CASTLE BIOSCIENCES

TissueCypher
Barrett's Esophagus

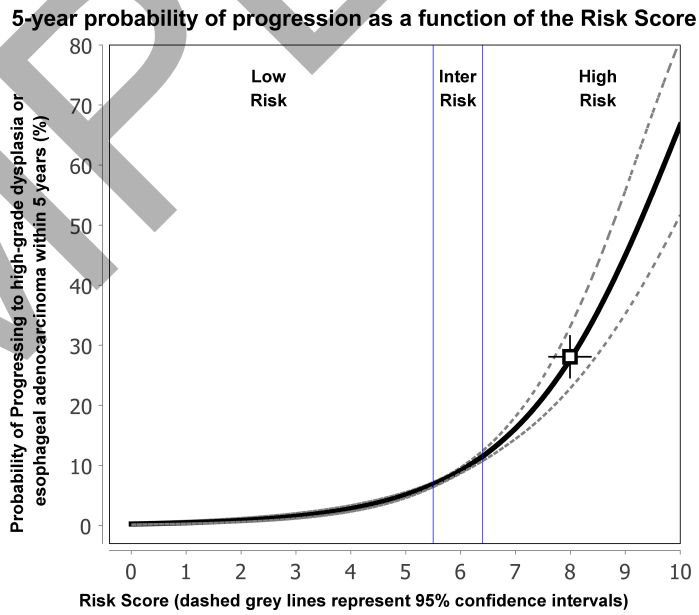
FINAL REPORT

Patient: John Doe
Sex: Male
DOB: 01/01/0001
Client: Shown Here
Provider: Shown Here

Specimen ID: Shown Here
Collected: Date
Received: Date
Reported: Date
Specimen Type: Esophageal Pinch Biopsy

TISSUECYPHER® RISK CLASS AND RISK SCORE

Risk Class*	**HIGH**
Risk Score	**8.0**
5-year Probability of Progression**	**28%** (95% C.I. 23,33)



* If multiple specimens were submitted for testing, the reported result is based on the highest scoring specimen.
** For reference, population-based studies and systematic reviews and meta-analyses have estimated that untreated patients with NDBE, IND and LGD have 5-year rates of progression to a combined endpoint of HGD/EAC of 3.2%, 7.5% and 8.5%, respectively.[1-3]

TISSUECYPHER BARRETT'S ESOPHAGUS TEST DESCRIPTION

The test uses whole slide digital images from formalin-fixed paraffin-embedded (FFPE) tissue sections from endoscopic biopsy specimens. Using a proprietary artificial intelligence-driven quantitative algorithm, a risk score for progression to high grade dysplasia or esophageal adenocarcinoma is generated from the image analysis results. The risk score ranges from 0-10, with 0 indicating lowest risk and 10 indicating highest risk, and patients are classified as low, intermediate or high risk for progression to high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) within five years.

The TissueCypher Barrett's Esophagus test is a multi-analyte assay with algorithmic analysis that uses automated image analysis to objectively quantify the expression and localization of nine biomarkers (p16, p53, alpha-methylacylCoA racemase [AMACR], HER2/neu, Cytokeratin-20 [K20], Cyclooxygenase-2 [COX-2], CD68, Hypoxia-inducible factor 1-α [HIF1A], and CD45RO) in the context of tissue morphology.[4]

CLINICAL EXPERIENCE

The TissueCypher Barrett's Esophagus test is indicated for patients diagnosed with non-dysplastic (NDBE), indefinite for dysplasia (IND) or low grade dysplasia (LGD) Barrett's esophagus. Risk of progression to high grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) within five years was determined from a pooled analysis of five multi-institutional clinical performance studies that have been completed and published involving 699 patients with Barrett's esophagus from five institutions.[5-11] The test has been shown to detect significantly more BE patients who progress to HGD/EAC (62.3%) than an expert pathology review diagnosis of LGD (28.3%). The test has also been shown to identify a high-risk subset of patients with NDBE who progress to HGD/EAC at a higher rate (16.7%)[6,7] than published estimates of progression in BE patients with LGD.[3] The clinical utility of the TissueCypher Barrett's Esophagust test to guide risk-aligned management has also been demonstrated.[12,13]

The results provided here are adjunctive to the ordering physician's workup for patients with Barrett's esophagus. The reported 5-year probability of progression was adjusted based on estimated prevalence; however, the prevalence of progression of Barrett's esophagus may vary between clinical institutions.[6]

COMPARISON WITH CLINICOPATHOLOGIC RISK FACTORS

Risk Factor		Hazard Ratio	P value
TissueCypher	Int vs Low	2.7	<0.0001
	High vs Low	7.8	<0.0001
Segment - Long vs Short		1.5	0.041
Hiatal Hernia - Present vs Absent		1.0	0.86
Age (per year)		1.02	0.0098
Sex - Male vs. Female		1.9	0.0055
Expert Review Dx - IND vs. NDBE		1.1	0.7390

This table presents univariate risk of progression to HGD/EAC for patients with specific clinical features, pathology diagnoses or TissueCypher risk results as hazard ratios. Hazard ratio represents the likelihood of HGD/EAC in the group with the risk factor compared to the group without the risk factor (e.g. patients with long segment BE have a progression risk that is 1.5 times greater than patients with short segment BE, and patients with TissueCypher high risk results have a progression risk that is 7.8 times greater than patients with a low risk result).[6]

Multivariate analysis demonstrated that the TissueCypher high- and intermediate-risk results (HR 5.3 and 2.2, respectively) predict progression to HGD/EAC independently of segment length, hiatal hernia, age and sex. An expert review diagnosis of LGD (HR 2.5) was also statistically significant in multivariate analysis.[6]

For additional information about the development and validation of the TissueCypher Barrett's Esophagus test, visit www.castlebiosciences.com/TCResults.

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Date: 2023.12.26 11:51:39 GMT-7'00'

Castle Biosciences, Inc. | Sherri Borman, PhD, HCLD, Lab Director

CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

REFERENCES

1. Wani, et al. *Clin Gastroenterol Hepatol* 2011 Mar;9(3):220-7. 2. Krishnamoorthi, et al. *Gastrointest Endosc* 2020. Jan;91(1):3-10.e3. 3. Singh, et al. *Gastrointest Endosc* 2014 Jun;79(6):897-909. 4. Prichard et al. *J Pathol Inform.* 2015 Aug 31;6:48. 5. Iyer et al., *Clin Gastroenterol Hepatol.* 2022 Dec;20(12):2772-2779.e8. 6. Davison, et al. *Gastroenterology.* 2023 May;164(Supplement). 7. Critchley-Thorne, et al. *Cancer Epidemiol Biomarkers Prev.* 2016 Jun;25(6):958-68. 8. Critchley-Thorne, et al. *Cancer Epidemiol Biomarkers Prev.* 2017 Feb;26(2):240-248. 9. Davison, et al. *Am J Gastroenterol.* 2020 Jun;115(6):843-852. 10. Frei, et al. *Clin Transl Gastroenterol.* 2020 Oct;11(10):e00244. 11. Frei, et al. *Am J Gastroenterol.* 2021 Apr;116(4):675-682. 12. Diehl, et al. *Endosc Int Open.* 2021 Mar;9(3):E348-E355. 13. Duits, et al. *Am J Gastroenterol.* 2023 Nov 1;118(11):2025-2032.