Risk Stratification and Management of Dysplastic Barrett's Esophagus

Beyond 2020 Vision: Current Management of Barrett's Esophagus

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Risk Stratification

"Process of assigning a patient to a particular risk status to help make management care decisions"

PRESENT NEED, TREATMENT

Is there neoplasia now?

"Process of quantifying the probability of a harmful effect (cancer) to individuals resulting from internal and external factors"

FUTURE RISK, PREVENTION

Will cancer develop?

EET or surveillance or no surveillance?

COURTESY OF CASTLE BIOSCIENCES

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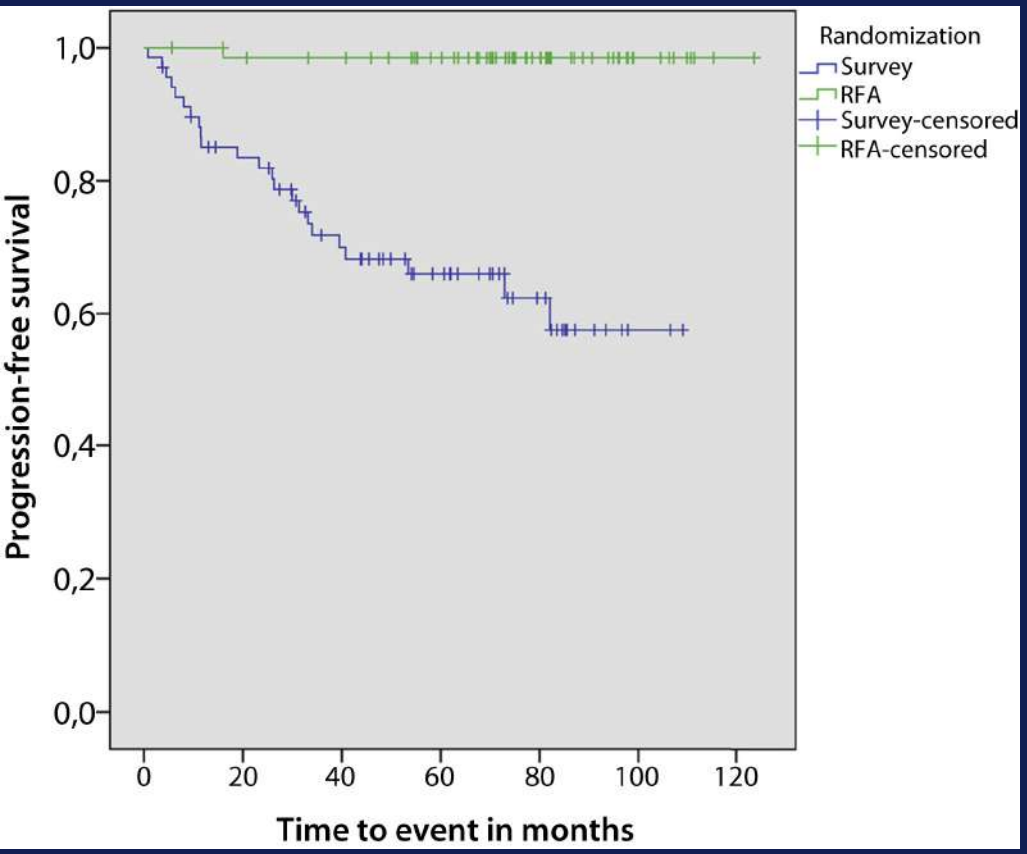
Why is risk stratification of dysplastic BE important?

- Natural history of dysplastic BE is variable
- Pathology - best biomarker for CA in BE but subject to variability, particularly for indef/LGD
- Dysplastic BE provides an opportunity for endoscopic intervention, to prevent ECA
- Need improved patient selection – minority of BE patients do not progress to ECA

Natural History of BE *Confirmed* LGD



- SURF trial (2007-2013)
- 136 pts. RCT RFA vs. surv
- HGD/CA 1.5% vs. 26.5% - recommendation for Tx BE LGD
- Median FU 73 mon (IQR48-85)
- Addnl 5 patients dev HGD/CA
- Absolute risk reduction 32%
- Surveillance 50/68 (74%) no prog
- Can we further refine selection criteria for EET?

Phoa et al, SURF trial, JAMA 2015
Pouw et al. SURF trial GIE 2021

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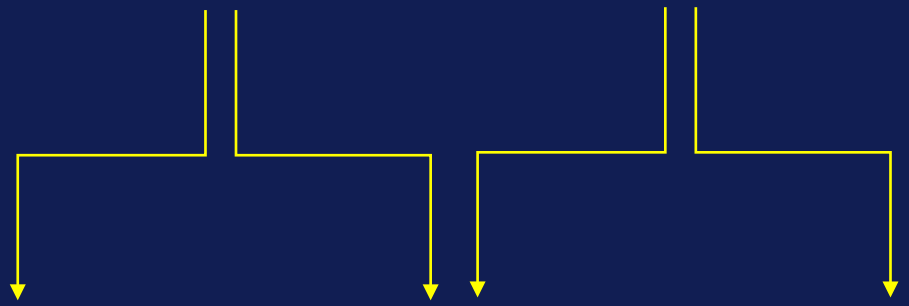
Risk Stratification Improves Selection for Endo Tx or Close Surveillance

Pathology

BE ND | BE IND | BE LGD | BE HGD

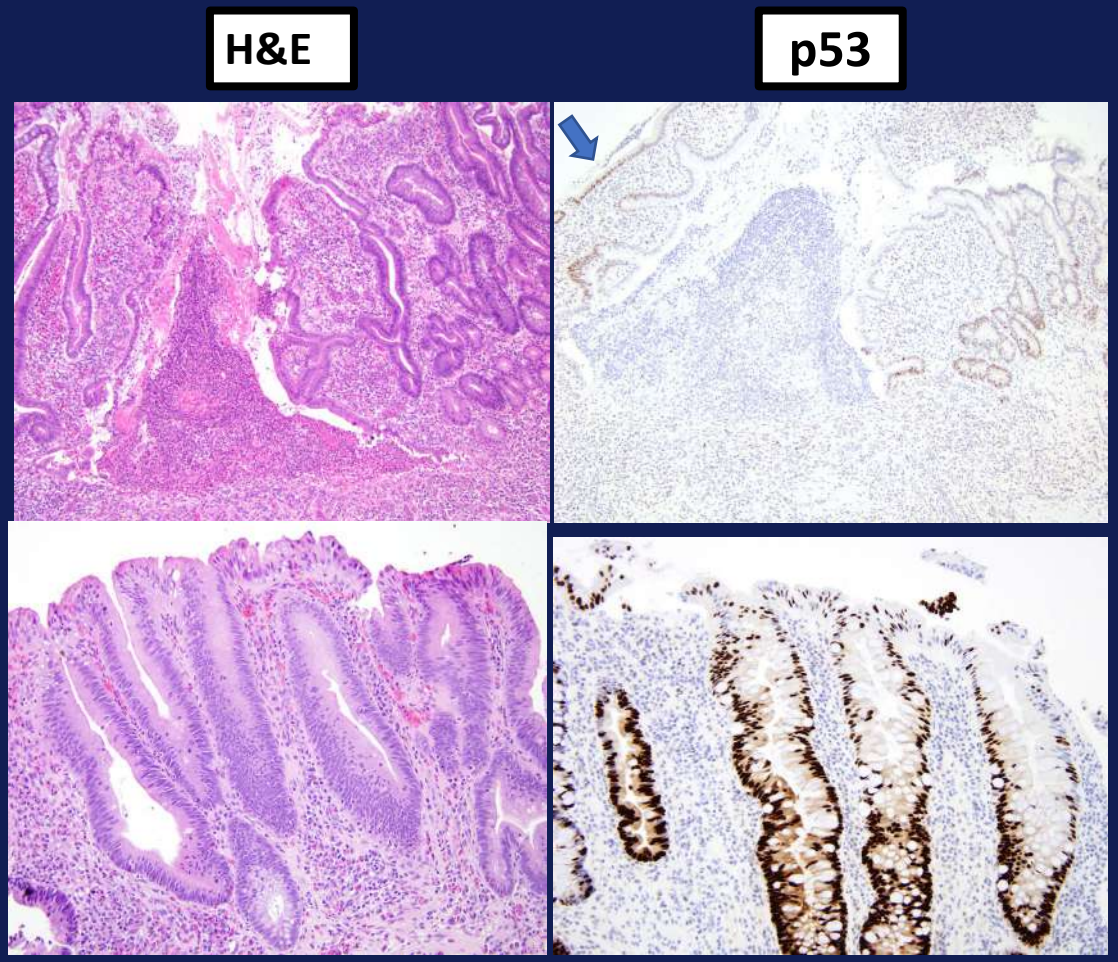


Clinical, demographic factors, other Biomarkers

ROUTINE SURVEILLANCE | CLOSE SURVEILLANCE | EET

Diagnosis of Prevalent Neoplasia

p53 Immunostaining to Aid in Dysplasia Diagnosis



BROWN IS BAD
(aberrant p53 overexpression)

COURTESY OF CASTLE BIOSCIENCES

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Predictors of Future Progression (Incident Neoplasia)

Clinico-Pathologic Factors Associated with Neoplastic Progression

Clinical/ Demographic

- Male gender
- Long BE
- Smoking

Pathologic

- LGD, HGD
- p53 immunostaining

Molecular

- Aneuploidy
- Somatic mutaions
- Epigenetic changes

Clinical Factors Predicting Progression of Patients with LGD/Indefinite for Dysplasia

- 465 patients, BE IND Cambridge UK, Mayo
- BE length correlated
  - Prevalent neoplasia OR 1.18/1 cm (p=0.033)
  - Incident neoplasia OR 1.02/1 cm (p=0.016)

- 299 patients CCF BE IND/LGD
- Progression
  - LGD at baseline
  - Male
  - Multifocality
  - Nodules
  - BE length
- Regression
  - IND at baseline
  - Older age
  - Short BE

Phillips.. Fitzgerald Di Pietro GIE 2021
Dhaliwal..Iyer CGH 2021
Thota CGH 2015

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P53 Immunostaining Can Help Predict Neoplastic Progression in BE ND/LGD

- Multiple large case-control and prospective studies
- Aberrant p53 overexpression
  - 64% in progressors versus 7.5% in non-progressors
  - Indep predictor: HR or RR 4 -17 ND, 6-21 LGD
  - Sens 64%, spec 92%, PPV 54%, NPV 95%
  - Strong biomarker for prevalent dysplasia
- Limitations
  - Interobserver variability in interpretation

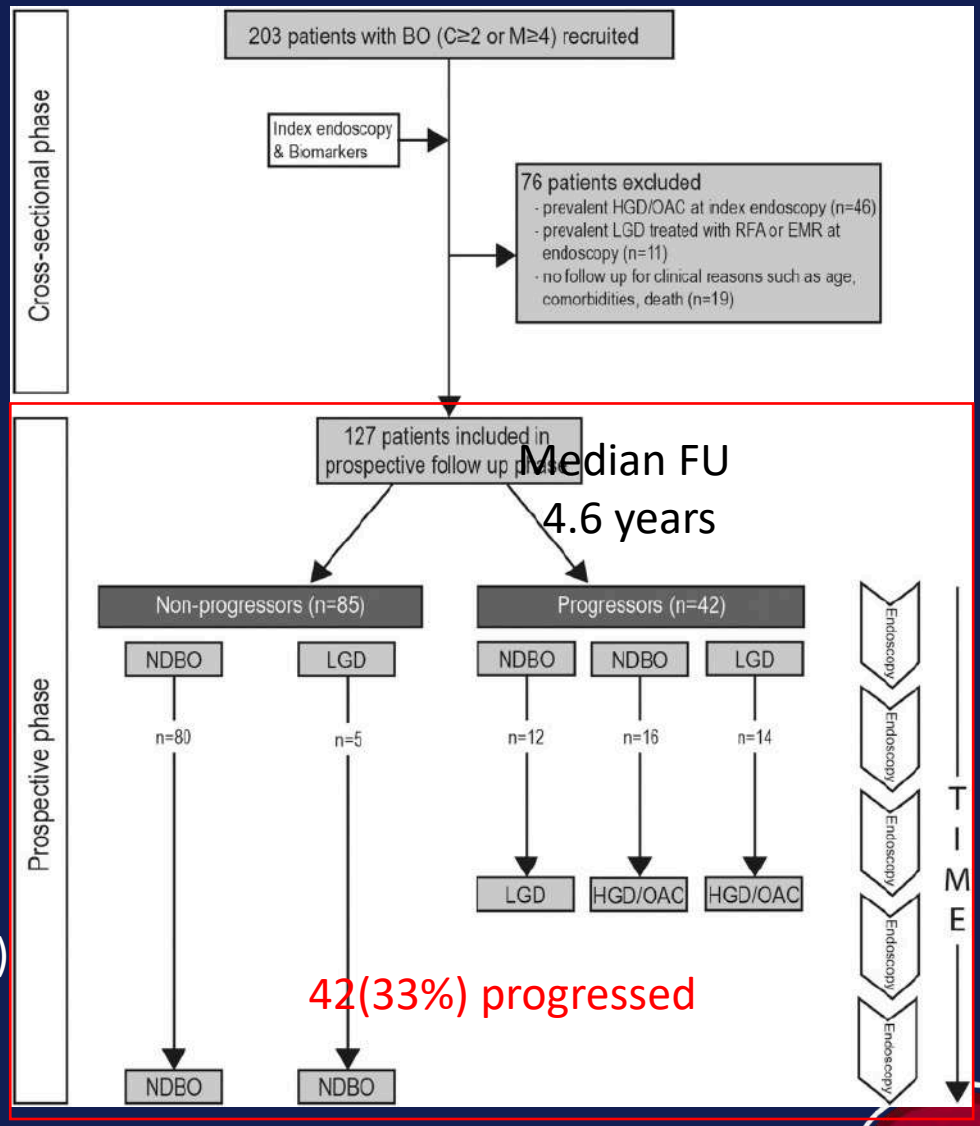
P53 + aneuploidy

Prospective multicenter cohort study
203 BE patients tested at index EGD for 9 biomarkers

Gene regulation
- p53 IHC in formalin-fixed slides
- CDKN2A (p16)
- RUNX3
- cyclin A expression

Epigenetic
HPP1 hypermethylation

Chromosomal
- Aneuploidy (fresh Bx, flow cytometry)
- Tetraploidy
- 9p, 1p LOH



COURTESY OF CASTLE BIOSCIENCES

Hadjinicolaou..Fitzgerald, Di Pietro EbioMedicine 2020

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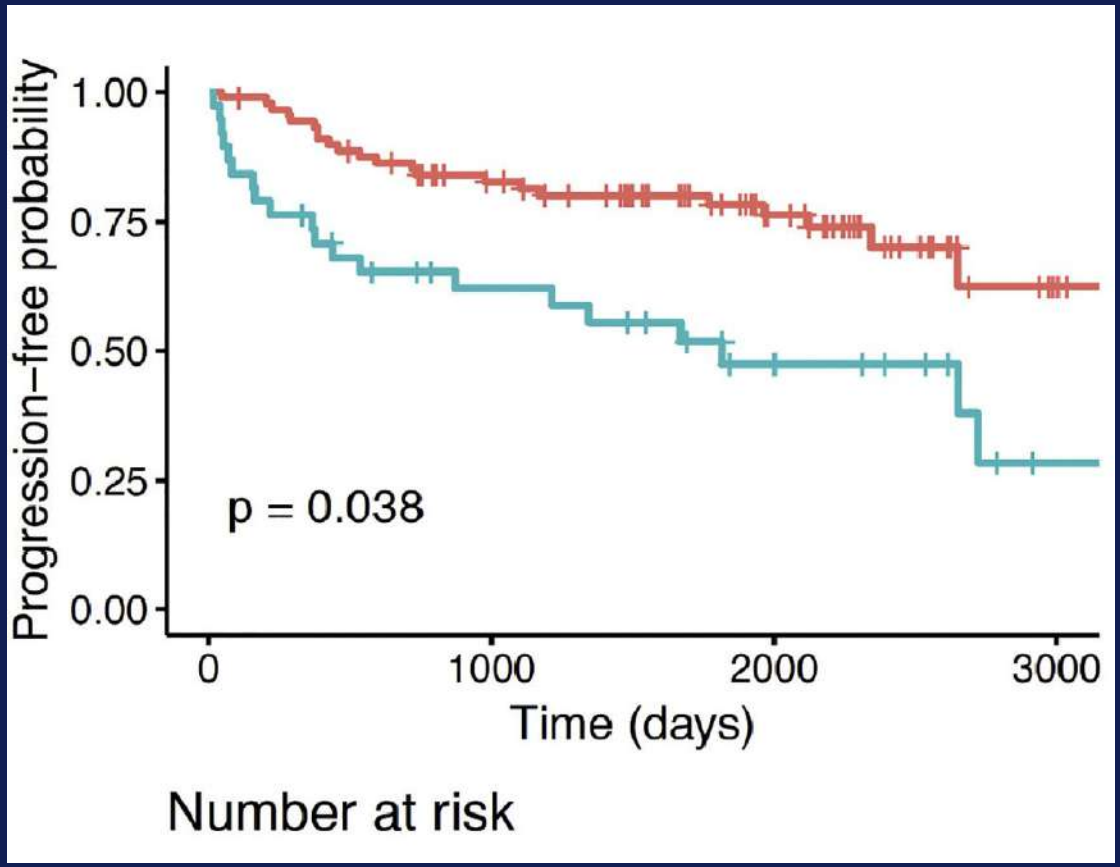
P53 overexpression at baseline predicted short term progression within 12 months (prevalent missed dysplasia)



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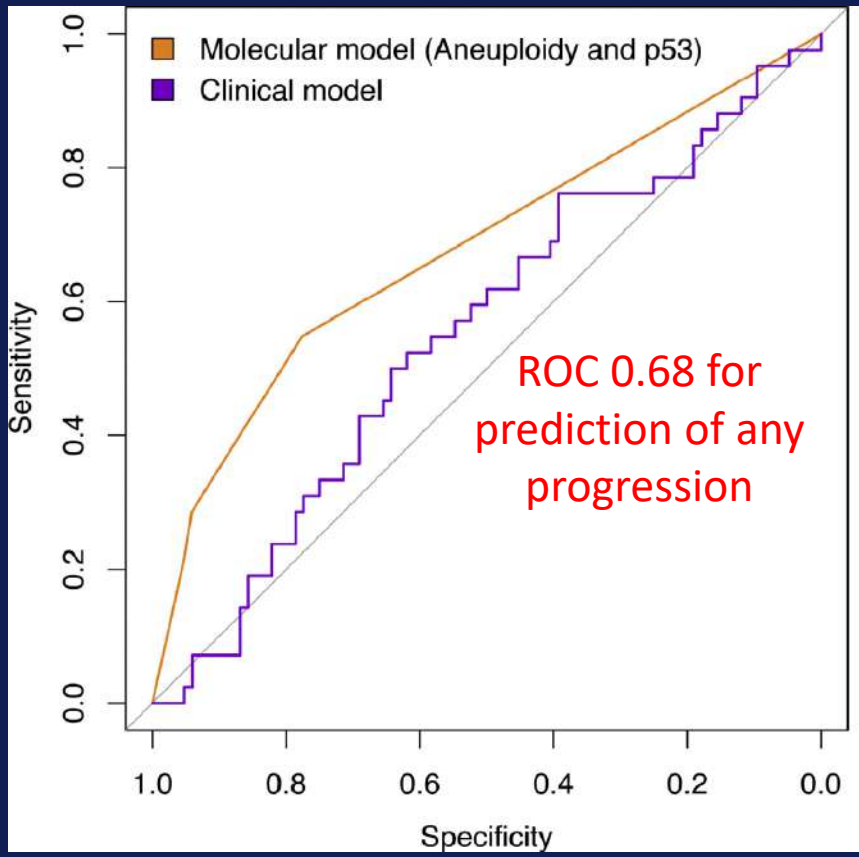
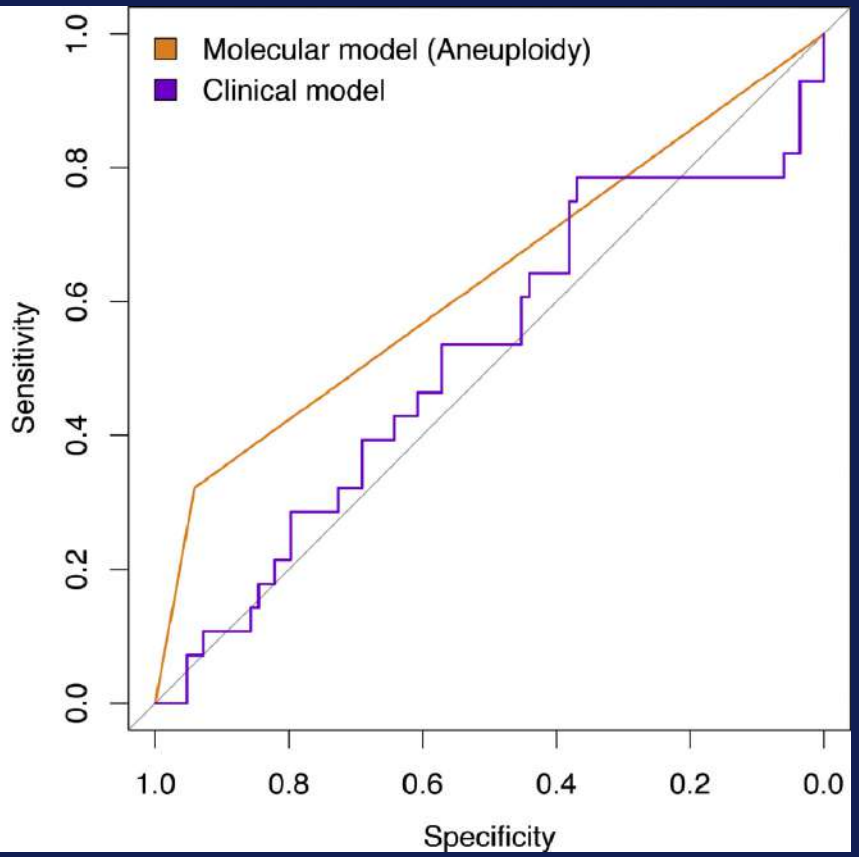
Molecular marker model (aneuploidy +/- p53) beat clinical risk factors (age, BE length





COURTESY OF CASTLE BIOSCIENCES

Hadjinicolaou..Fitzgerald, Di Pietro EbioMedicine 2020

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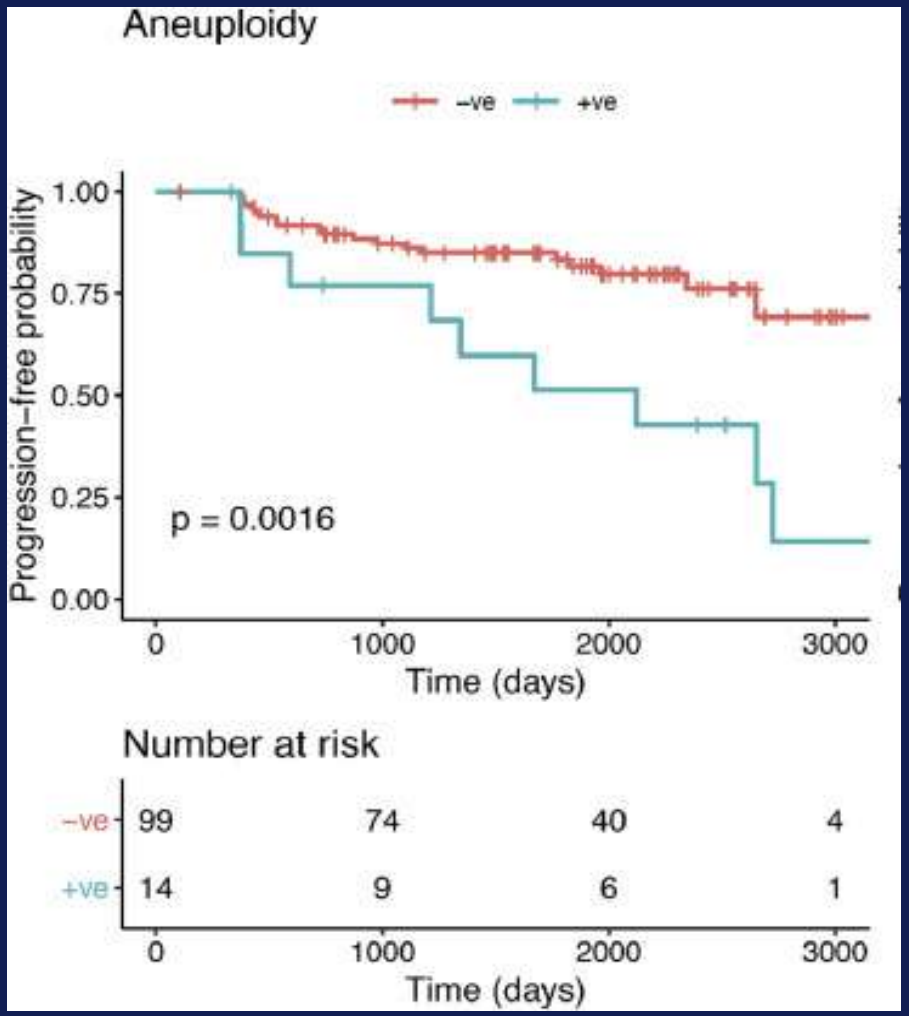
Aneuploidy was only predictor of progression of BE ND to HGD/ECA



- 6.6 fold increased risk if (+)
- Limitations
  - Sensitivity low 32% (CI 16-52%) – positive test more actionable (early ablation)
  - Fresh biopsies, flow cytometry not widely available; alternative image cytometry on FFPE
  - Tissue sampling critical, targeted biopsy with AFI, NBI, AA chromoendoscopy, or brushings

Hadjinicolaou..Fitzgerald, Di Pietro EbioMedicine 2020

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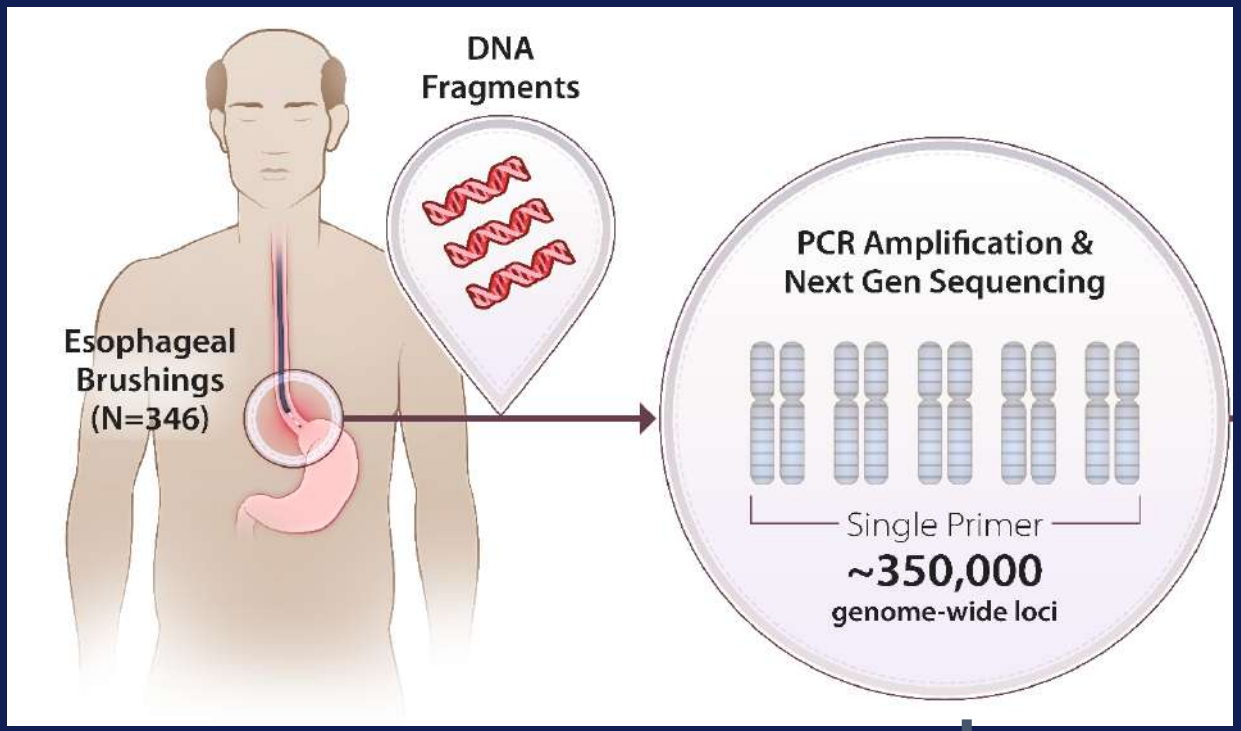
Global Aneuploidy Score (GAS)



Minimal DNA, may be applicable to non-endoscopic screening

Integrates Chromosome Arms using supervised machine learning into a Global Aneuploidy Score (GAS)

Douville, Gastroenterology, in press

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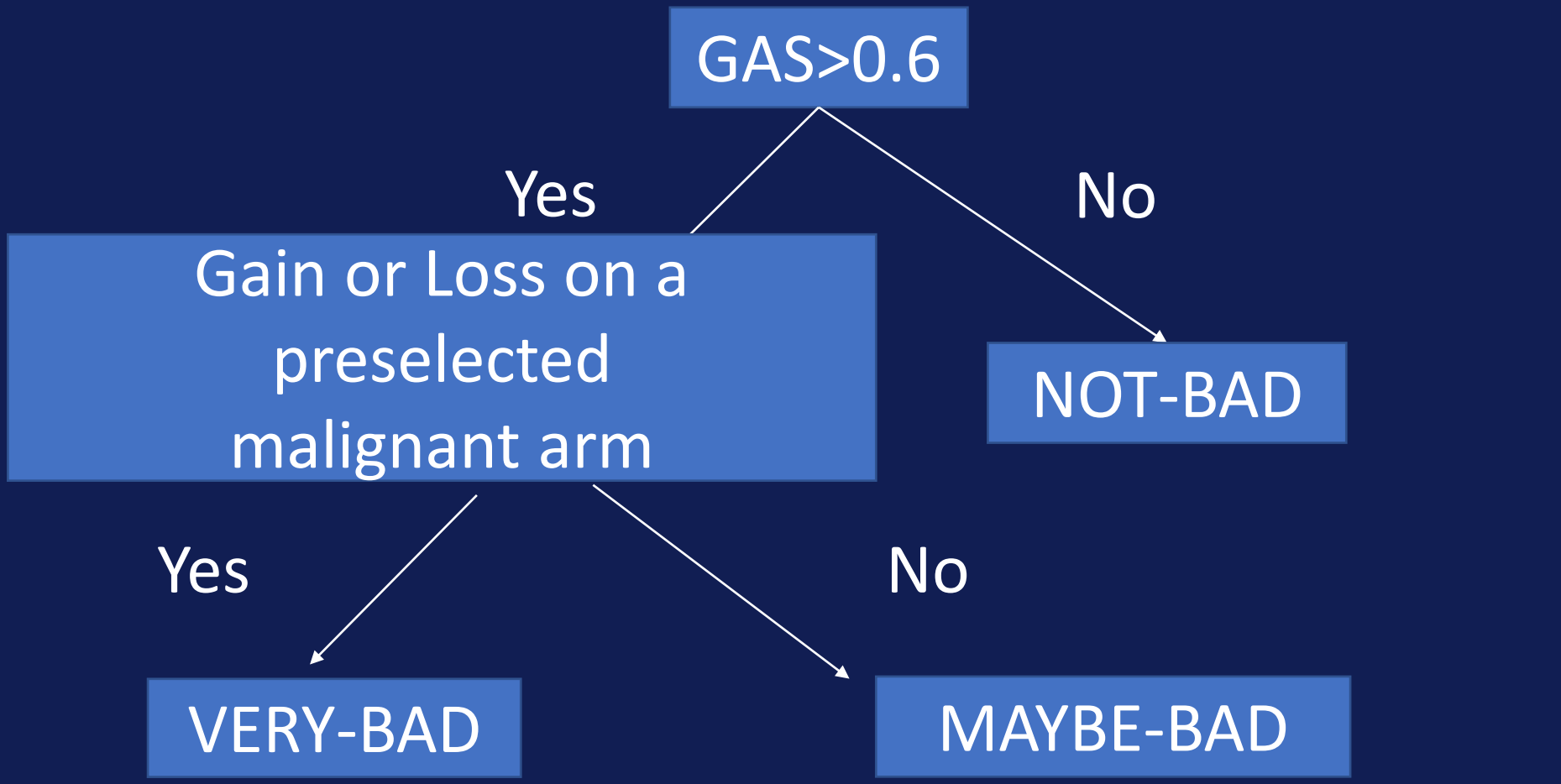
Barrett's Aneuploidy Decision (BAD) Classifier



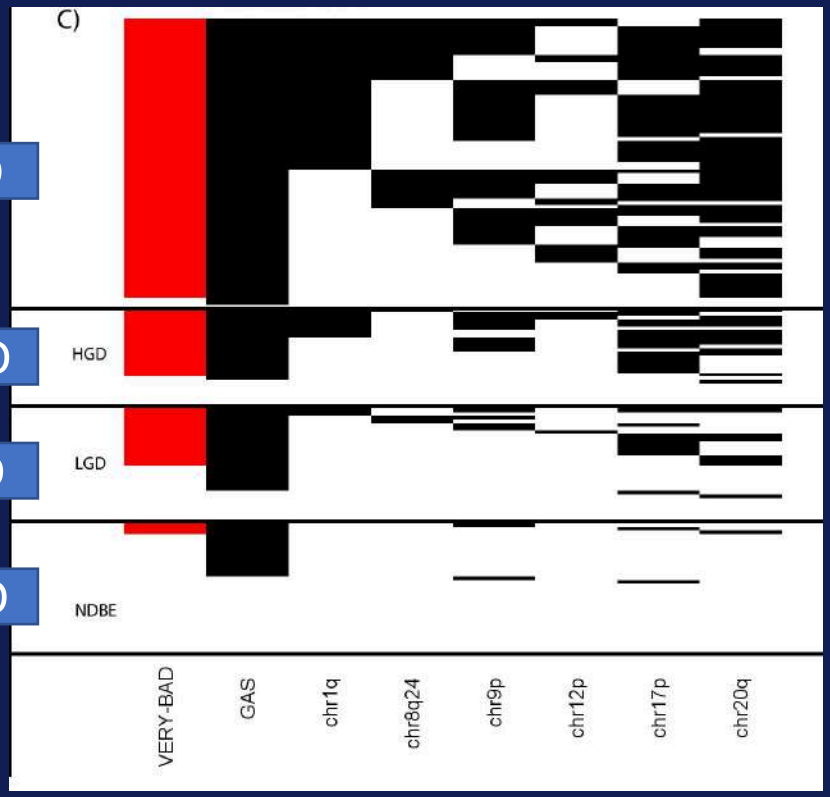
Does BAD classifier predict progression?

EAC: 96% VERY-BAD

HGD: 68% VERY-BAD

LGD: 50% VERY-BAD

NDBE: 7% VERY-BAD



2/4 progressed

0/56 NOT BAD/mayBAD did not progress

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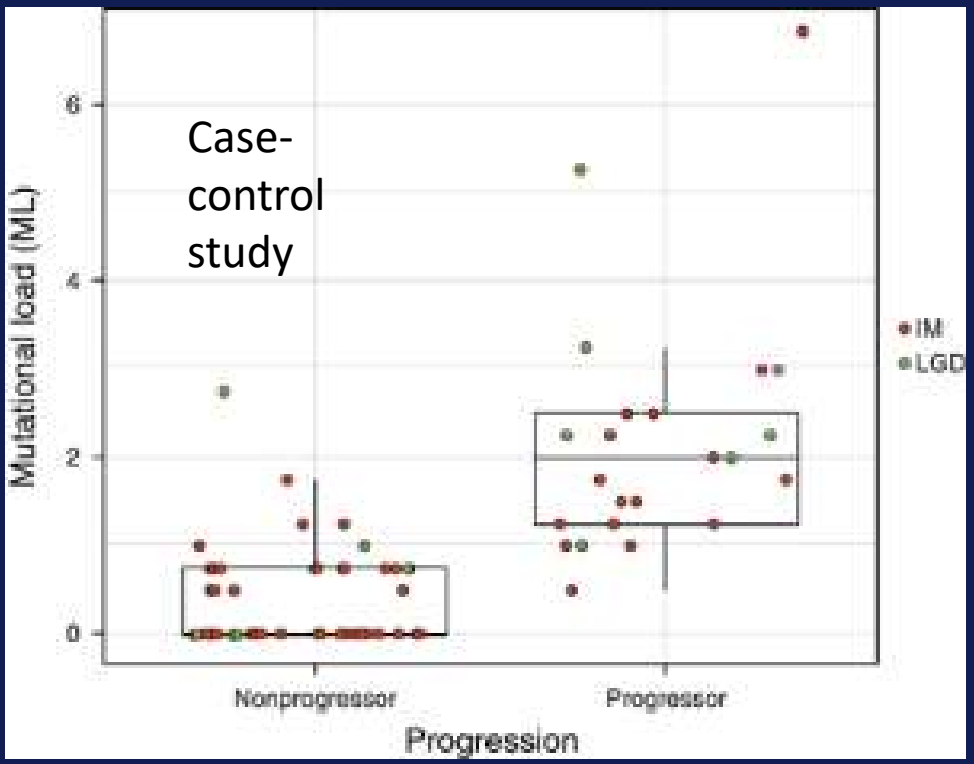
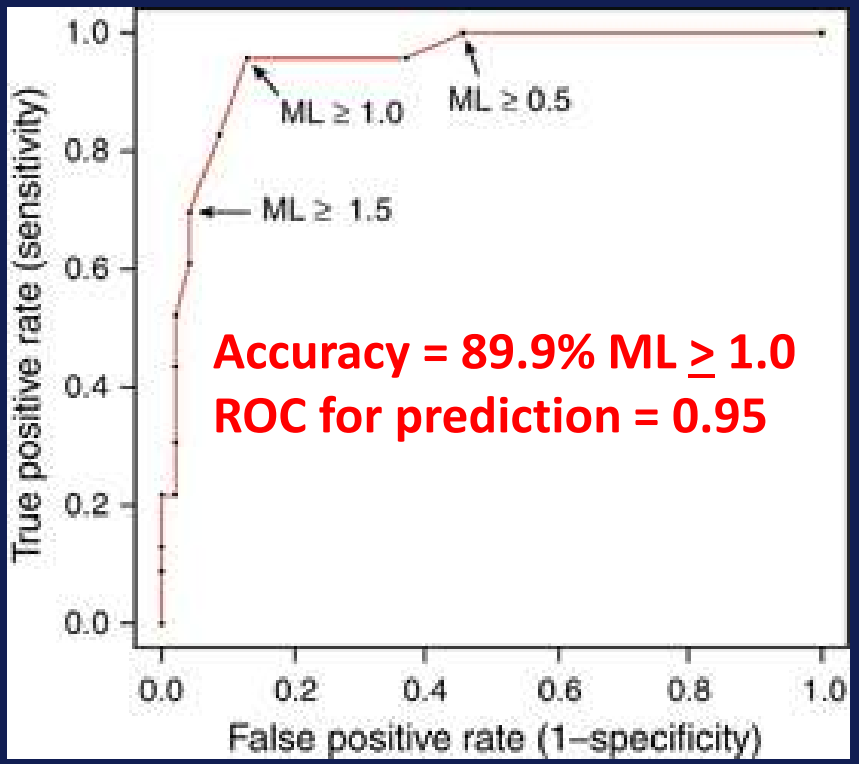
Mutational Load (BarreGEN)

Commercially available test measures mutational load in BE biopsy specimens microdissected for worrisome features of neoplasia





Mutational load (chromosome number change and LOH) is an index of genomic instability (score 0-10)

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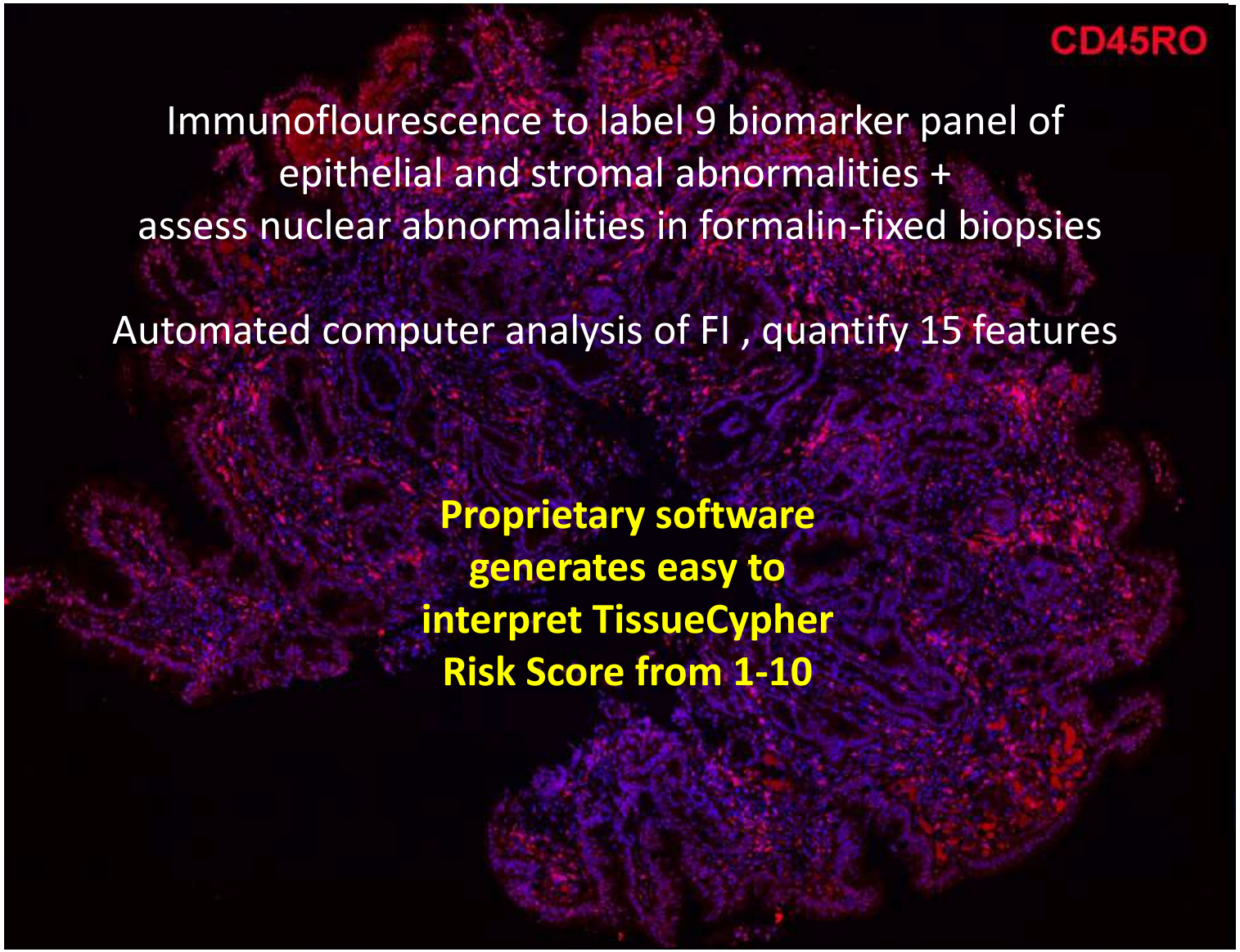
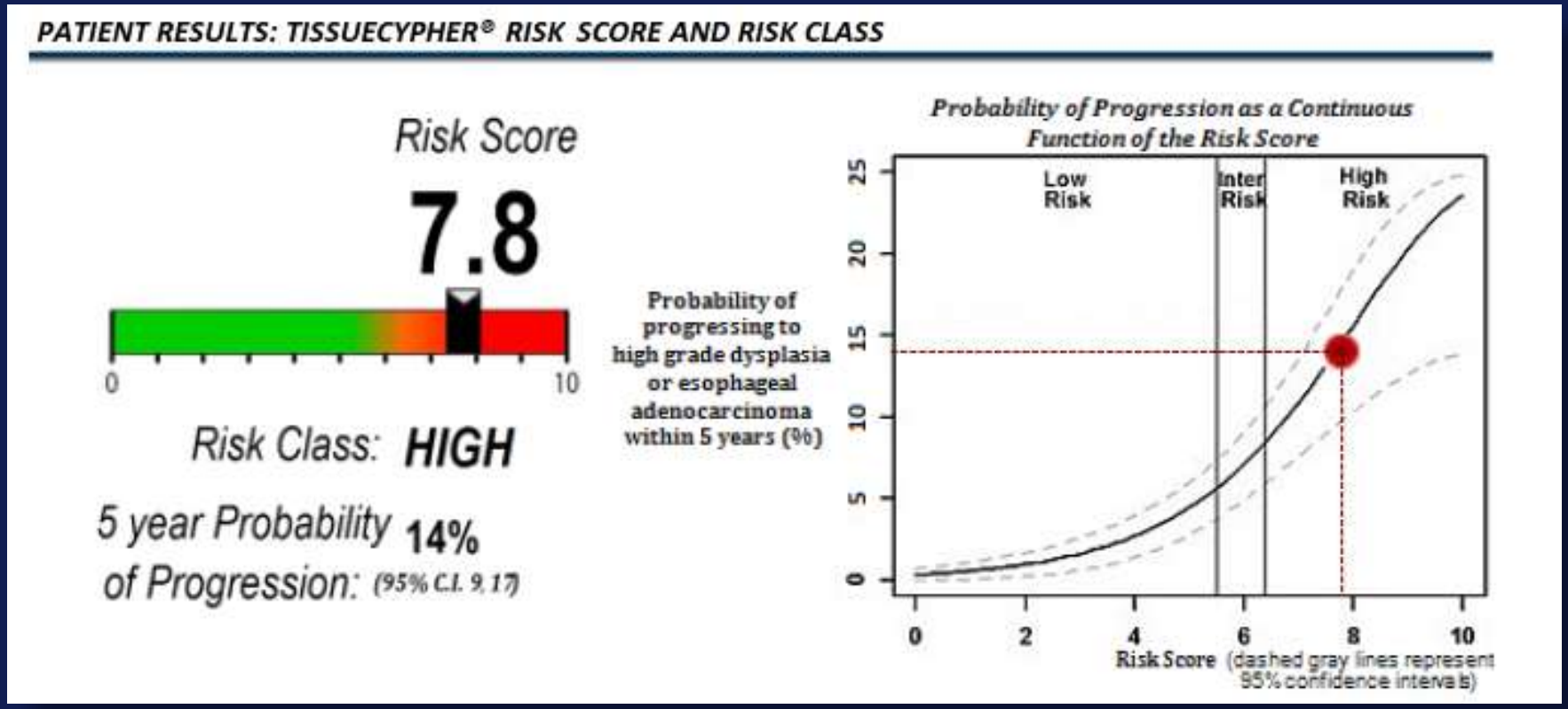
TissueCypher:
A Tissue Systems Pathology Assay



Risk Score Predicts 5-Year Progression Probability



TissueCypher Clinical Validation

Study	n	Key Findings
2016	366 (287 non-progressors, 79 incident progressors)	• 1st validation study: predicts incident progression from ND/IND/LGD to HGD/EAC. • Outperformed predictions based on expert GI pathology, segment length, age, sex, or p53
2017	30 (30 patients with prevalent HGD/EAC)	• 2nd validation study ; diagnoses prevalent HGD/EAC in patients with expert GI pathologist diagnosis of ND/IND/LGD (field effect)
2020	268 (210 non-progressors, 58 incident progressors)	• 3rd validation study; predicted incident progression from ND/IND/LGD to HGD/EAC (2 U.S. centers) • At 5 yr: Sens 29%, Spec 86%, PPV 23%, NPV 96%

Critchley-Thorne, et al. Cancer Epidemiology Biomarkers and Prevention, 2016
Critchley-Thorne et al. Epidemiology Biomarkers and Prevention, 2017
Davison et al. American Journal of Gastroenterology, 2020

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TissueCypher Predicts Progression of Non-Dysplastic BE

- 76 patients (38 incident progressors, 38 non-progressors, from ReBus registry)
- 4th validation study, predicted incident progression from ND to HGD/EAC
- Identified a subset of patients with ND BE who progress at a higher rate than patients with expert GI pathologist diagnosis of LGD
- Increased sensitivity up to 69% by including tissue from multiple levels w/o affecting specificity (95%)

Frei et al.. Clinical & Translational Gastro, 2020

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TissueCypher Diagnoses Prevalent Neoplasia and Predicts Progression of LGD

- 155 patients (34 progressor, 121 non-progressors, screening cohort for SURF RCT)
- 5th validation study; predicted incident progression and prevalent HGD/EAC in patients with community-based LGD
- Detected 50%-56% of progressors that were downstaged from LGD to ND BE by expert GI pathologists (using H&E & p53 IHC)

Total 882 unique patients:

231 progressors & 651 non-progressors

Frei NF, et al. Amer Journal of Gastro, Nov 2020

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TissueCypher Diagnoses Prevalent Neoplasia and Predicts Progression

Study	n	Key Findings
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Total 882 unique patients:
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TissueCypher
Clinical Utility, Impact on Decision-Making

- 60 patients (patients (ND n = 18; IND n=25; LGD n=17) Geisinger prospective cohort

Management Plan Impacted 55%

Upstage risk in 22%

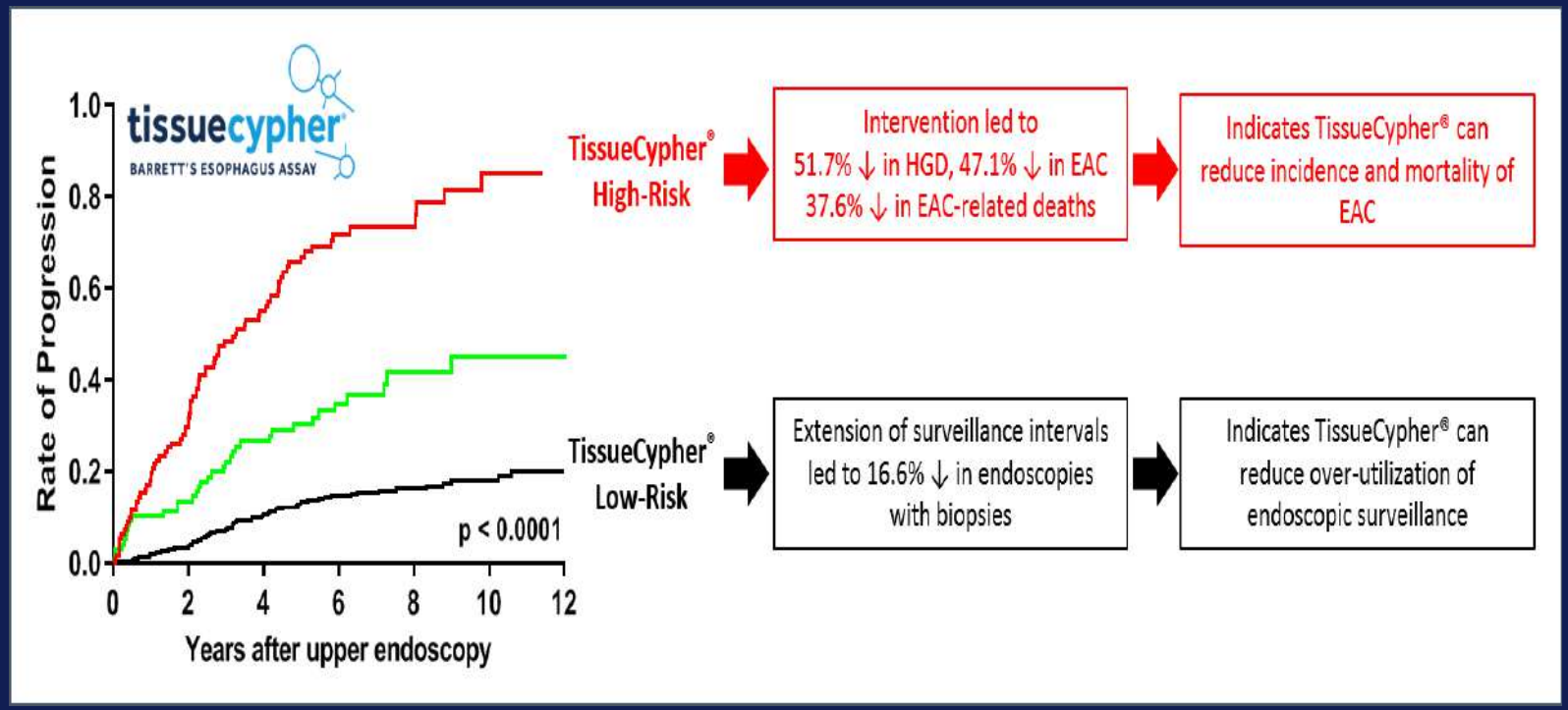
EET or closer surveillance

Downstage risk in 33%

Surveillance

Diehl DL et al., Endoscopy International Open, 2021

TissueCypher Cost-Effectiveness



Markov decision modeling: compare cost and QALYs from a U.S. health insurer perspective, care in an integrated health system (Geisinger)

- ICER was $52,483/QALY (base-case model results for 5 year period)
- CE when used to downstage low-risk patients and upstage high-risk

Hao et al, ClinicoEcon Outcomes Research, 2019

Conclusions

- Risk stratification can help us
  - Distinguish progressors from non-progressors, select high risk patients for EET
  - Lengthen surveillance for low risk BE, minimize over-treatment
- Dysplasia grade is still most valuable predictor
- Biomarkers can identify high risk HGD/CA BE patients - ready for prime time

Thank you!