TISSUECYPHER **PUBLISHED CLINICAL VALIDATION & UTILITY STUDIES**

TissueCypher
▸ Barrett's Esophagus

STUDY	KEY FINDINGS	REFERENCE
Technical Feasibility	• Demonstrated that assessing Barrett's esophagus tissue for epithelial cell abnormalities and cellular changes in the lamina propria may serve as an adjunct to conventional pathology in the assessment of BE	Prichard JW, Davison JM, Campbell BB, et al. TissueCypher: A Systems Biology Approach to Anatomic Pathology. *J Pathol Inform.* 2015;6(1):48.
GAPP1 Study	• Clinical validation demonstrating TissueCypher predicts risk of future progression to HGD or EAC in Barrett's patients with baseline histologic diagnosis of ND, IND or LGD	Critchley-Thorne RJ, Duits LC, Prichard JW, et al. A Tissue Systems Pathology Assay for High-risk Barrett's Esophagus. *Cancer Epidemiol Biomarkers Prev.* 2016 Jun;25(6):958-968.
GAPP2 Study	• Clinical validation of locked assay to detect prevalent HGD/EAC missed by standard white light endoscopy and histology in patients with Barrett's esophagus	Critchley-Thorne RJ, Davison JM, Prichard JW, et al. A Tissue Systems Pathology Test Detects Abnormalities Associated with Prevalent High-grade Dysplasia and Esophageal Cancer in Barrett's Esophagus. *Cancer Epidemiol Biomarkers Prev.* 2017 Feb;26(2):240-248.
CC/UP Study	• Independently validated the ability of TissueCypher to predict risk of future progression to HGD/EAC within 5 years in BE patients with ND, IND or LGD • Demonstrated that TissueCypher identifies an"at-risk" subset of patients with NDBE who progress at a higher rate than patients with expert-confirmed LGD	Davison JM, Goldblum J, Grewal US, et al. Independent Blinded Validation of a Tissue Systems Pathology Test to Predict Progression of Patients with Barrett's Esophagus. *Am J Gastroenterol.* 2020;115:843-852.
CE Study	• Demonstrated cost-effectiveness of TissueCypher-directed management versus standard of care-directed surveillance and treatment • Indicated change in healthcare utilization and potential improvement in patient outcomes associated with TissueCypher-directed management	Hao J, Critchley-Thorne RJ, Diehl DL, et al. A Cost-Effectiveness Analysis of an Adenocarcinoma Risk Prediction Multi-biomarker Assay for Patients with Barrett's Esophagus. *Clinicoeconomics Outcomes Res.* 2019;11:623-635.
AMC Spatial and Temporal Study	• Confirmed ability of TissueCypher to predict incident progression in NDBE patients • Confirmed ability of TissueCypher to identify NDBE patients that progress at a higher rate than patients with expert-confirmed LGD • Demonstrated that evaluation of additional spatial and temporal specimens increases the predictive performance of TissueCypher	Frei NF, Konte K, Bossart EA, et al. Independent Validation of a Tissue Systems Pathology Assay to Predict Future Progression in Non-dysplastic Barrett's Esophagus: A Spatial-temporal Analysis. *Clinical and Translational Gastroenterology.* 2020; Oct 11(10):e00244.
SURF Biomarker Study	• Retrospective analysis of completed prospective randomized clinical trial[1] • Independently validated the ability of TissueCypher to predict risk of progression to HGD/EAC in patients with community practice diagnosis of LGD	Frei NF, Khoshiwal AM, Konte K, et al. Tissue Systems Pathology Test Objectively Risk Stratifies Barrett's Esophagus Patients with Low-grade Dysplasia. *Am J Gastroenterol.* 2021;Apr 116(4)675-682.
Geisinger Decision Impact Study	• TissueCypher changed the management plan for 55% of BE patients studied at an expert center • TissueCypher led to upstaging of management plan in 21.7% of patients, indicating potential to improve outcomes • TissueCypher led to downstaging of management plan in 33.4% of patients, supporting surveillance rather than therapy	Diehl DL, Khara HS, Akhtar N, Critchley-Thorne RJ. TissueCypher Barrett's Esophagus Assay Impacts Clinical Decisions in the Management of Patients with Barrett's Esophagus. *Endosc Int Open.* 2021; 09(03): E348-E355.
Mayo Pooled Analysis Study	• Across all analyses, TissueCypher was the strongest and most significant predictor of progression to HGD or EAC • Predictive performance of clinicopathologic factors was significantly improved by the inclusion of the TissueCypher risk classes • In the NDBE patient cohort, a TissueCypher high risk score predicted an 18-fold increased risk of progression vs. TissueCypher low risk score and identified 52% of the NDBE progressors, all of whom were missed by the standard of care	Iyer PG, Codipilly DC, Chandar AK, et al. Prediction of progression in Barrett's esophagus using a tissue systems pathology test: A pooled analysis of international multicenter studies. *Clin Gastroenterol Hepatol.* 2022.

List of Abbreviations Used in the Table: Barrett's esophagus (BE), esophageal adenocarcinoma (EAC), high-grade dysplasia (HGD), indefinite for dysplasia (IND), low-grade dysplasia (LGD), non-dysplastic (ND), non-dysplastic Barrett's esophagus (NDBE)

1 Phoa et al., Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. *JAMA* 2014;311:1209-17.

CASTLE BIOSCIENCES

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