TissueCypher
Barrett's Esophagus

It’s time to think BEyond dysplasia

Which of these **Barrett’s esophagus (BE)** patients are most likely to progress towards esophageal cancer?

What is the Barrett's Conundrum?

Safe and effective treatments can prevent esophageal cancer, **but clinicopathologic factors have limited ability** to identify patients that would benefit most from these curative treatments.

The primary goal of Barrett's esophagus (BE) management is the prevention of esophageal cancer. Endoscopic eradication therapy (EET) is recognized by guidelines for its ability to stop progression in high-risk patients who are diagnosed with dysplastic changes. **The challenge is that 89% of BE patients are non-dysplastic**[1], where reliance on clinicopathologic factors has minimal ability to predict a patient's individual risk of progression to esophageal adenocarcinoma (EAC).

50%

of annual progressors in surveillance were initially diagnosed as non-dysplastic BE[2]

25%

of progression events occur within 1 year of an endoscopy[3,4]

Prognostic testing to solve the Barrett's Conundrum

TissueCypher is the first precision **risk stratification test** designed to guide **better management** for Barrett's esophagus patients. The AI-driven risk classifier provides each patient with their **individualized 5-year risk of progression**.

THE POWER OF THE POSITIVE

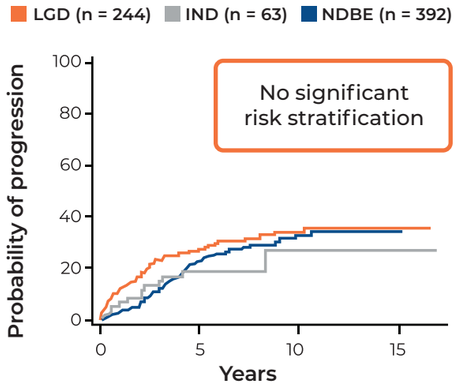
An intermediate- or high-risk TissueCypher score enables escalation of care including short-interval surveillance to detect EAC at early treatable stages or early use of endoscopic eradication therapy to prevent EAC.

THE VALUE OF NEGATIVE

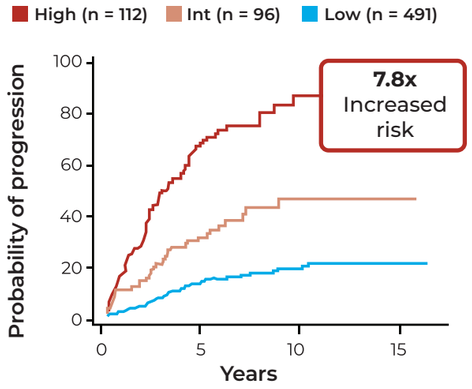
A low-risk TissueCypher score helps reduce over-treatment and supports extension of surveillance intervals to guideline recommendations.

Histologic grading **misses progressor patients** that TissueCypher can help identify

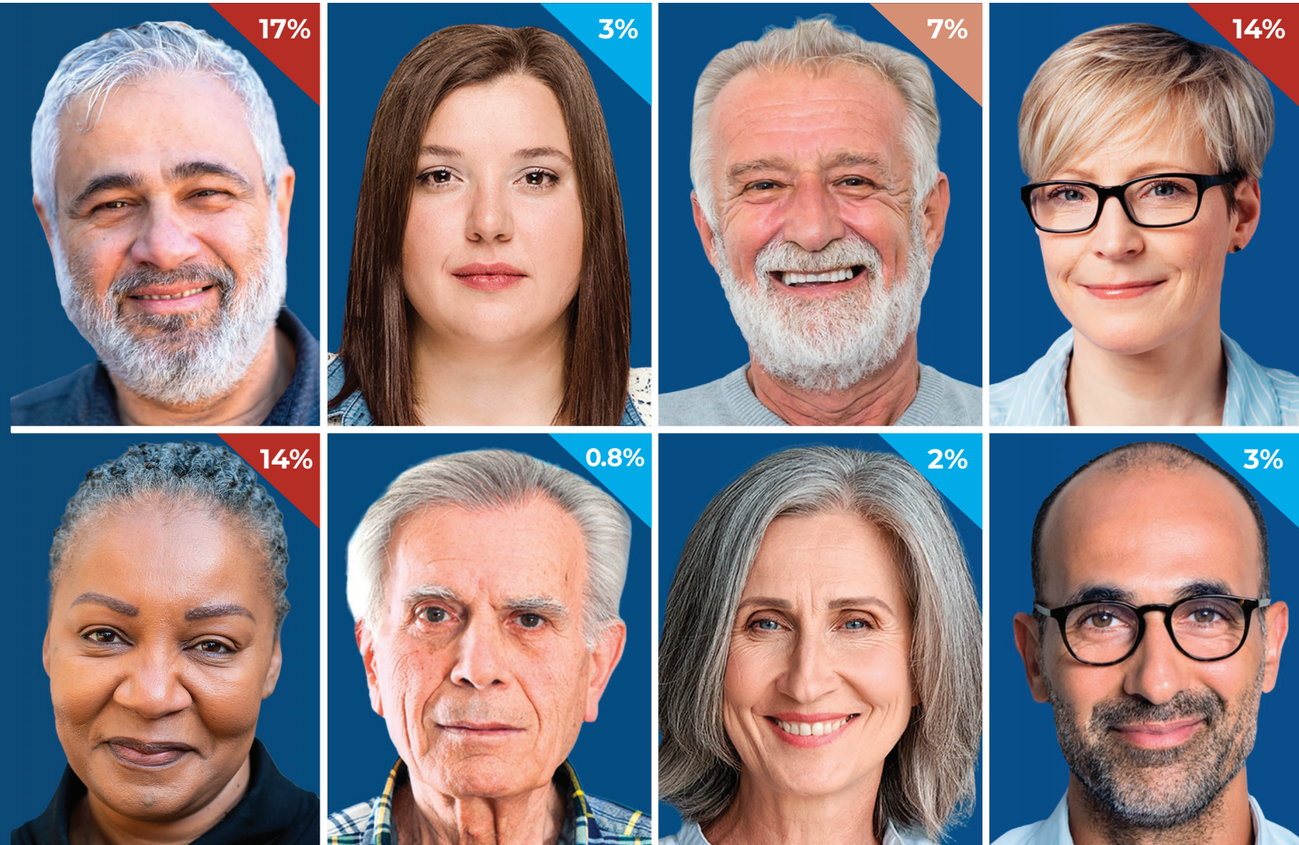
HISTOLOGIC GRADING



TISSUECYPHER RISK CLASS



Davison pooled analysis[5]: n=699 patients
150 incident progressors, 40 prevalent progressors, 509 non-progressors
LGD – Low-grade dysplasia; IND – Indefinite for dysplasia; NDBE – non-dysplastic Barrett's esophagus



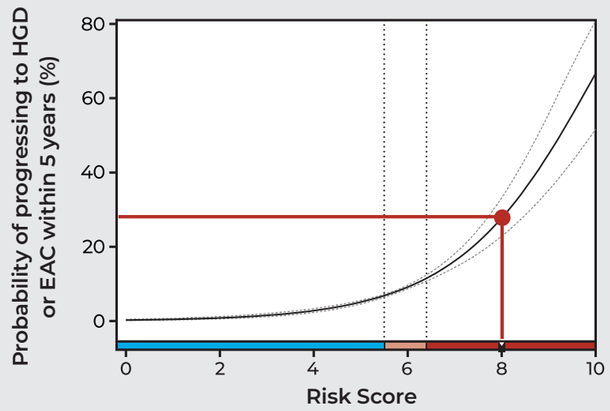
AI-powered spatialomics uncovers risk from multiple pathways of progression

Spatialomics is a powerful tool that simultaneously evaluates changes to tissue structure and protein expression and generates millions of data points of raw information. TissueCypher's AI-driven algorithm leverages nine protein biomarkers and seven cellular structures to extract 15 features that have been shown to be relevant in predicting future progression of Barrett's esophagus to high-grade dysplasia (HGD) or esophageal cancer.

The first and only independent predictor of BE progression

TissueCypher results provide an actionable risk score that is associated with a patient's 5-year risk of progression. **This score was derived from training with one of the largest sets of BE progressor patients ever assembled.** An analysis performed by researchers at Mayo Clinic confirmed that TissueCypher outperforms clinical and pathologic risk factors in identifying patients at high risk of progression[6].

TISSUECYPHER RISK CURVE



The **risk classification** groups patients based on their risk of progression.

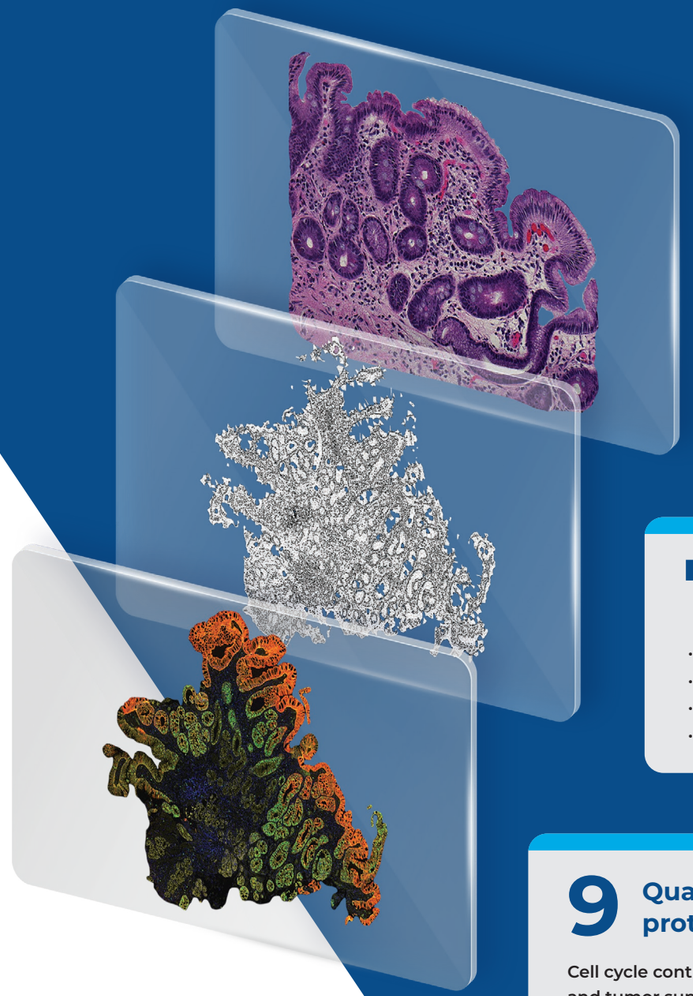
- HIGH RISK
- INTERMEDIATE RISK
- LOW RISK

The **risk score** is based on a scale from 0-10. The lower the number, the lower the risk of progression.

0.0-10.0

A **5-year probability of progression** is associated with the patient's risk score.

0.20-67%



1 Esophageal pinch biopsy

Standard FFPE tissue block or slides diagnosed with Barrett's esophagus (NDBE, IND, LGD)

7 Characterized cellular structures

- Cells
- Stroma
- Nuclei
- Cytoplasm
- Metaplastic epithelium
- Epithelial nuclei
- Epithelium

9 Quantified protein biomarkers

Cell cycle control and tumor suppression
p53, p16, AMACR

Angiogenesis and memory lymphocyte infiltration
HIF1alpha, CD45RO

Cancer growth and cell transformation
HER-2, CK20

Immune and inflammation markers
CD68, COX2

AI-DRIVEN RISK CLASSIFIER

15 Spatialomic features

Spatialomic features are quantitative data points that measure biomarkers in the context of cellular and tissue architecture. TissueCypher's 15 features have been validated as significant in predicting progression to HGD or EAC.

Extensively studied, clinically actionable

TissueCypher has been validated for performance and clinical utility in **14+ peer-reviewed publications** conducted on one of the largest sets of BE progressor patients ever assembled. It consistently **outperforms clinical and pathologic risk factors** in predicting progression and is designated as an Advanced Diagnostic Laboratory Test (ADLT) by Medicare.

View all publications

PUBLISHED TISSUECYPHER HIGHLIGHTS

NDBE PATIENTS

scoring **high-risk** are **18x more likely**[6] to progress than similar patients with low-risk scores

FEMALE PATIENTS

scoring **high-risk** are **17x more likely**[5] to progress than similar patients with low-risk scores

SHORT SEGMENT PATIENTS

scoring **high-risk** are **9x more likely**[5] to progress than similar patients with low-risk scores

PREVALENT PROGRESSORS

Patients harboring prevalent disease are **46x more likely**[7] to return a **high-risk** score*

*When comparing TissueCypher high-risk scores to TissueCypher low-risk scores

2022 AGA Clinical Practice Update[8]

Best Practice Advice Statement #9: Tissue systems pathology-based prediction assay [TissueCypher] may be utilized for risk-stratification of patients with non-dysplastic BE.

Objective results to escalate and de-escalate care

TissueCypher is an **independent risk factor** that helps guide management decisions for patients with a Barrett's esophagus diagnosis of non-dysplastic (NDBE), indefinite for dysplasia (IND), or low-grade dysplasia (LGD).

High/Intermediate Risk: Escalate

NDBE + High/Int Risk TissueCypher
Rule out prevalent HGD/EAC and consider EET or surveillance in 1 year

IND + High/Int Risk TissueCypher
Rule out prevalent HGD/EAC and consider EET

LGD + High/Int Risk TissueCypher
Consider EET

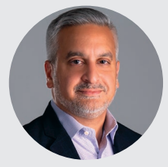
"This is my lucky penny; this is my needle in the haystack. [This patient] is one that I can actually do something about.

Dr. Harshit Khara, Director of Endoscopy at Geisinger Medical Center, speaking of a 35-year-old whose TissueCypher results came back high-risk.

Low Risk: De-escalate

NDBE + Low Risk TissueCypher
Consider surveillance in 3 to 5 years

IND/LGD + Low Risk TissueCypher
Consider surveillance in 12 months



"[TissueCypher] allowed us to reassure a patient who is very anxious... that he had a low risk of progression and surveillance was an appropriate option.

Dr. Jay Yepuri, Partner & Executive Committee Member at Digestive Health Associates of Texas, speaking of a 52-year-old who he was able to de-escalate to guideline-based surveillance.

Watch these physicians and others talk about real cases where TissueCypher influenced patient management

TissueCypher
Barrett's Esophagus

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The established leader in prognostic testing for Barrett's esophagus

8,000+
Patients studied including independent validation

14+
Peer-reviewed, published studies

30,000+
Patients with TissueCypher results from more than 2,000+ clinicians*

Medicare+
Covered by Medicare and multiple private insurers with an industry-leading patient assistance program

*Castle Data as of January 2025

Castle Biosciences is committed to providing high-quality molecular testing to all patients

We are committed to providing high-quality molecular testing to all patients by working with insurance providers, including Medicare, Medicaid, commercial insurers, and Veterans Affairs (VA) to secure payment coverage for our testing. We manage claims on your patients' behalf and our patient assistance program keeps the test from being cost-prohibitive for all patients.

References:

1) Merative™ MarketScan® Databases. 2023; **2)** Wani S, et al. Clin Gastroenterol Hepatol. 2011; Overholt BF, et al. Gastrointest Endosc. 2005; **3)** Visrodia K, et al. Gastroenterology. 2016; **4)** Wani S, et al. Gastroenterology. 2023; **5)** Davison JM, et al. Clin & Transl Gastroenterol. 2023; **6)** Iyer PG, et al. Clin Gastroenterol Hepatol. 2022; **7)** Critchley-Thorne et al. Cancer Epidemiol Biomarkers Prev 2017; **8)** Muthusamy VR, et al. Clin Gastroenterol Hepatol. 2022.

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