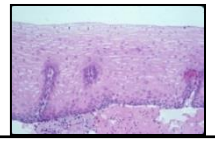
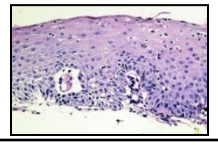
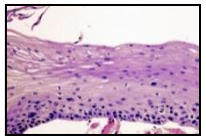
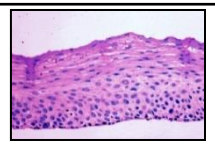
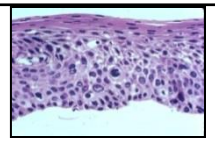
Dawsey et al Cancer 1994; Wang et al Gut 2010

Endoscopic Localization of Dysplasia

Mucosal staining with Lugol's iodine solution

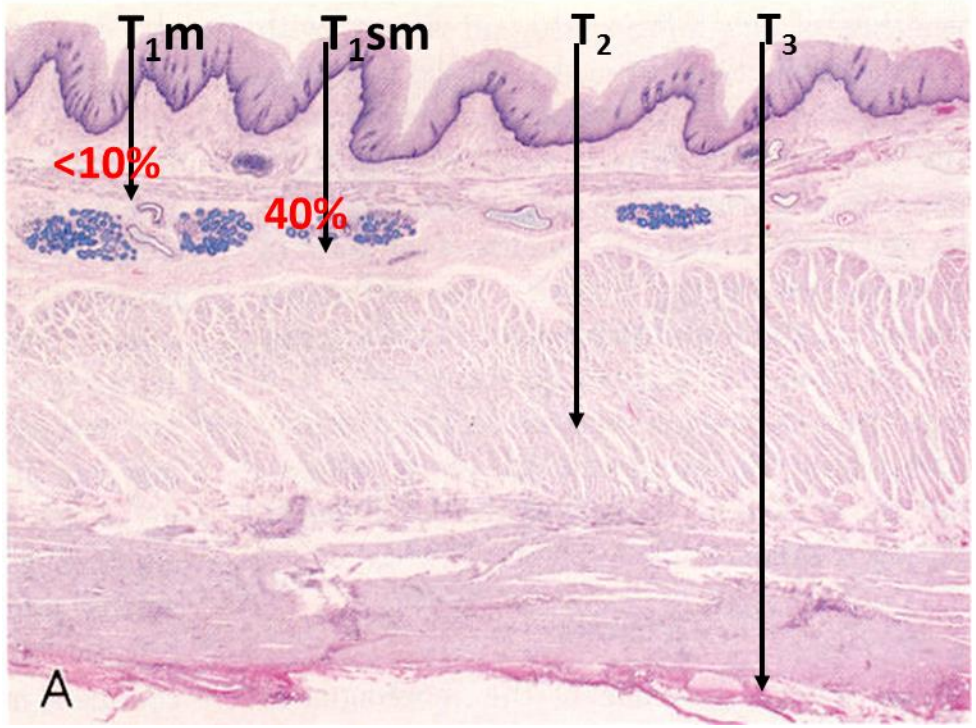
- Iodine reversibly stains glycogen → normal epithelium is brown, dysplasia is unstained

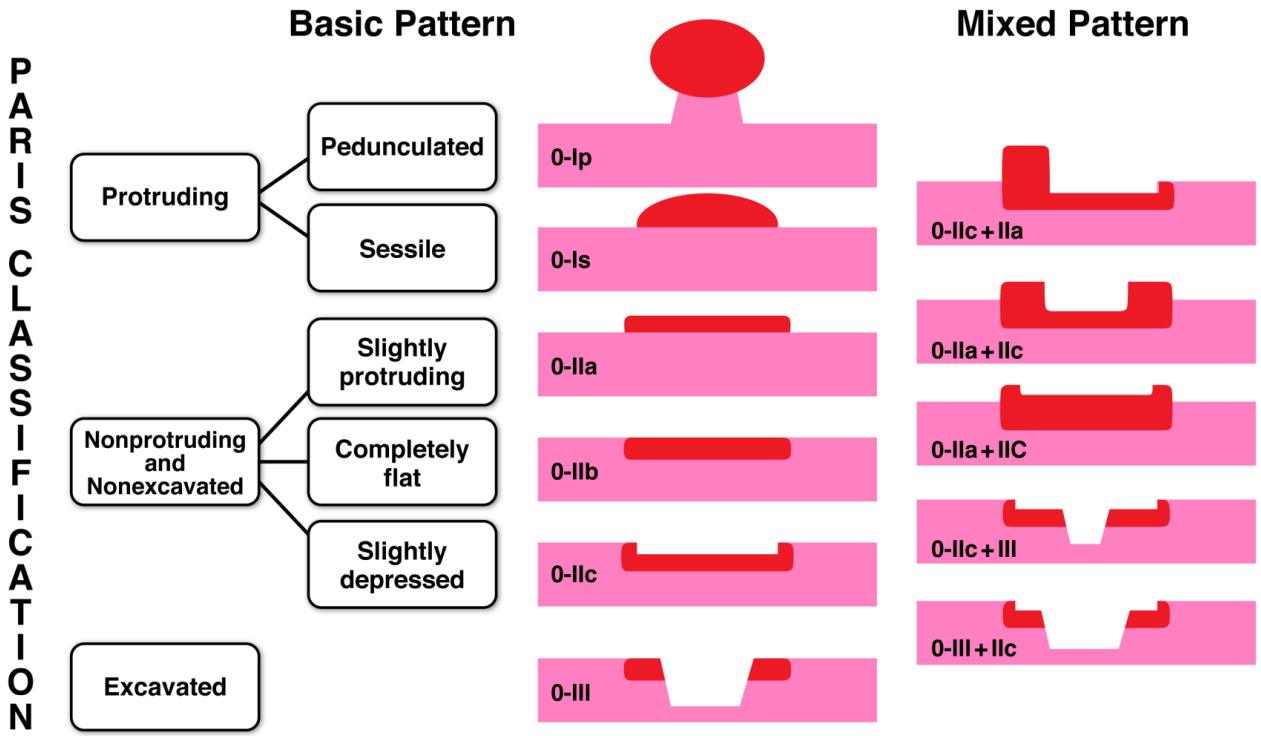


Diagnosis		Sensitivity of USLs
Normal		---
Esophagitis		---
Mild Dysplasia		63%
Moderate Dysplasia		93%
Severe Dysplasia		96%

Dawsey et al Cancer 1998

Staging

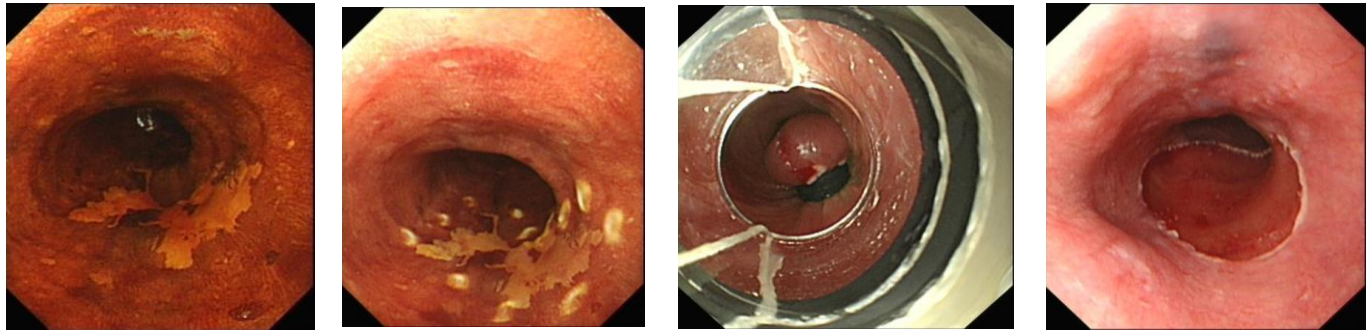

T1m
T1sm
T2
T3
<10%
40%
A


PARIS CLASSIFICATION
Basic Pattern
Mixed Pattern
Protruding
Pedunculated
Sessile
Nonprotruding and Nonexcavated
Slightly protruding
Completely flat
Slightly depressed
Excavated
0-Ip
0-Is
0-IIa
0-IIb
0-IIc
0-III
0-IIc+IIa
0-IIa+IIc
0-IIa+IIC
0-IIc+III
0-III+IIc

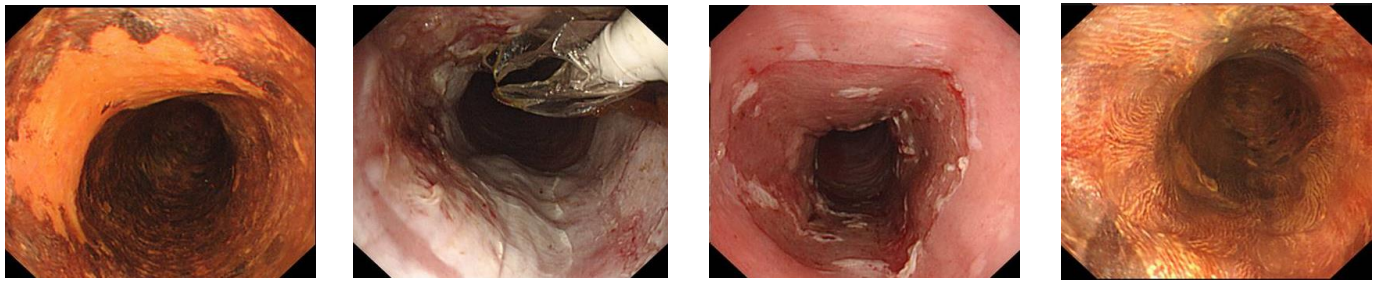
Endoscopic Therapy for Early Esophageal Squamous Neoplasia

(Moderate Dysplasia, Severe Dysplasia, T1m2 ESCC)

- **Excisional methods (EMR, MBM, ESD)**

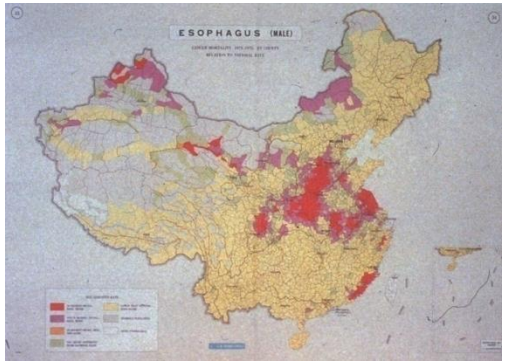


- **Ablative methods (APC, RFA)**



Pictures courtesy of Jacques Bergman

The National Esophageal Cancer Early Detection and Treatment Program of China



- **Lugol's chromoendoscopy, biopsy USLs > 5mm**
- **Endoscopic Therapy of flat HGD**
- **10-year F/U → 33% reduction in ESCC mortality**

- **>100 Field Sites, each screening ~ 2,000 asx 40-69yo adults/yr**
- **> 200,000 screened each year**
- **> 40,000,0000 adults of this age live in the high risk areas**

- **Need an accurate non-endoscopic primary screen that can screen millions and triage those at highest risk to endoscopy**

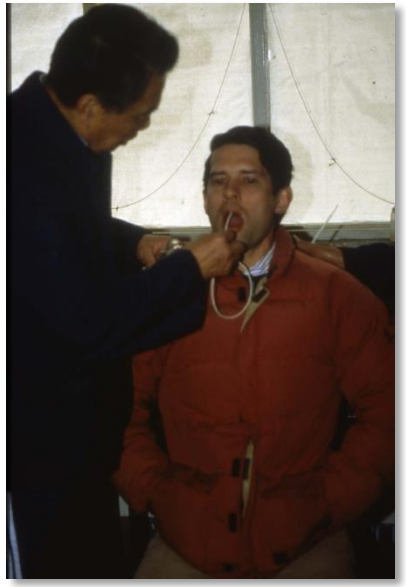
Esophageal Cancer Incidence Rates in Population-Based Cancer Registries

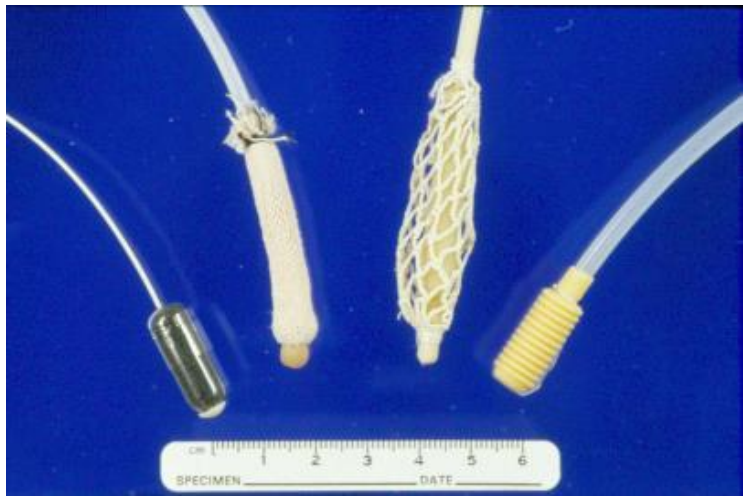
	Males	Females
Cixian, China	193	109
Yanting, China	101	68
Golestan, Iran	23	19
Nairobi, Kenya	21	15
Blantyre, Malawi	38	23
Eastern Cape Province, RSA	32	20

Cancer Incidence in Five Continents, Vol X, IARC

- **Endoscopic screening may be cost-effective in Cixian or Yanting, but it will never be cost-effective in most other HR populations**
- **We need a less expensive non-endoscopic primary screening test that can accurately triage patients to or away from endoscopy**

Esophageal Balloon Cytology





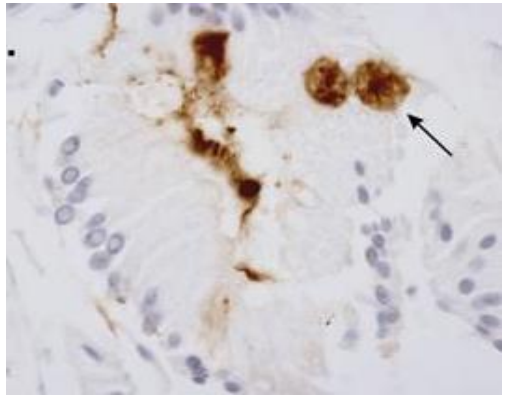
Esophageal Balloon Cytology
Cytology - Histology Comparisons

	CSS1	CSS1	CSS2	CSS2
				
Sensitivity	**47%**	**24%**	**46%**	**39%**
Specificity	**81%**	**92%**	**84%**	**85%**

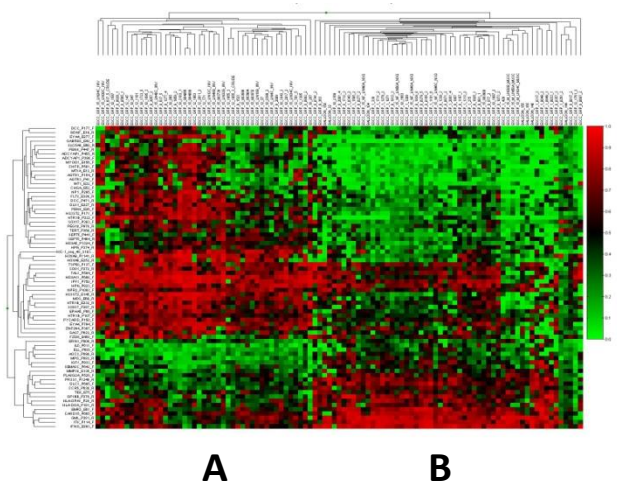
Roth et al, Cancer 1997; Pan et al, Acta Cytol 2008

- **Current EBC methods are insufficient for primary screening**
- **Can molecular markers help?**
  - **An adjunct to cytology**
  - **Separate from cytology**
  - **Screening for dysplastic cells**
  - **Screening for a field effect**

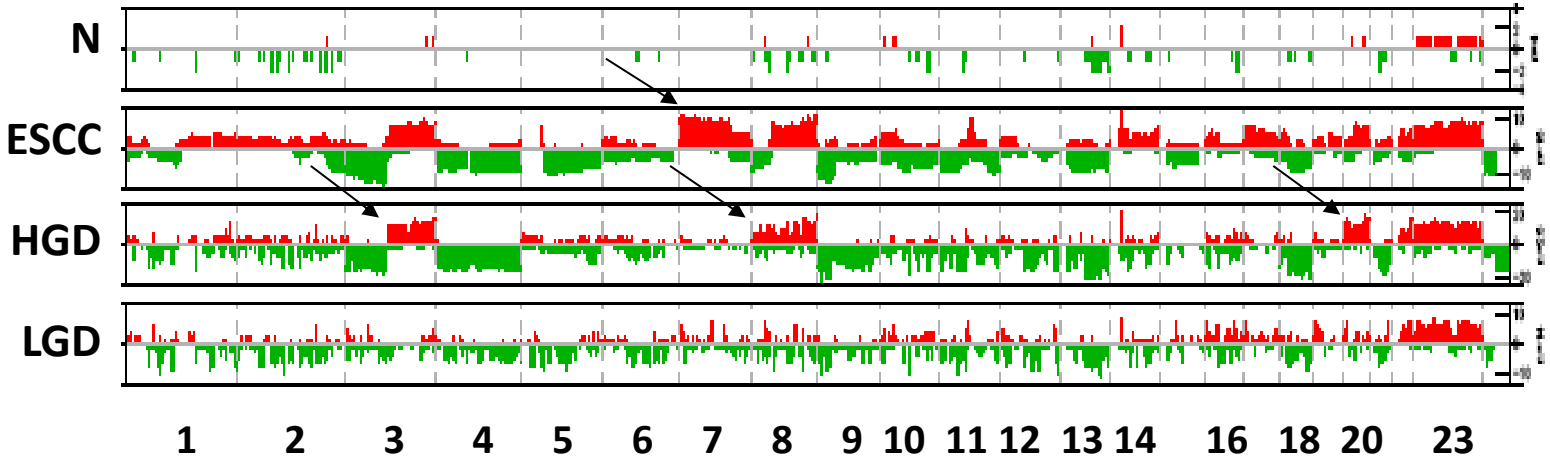
Potential Molecular Markers for ESCC Screening



Cytosponge – TFF3 Staining in BE



Methylation Profiling



Copy Number Variation

Using Methylated DNA Markers for Detection of BE

Phase 1

- Identify discriminant methylated DNA markers (MDMs) for BE by whole-methylome discovery and subsequent biologic validation of biopsies of squamous epi, BE, and cardia

Phase 2

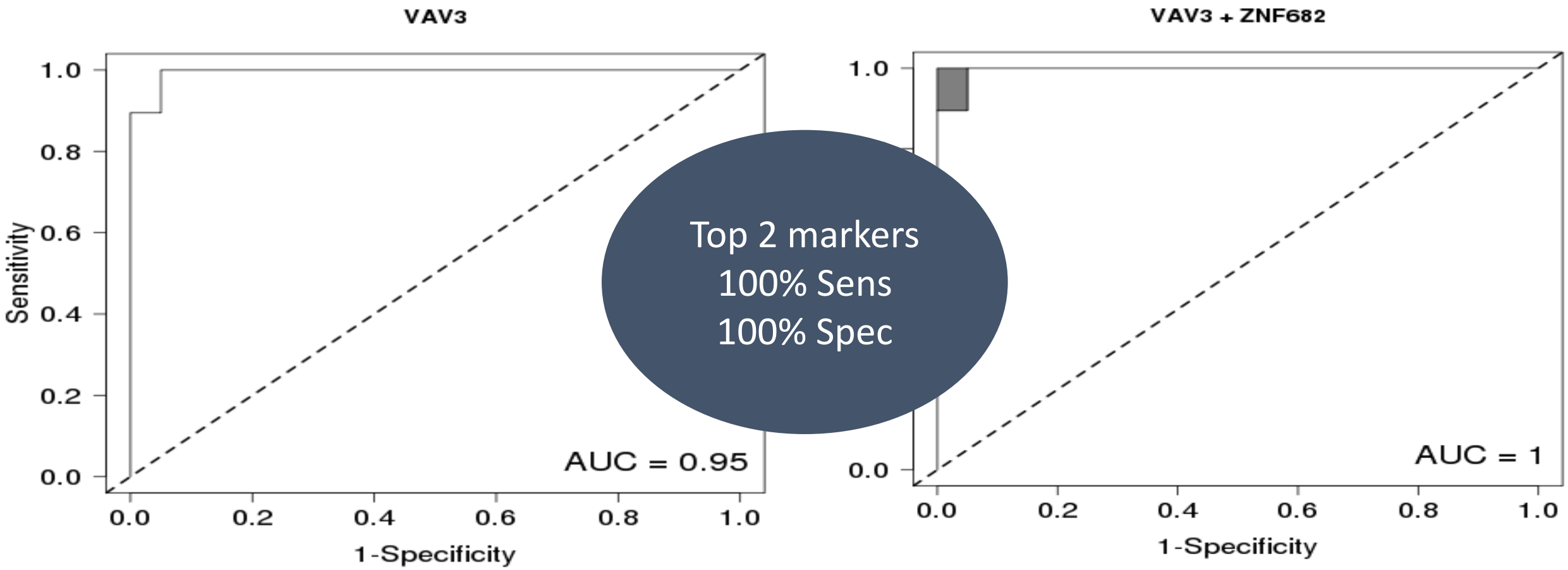
- Assess accuracy of candidate MDMs for BE in *endoscopic brushings* from whole esophagus and cardia

Phase 3

- Pilot test best candidate MDMs on cytology specimens from a *sponge capsule device*

Iyer, Ahlquist et al, DDW 2016

Phase 3: Summary Results



Top 2 markers
100% Sens
100% Spec

Iyer, Ahlquist et al. DDW 2016

Esophageal Squamous Cell Carcinoma
How Can We Improve the Current Situation?

Game Changers

- Find an infectious cause/co-factor
- Develop a clinically useful non-endoscopic primary screening test for HGD

Significant Improvements

- Etiologic studies in Africa
- Selenium added to fertilizer in low-Se HR areas
- Chimneys on cookstoves in HR areas
- Making stents available for palliative care