Know your patient's individual risk of progression to esophageal cancer

TissueCypher
Barrett's Esophagus

The FIRST and ONLY precision medicine test that:

- Predicts future development of esophageal cancer in patients with Barrett's esophagus (BE).
- Is an INDEPENDENT risk predictor from tissue histology and other clinical risk factors.

TissueCypher can transform patient management by enabling upstaging or downstaging based on individual patient risk.

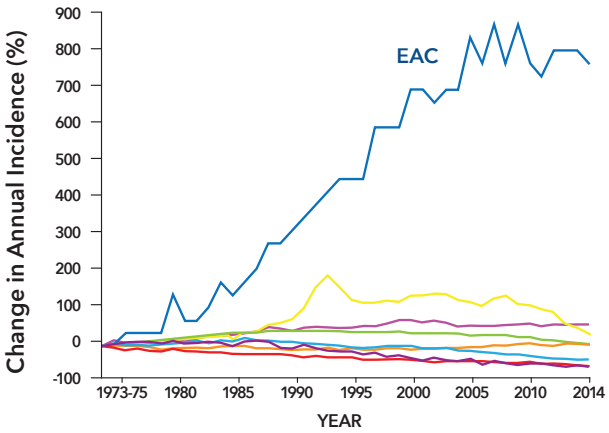
CASTLE BIOSCIENCES

TissueCypher.com

Identifying High-Risk BE Patients to Prevent Esophageal Cancer Is Clinically Important

- Esophageal adenocarcinoma (EAC) is increasing at a rate faster than any other cancer
- BE is the only known precursor to EAC
- BE can be treated to prevent EAC
- **The challenge is finding high-risk BE patients.**

Change in Annual Incidence of Esophageal Cancer vs. Other Solid Tumors[1]



Histopathologic Grade Alone Is Insufficient

Prognostic accuracy needs to be improved to avoid uncertainty and better inform patient management decisions

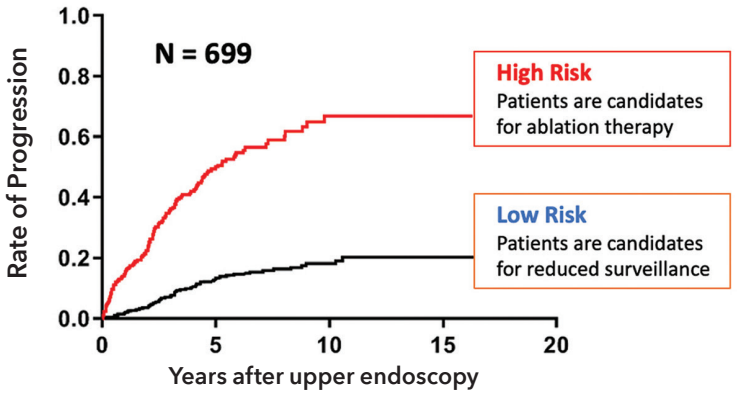
Histologic Diagnosis *~400,000 upper GI endoscopies/year*		Progressors in Each Category		Clinical Implication
High-grade Dysplasia (HGD) *16,000 patients/year; >10%/year progression*[2]	>	~37% of progressors	>	All treated with EET; EAC prevented
Low-grade Dysplasia (LGD) *13,000 patients/year; 1.7%/year*[3]	>	5.1% of progressors	>	Potentially overtreating 91% of LGD over five years
Indefinite for Dysplasia (IND) *23,000 patients/year; 1.5%/year*[4]	>	7.9% of progressors	>	1. Majority of progressors are undetected (missed) by the standard of care 2. Opportunity to reduce anxiety in a large number of very low-risk patients
Non-dysplastic (ND or NDBE) *348,000 patients/year; 0.26-0.63%/year*[5]	>	Up to ~50% of progressors		

- Most (~58%) progressor patients come from the **"low-risk"** grades
- **High-risk NDBE** patients have high chance of survival if caught early (pre-dysplastic) and treated with ablation therapy, yet are **missed by traditional histopathologic risk assessment**
- **Low-risk** patients undergo "recurrent indefinite" surveillance procedures that are uncomfortable and possibly unnecessary

TissueCypher Extracts Clinically Actionable Risk Information from Esophageal Biopsies

TissueCypher identifies patients who progress at a rate 3-5x the standard of care — AND — patients at a very low-risk of progression[6-11]

TissueCypher Performance from Five Independent Validation Studies



TissueCypher provides:

- Independent prognostic information not available via other clinical means
- High negative predictive value (NPV) identifies patients at very low risk of progression to HGD/EAC
- Identification of progressor patients missed by the current standard of care
- Prognostic risk assessment using standard esophageal pinch biopsies with no extra work for the endoscopist

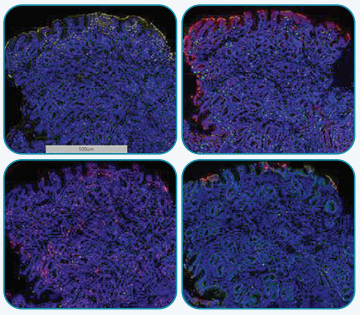
Two ND patients nearly identical by pathology and clinical factors:

CLINICAL CHALLENGE:
Similar clinical risk factors and pathology based on traditional biopsy report

Using the esophageal pinch biopsy tissue, **TissueCypher** extracts high dimensional spatial biology data transformed by AI-driven algorithm

RESULT:
Clinically actionable risk information to enable risk-aligned patient management decisions

NDBE 4cm
Hiatal Hernia | No Lesions

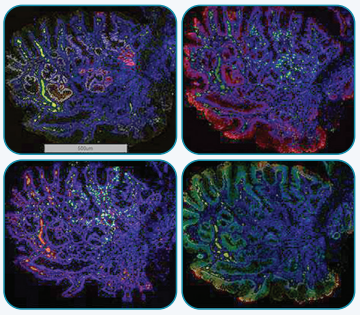


TissueCypher Score/Risk Class
3.6/Low Risk

Five-year Progression Risk
2.2%

Outcome
Progression-free for 6.7 years

NDBE 3cm
Hiatal Hernia | No Lesions



TissueCypher Score/Risk Class
9.6/High Risk

Five-year Progression Risk
58%

Outcome
Progressed to HGD in 2.7 years following baseline

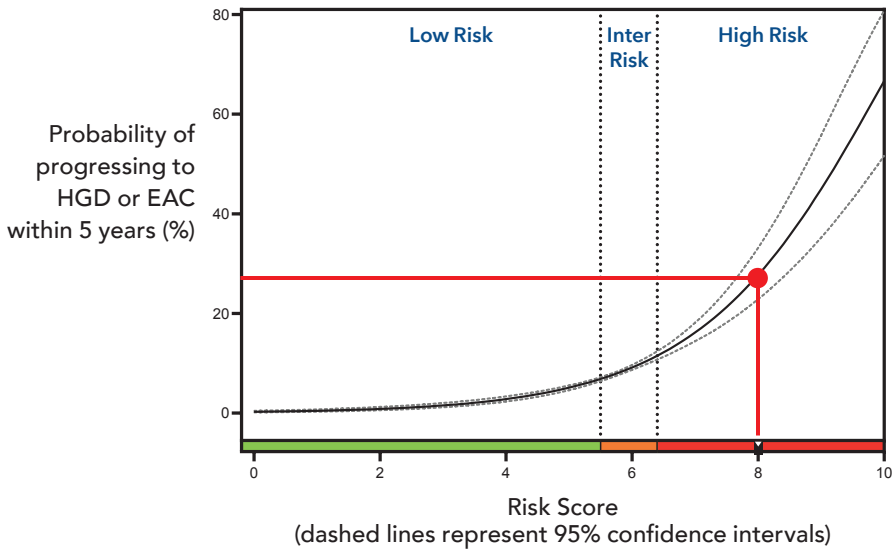
Easy-to-Interpret Results Aid in Your Care Pathway Decisions

RISK SCORE:
8.0

RISK CLASS:
HIGH

5-YEAR PROBABILITY OF PROGRESSION:
28% *(95% C.I. 23, 33)*

Probability of Progression as a Continuous Function of the Risk Score



TissueCypher is validated for use in patients with confirmed BE graded NDBE, IND, or LGD; and provides five-year individual risk of progression to HGD or EAC.

TissueCypher has extensive evidence supporting performance:

- 5 clinical validation studies[6-10]
- Mayo Clinic pooled analysis of international, multicenter studies[12]
- Clinical use study demonstrating 55% change in management[13]

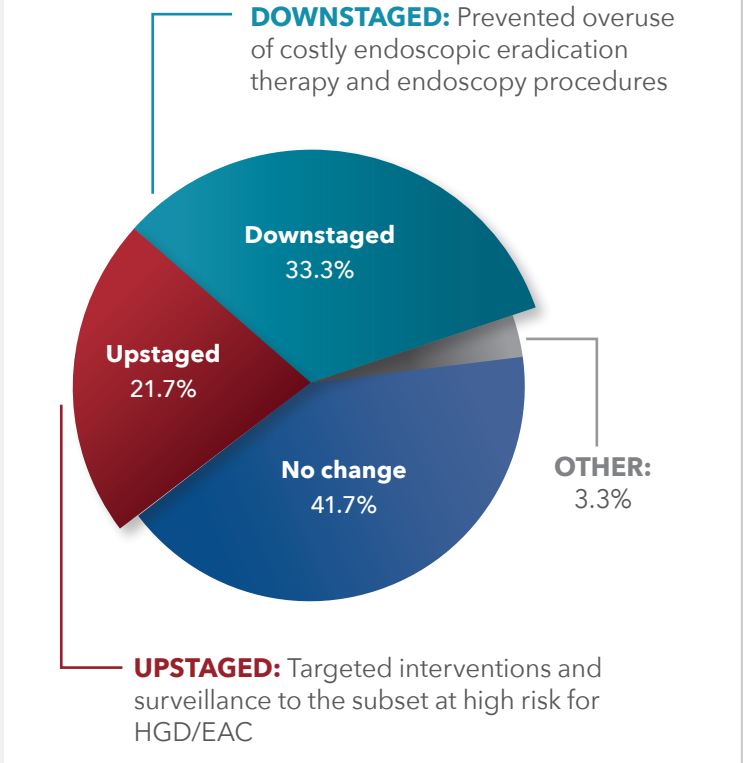
TissueCypher provides clinically actionable information independent of other clinical risk factors, enabling optimization of treatment and surveillance approaches.

Integrate TissueCypher into Your Practice

	NDBE	IND	LGD
Possible Approach HIGH/INT Risk Class ↑ TissueCypher ▸ Barrett's Esophagus	Rule out prevalent HGD/EAC and consider EET or surveillance in 1 year	Rule out prevalent HGD/EAC and consider EET and PPIs as needed	
Current Clinical Guidelines[14]	3 years if segment length ≥3 cm; 5 years if segment length <3 cm	3-6-month surveillance following PPI; then every 12 months	EET or 6-12-month surveillance
Possible Approach TissueCypher ▸ Barrett's Esophagus ↓ LOW Risk Class	Consider surveillance in 3 to 5 years	Consider surveillance in 12 months and PPIs as needed	

Clinical Utility

TissueCypher can change management decisions up to 55% of the time[10]



Benefits of Adding TissueCypher

Informs Key Clinical Management Decisions

- Identifies high-risk BE patients who will progress at a 3-5x higher rate than standard of care
- Identifies low-risk BE patients who are unlikely to progress
- Allows upstaging/downstaging based on individual patient risk

Extensively Supported by Published Data

- 5 clinical validation studies[6-10]
- Mayo Clinic pooled analysis of international, multicenter studies[12]
- Clinical use study demonstrating 55% change in management[13]

Easily Integrates into Your Practice

- Order using requisition forms available at TissueCypher.com or order online via Castle's secure portal
- Uses standard biopsies or EMR already obtained from surveillance endoscopies
- Castle coordinates specimen collection and provides pre-paid shipping
- Castle offers patient-focused financial assistance and insurance billing services
  - Castle will submit and track insurance claims on your patients' behalf throughout the billing process, including appeals if necessary
  - Castle offers an industry-leading financial assistance program for both insured and uninsured patients

Order a TissueCypher test

- Test order forms, online ordering, and patient reports for all Castle tests are available at **Portal.CastleBiosciences.com**
- Results available approximately 14-18 days from sample receipt

REFERENCES 1. Hang T-VP et al. Poster presentation (P0265), ACG. October 2018. **2.** Rastogi A et al. *Gastrointest Endosc* 2008;67:394-8. **3.** Singh S et al. *Gastrointest Endosc* 2014;79(6):897-909.e4; quiz 983.e1, 983.e3. **4.** Krishnamoorthi R et al. *Gastrointest Endosc* 2020;91(1):3-10.e3. **5.** Wani S et al. *Clin Gastroenterol Hepatol* 2011;9(3):220-7; quiz e26. **6.** Critchley-Thorne RJ et al. *Cancer Epidemiol Biomarkers Prev* 2016;25(6):958-68. **7.** Critchley-Thorne RJ et al. *Cancer Epidemiol Biomarkers Prev* 2017;26(2):240-8. **8.** Davison JM et al. *Am J Gastroenterol* 2020;115:843-52. **9.** Frei NF et al. *Clin Transl Gastroenterol* 2020;11(10):e00244. **10.** Frei NF et al. *Am J Gastroenterol* 2020;116(4):675-82. **11.** Data on file, Castle Biosciences. **12.** Iyer PG et al. *Clin Gastroenterol Hepatol* 2022. **13.** Diehl DL et al. *Endosc Int Open* 2021;9(3):E348-E355. **14.** Shaheen NJ et al. *Am J Gastroenterol* 2022.

CASTLE BIOSCIENCES

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