enowSOLUTIONS

The Role of TissueCypher

(Tissue Systems Pathology) based Risk Stratification for patients with Barrett's Esophagus and Barrett's Related Neoplasia

A Clinical Practice Model

Introduction

This Clinical Practice Model (CPM) was developed by a group of esteemed medical professionals to discuss the adoption, application, appropriate positioning of, and the challenges associated with, incorporating TissueCypher (a molecular diagnostic tool for Barrett's Esophagus (BE) risk stratification) into clinical practice.

This detailed executive summary expands upon the key themes, discussions, and outcomes from the session, providing a comprehensive view of the challenges and opportunities surrounding the adoption of TissueCypher.

Clinical Practice Model KOL Team:

Vivek Kaul, MD
Physician Project Coordinator

Jennifer Kolb, MD
UCLA (Interventional Endoscopist)

Harshit Khara, MD
Geisinger Medical Center (Interventional Endoscopist)

Jay Yepuri, MD
Digestive Health Associates of Texas, Bedford, GI Alliance (Gastroenterologist)

George Sun, MD
Digestive Health Associates of Texas, Houston (Gastroenterologist)

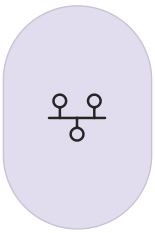
Session Objectives

The primary objectives of the session included:

Evaluating how TissueCypher is currently utilized in clinical practices.

Identifying the barriers and facilitators to its adoption across different practice settings.

Developing strategies to optimize its implementation.



Outlining a roadmap to create a clinical playbook that supports healthcare providers in deploying this technology effectively.

Participants aimed to bridge the gap between robust scientific evidence and practical application, ensuring that TissueCypher could be effectively leveraged to enhance patient care.

1. Current Practices in Barrett's Risk Stratification

Clinical Approaches

Participants shared their approaches to risk stratification, which predominantly involved traditional methods:

Histopathology: Routine histopathology remains the gold standard for diagnosis and risk assessment, although it is supplemented by emerging technologies such as TissueCypher in some practices.

Segment Length: Segment length was cited as a critical factor in determining surveillance intervals, with longer segments associated with higher cancer risk.

Family History: Family history of EAC and BE were frequently considered in clinical decisions.

GERD: As the predominant cause of BE/EAC uncontrolled reflux is a risk factor. However, the panel agreed that GERD symptoms are not an accurate representation of reflux burden.

Obesity: Patients particular with central obesity and higher BMI (>35) were felt to be of higher risk for development of BE/EAC.

Tobacco Use: Current and Previous heavy tobacco use was considered a risk factor.

Current Use of TissueCypher

While TissueCypher is increasingly recognized for its potential, its adoption remains uneven:

High-Risk Identification

TissueCypher's ability to identify high-risk non-dysplastic Barrett's patients is a game-changer. This ability could allow for identifying patients with potentially increased risk for early or rapid progression to HGD/ adenocarcinoma to be found sooner allowing for increased surveillance, earlier endoscopic eradication therapy (EET) or more aggressive medical plus/minus surgical intervention.

Low-Risk Identification

TissueCypher's ability to identify low-risk non-dysplastic patients means potentially extending surveillance out for both short and long segment Barrett's patients. Additionally, a low-risk result even in a low grade/indefinite for dysplasia patient is lower risk than the histology alone would indicate. Therefore, these patients if not good candidates for ablation or increased surveillance could be reassured that their disease may have less likelihood to progress than based on the histology alone.

Supplementary Tool

It is not used as a standalone diagnostic tool but rather as an adjunct to histopathology, endoscopic findings and other clinical criteria.

Biomarkers

Staining for p53 is not common although select sites/pathologists may be doing this. The true value for risk stratification remains unclear.

Endoscopic Surveillance Intervals

Participants largely adhere to guideline-based surveillance intervals, however there is some deviation from these guidelines based on patient/provider concerns:

3-Year Intervals

Patients with higher-risk features, such as longer segment lengths or significant family history, are typically monitored every three years or less. If patient with TissueCypher high risk, they should be evaluated/ followed at sooner interval and treatment considerations entertained depending on the clinical scenario.

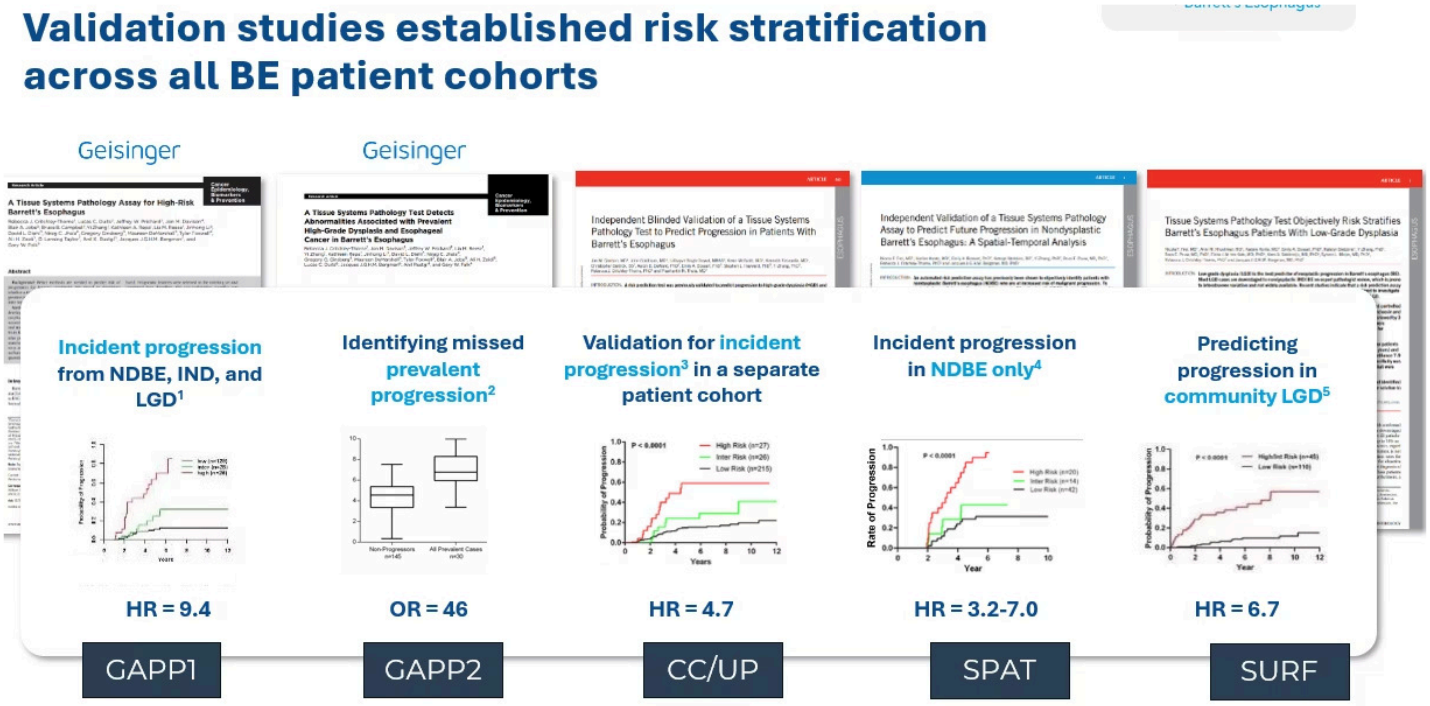
5-Year Intervals

Short-segment Barrett's patients without additional risk factors are generally recommended for surveillance endoscopy every five years. It is agreed that there is wide variability in how GI Docs comply with this recommendation, in many cases bringing the patient back much sooner for a variety of patient/provider concerns. The potential for TissueCypher to help GI Docs risk stratify this pool of SSBE patient and then allow them to adhere to the 5 year surveillance recommendation for SSBE was felt another good application of TC.

2. Insights from Current Literature

Strengths of TissueCypher Data

Pivotal studies are represented in below slide:



Validation Studies

There are 14 published, peer reviewed studies demonstrating the risk stratification provided by TissueCypher using one of the largest BE progressor populations from various academic as well as community practices. There have been 5 pivotal studies, including GAP1, GAP2, CC/UP, SPAT, and SURF which have validated TissueCypher's ability to stratify risk effectively in 895 unique patients including 239 progressor and 656 non-progressors. These studies have demonstrated the tests' value in both dysplastic and non-dysplastic patient populations.

Predictive Value

TissueCypher demonstrates both a strong positive as well as a strong negative predictive value.

HIGH Risk Score Impact

- 18-fold higher rate of progression in patients with non-dysplastic Barrett's
- 6.7 fold higher rate of progression in patients with low grade dysplasia
- 46 times more likely for progression in patients harboring prevalent high grade dysplasia
- 9.4 times more likely for incident progressors within 1-5 years
- 17-fold more likely to progress even in females
- 9 times more likely to progress even in short segment Barrett's

LOW Risk Score Impact

- 3.2 times less likely to progress with non-dysplastic Barrett's
- 2.5 times less likely to progress with low grade dysplasia

A LOW risk TissueCypher score in patients with low-grade dysplasia may be less worrisome than histologic diagnosis of non-dysplastic Barrett's.

Clinical Impact

These score reports have shown to impact clinical decision making and change management protocol within current practice guidelines more than 55% of the time.

These prediction models help better allocate institutional resources and provide societal benefits by appropriately identifying high-risk actionable patients, which could reduce esophageal cancer incidence.

Prevalent Dysplasia Detection: The tool's ability to identify missed or prevalent dysplasia, even in cases of non-dysplastic Barrett's, was emphasized.

Comprehensive Literature

A comprehensive list of published literature is compiled below:

STUDY	REFERENCE	KEY FINDINGS
Technical feasibility study	Prichard JW, Davison JM, Campbell BB, et al. TissueCypher: A systems biology approach to anatomic pathology. *J Pathol Inform.* 2015;6(1):48.	• 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.
GAPP1 study	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.	• Clinical validation demonstrating TissueCypher predicts risk of future progression to HGD or EAC in patients with BE who have baseline histologic diagnosis of ND, IND or LGD.
GAPP2 study	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.	• Clinical validation of locked assay to detect prevalent HGD/EAC missed by standard white light endoscopy and histology in patients with Barrett's esophagus.
CC/UP study	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.	• 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.
CE study	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. *Clinicoecon Outcomes Res.* 2019;11:623-635.	• 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.
AMC spatial and temporal study	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. *Clin Transl Gastroenterol.* 2020; Oct 11(10):e00244.	• 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
SURF biomarker study	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.	• 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.
Geisinger decision impact study	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.	• 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.

Comprehensive Literature (cont.)

STUDY	REFERENCE	KEY FINDINGS
Mayo pooled analysis study	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 Dec;20(12):2772-2779.e8.	• 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.
SURF utility study	Duits LC, Khoshiwal, AM, Frei, NF et al. An automated tissue systems pathology test can standardize the management and improve health outcomes for patients with Barrett's esophagus. *Am J Gastroenterol.* 2023; 118(11):p 2025-2032.	• Incorporating TissueCypher into the standard of care can increase the early detection of progressors who can receive therapeutic interventions or short-interval surveillance, while also increasing the percentage of non-progressors who can avoid unnecessary therapy and be managed by surveillance alone. • TissueCypher guidance clinically and statistically improved the standard of care by increasing the likelihood of appropriate management decisions for all patients and decreasing the variability in management that results from basing care solely on the diagnoses of dysplasia.
Expanded SURF biomarker study	Khoshiwal AM, Frei NF, Pouw RE et al. A tissue systems pathology test outperforms pathology review in risk stratifying patients with low-grade dysplasia. *J. Gastroenterol.* 2023; 165(5):p 1168-1179.E6.	• The study confirmed that TissueCypher is an objective test that outperformed a group of 16 generalist and 14 expert pathologists. • Compared with known patient outcomes, pathologists showed weak agreement in diagnoses. One group of pathologists tended to over-diagnose and another group tended to under-diagnose.
Enhanced pooled analysis study	Davison JM, Goldblum JR, Duits LC, et al. A tissue systems pathology test outperforms the standard of care variables in predicting progression in patients with Barrett's esophagus. *Clin Transl Gastroenterol.* 2023; 14(11):p e00631.	• TissueCypher is superior to clinicopathologic features in risk stratifying BE patients, has significantly higher sensitivity than pathology, identifies majority of progressors at the NDBE stage. • TissueCypher risk stratifies in all clinically relevant subsets of BE patients, including those considered low risk per current clinical variables, e.g. female patients, short segment.
QURE utility study	Peabody JW, Cruz JDC, Ganesan D, et al. A randomized controlled study on clinical adherence to evidence-based guidelines in the management of simulated patients with Barrett's esophagus and the clinical utility of a tissue systems pathology test: results from Q-TAB. *Clin Transl Gastroenterol.* 2024; 15(1) e00644.	• Use of TissueCypher significantly improved physician adherence to clinical guidelines for surveillance and treatment of both BE patients at high and low risk for disease progression. • Use of TissueCypher can enable physicians to make risk-aligned management decisions, leading to improved patient health outcomes.
Clinical experience study	Villa NA, Ordonez-Castellanos M, Yodice M, et al. The tissue systems pathology test objectively risk-stratifies patients with Barrett's esophagus results from a multicenter US clinical experience study. *J Clin Gastroenterol.* 2024 Jul 2. doi: 10.1097/MCG.0000000000002040. Online ahead of print.	• Across 8,080 patients, TissueCypher provided objective risk stratification within all clinically relevant patient subsets. • Even in patient populations with low-risk clinical features (i.e. female, short-segment), TissueCypher identified patients with a higher risk of progression to HGD/EAC.

Challenges in Interpretation

Sensitivity Concerns

Sensitivity rates of approximately 60% were noted, leading to some skepticism about the tool's comprehensiveness. However, current practice guidelines based on histology alone do not provide significant insight into which patients are at risk of progression. The use of TissueCypher which is completely independent of the patient's histologic classification, increases the sensitivity in detecting these high-risk patients from nonexistent to 62%, hence the gain of 62% sensitivity still adds a significant improvement to our existing data.

Odds Ratios and Risk Communication

The reliance on statistical metrics like odds ratios can complicate communication with both clinicians and patients.

Intermediate Probability Cases

What to do with intermediate probability cases is more nuanced and best individualized.

The test cutoff was made for 'intermediate probability' for a score from 5.5 which is where the risk curve shows the first upslope. Even with an intermediate risk section, the risk of progression should be discussed with the patient for a case-by-case joint decision making with the patient for change in surveillance or treatment decision.

The 63% sensitivity calculation noted in the Davison study already pairs high & intermediate risk as actionable. Broadly speaking, the guidance is for clinicians to manage high- and intermediate-risk patients similarly, using shared decision making approach.

Test Frequency and Responsibility

How often should the test be repeated?

The initial validation studies were done with 5 years follow up. Based on those studies, TC was validated to predict the 5-year risk of progression to EAC. Hence the current guidance is to repeat the TC test at 5 years. However, if a patient undergoes interval EGD with biopsies prior to the recommended ACG practice guidelines (i.e. 3 years for long segment or 5 years for short segment NDBE), TC may be repeated in the event that there are new findings / changes in the examined BE segment that may benefit from repeat prognostication. Future studies should add to this existing data set and help address the issue of timing for repeat testing as well as test the validity of the score results further out than 5 years.

Who takes responsibility of test results follow up?

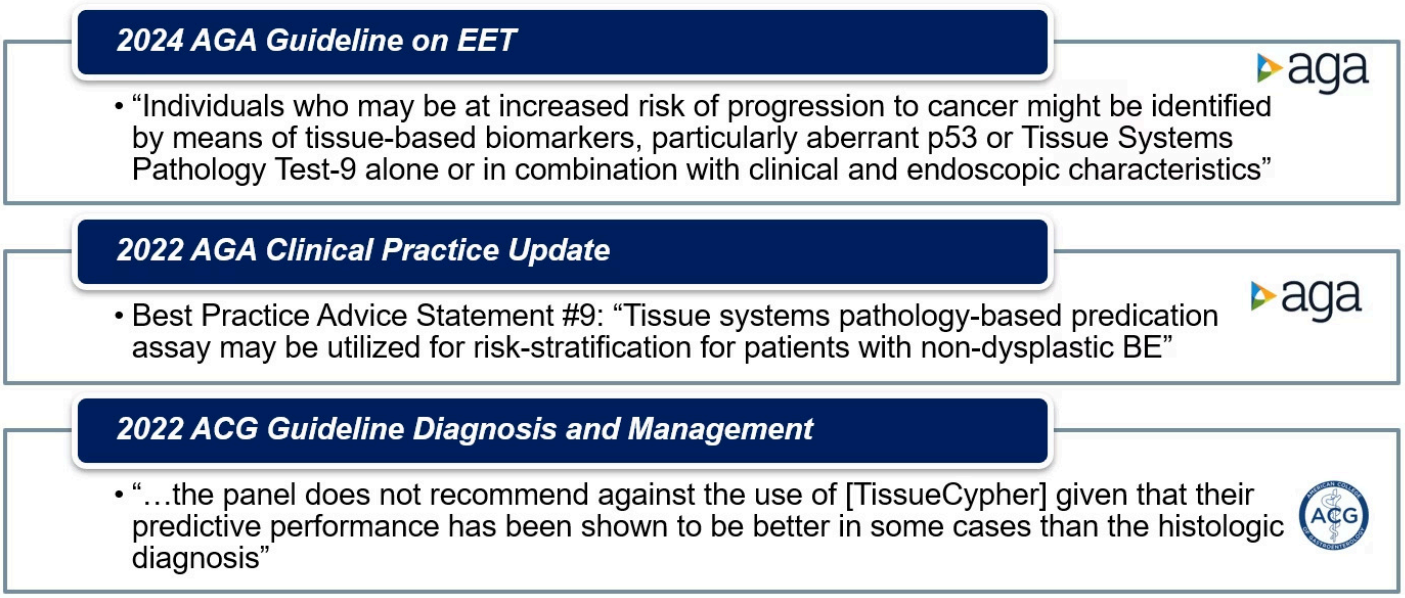
If a non-endoscopist orders the test, each practice will need to address this internally and come up with a workflow/plan that ensures appropriate and timely follow-up of test results.

Opportunities for Future Research

- Expanding studies to diverse populations to enhance generalizability.
- Checking for longer follow up data and correlating with any change in patient's disease state such as segment length or histology.
- Integrating AI-based analysis for better predictive modeling and risk stratification.

Guideline and Clinical Practice Updates

Positioning of TC in current guidelines/clinical practice updates is as below:



Gastroenterology 2024;166:1020–1055; Clinical Gastroenterology and Hepatology 2022;20:2696–2706; Am J Gastroenterol 2022;117:559–587

- Collaborating with professional societies to include TissueCypher in updated clinical guidelines as further data comes
- Position TissueCypher as an enhancement to histopathology-based risk assessment and not a replacement
- Develop flowcharts where TissueCypher fits into clinical decision making and providing a clearer framework for its use, than currently exists
- Share this CPM with these societies and ensure the value to clinical practice is clear

3. Barriers to Adoption

Operational Barriers

Logistical Issues

Challenges in sample handling and processing were identified, particularly in practices with limited pathology infrastructure.

Workflow Integration

Incorporating TissueCypher into existing clinical workflows remains a hurdle. It is essential to have a clear flow from the endoscopist to their assistant or nurse to pathology in a seamless fashion to avoid delays and added labor to the workflow. Adding education for staff and the pathology team could be very valuable to eliminate the headache for the GI docs.

Clinician Skepticism

Resistance to Change

Some clinicians remain hesitant to adopt TissueCypher, citing concerns about its added value compared to traditional methods.

Data Interpretation

The complexity of interpreting results and integrating them into decision-making contributes to hesitancy. This is especially true for inconclusive test results such as "intermediate" probability. Education around exact clinical scenarios where the impact is greatest would be of great educational value. In addition, demonstrating the clinical change in management for low risk vs. high risk and associated value/outcomes would be very important for future discussion.

Patient Factors and Healthcare Economics

- ## Patient Factors

Shared Decision-Making

Patients often arrive with preconceived notions regarding their management plans, influenced by previous consultations or online information, complicating risk-based discussions. For example, a patient referred for endoscopic ablation may not easily subscribe to a surveillance recommendation based on a "low risk" TC score.

Preference for Conservative Approaches

Many patients are reluctant to embrace advanced diagnostics due to perceived invasiveness or cost concerns, despite assurances of clinical value and/or financial coverage. Patients should be reassured though that their providers will work on their behalf with the manufacturer to submit, manage, and as necessary, make appeals to insurance companies for non-covered claims.

- ## Healthcare Economics

Test Coverage

Test coverage outside of commercial insurance/Medicare: health systems with their own insurance plans need to negotiate the cost per test directly with the company.

Overall Cost Effectiveness

Balance the burden of additional cost to the healthcare system for using TissueCypher with the potential cost savings from attenuated surveillance.

4. Proposed Solutions

Educational Initiatives

Clinician Training/Education

Developing comprehensive training programs to familiarize healthcare providers with TissueCypher's utility and interpretation and equip physicians with evidence based talking points. Furthermore, using this CPM to educate MD's, administrators, and pathologists would be of great value.

CME Programs & Webinars

Offer educational modules to potential TissueCypher users such as through the platform EndoscopyNow.

Patient Education

Creating patient-focused easy to understand materials to explain the benefits and limitations of TissueCypher (videos, infographics).

Decision Support Aids

Create interactive tools that allow patients to input their data and understand their personalized risk.

Enhancing Messaging and Workflow Integration

Enhancing Messaging

Reframing statistical data into relatable metrics, such as the number needed to test, to improve comprehension and acceptance among clinicians and patients.

Develop concise, actionable risk stratification flowcharts that highlight clear next steps for clinicians for all test outcomes.

Provide concise, data driven comparisons and real-world examples where TissueCypher altered management and improved outcomes.

Clearly explain in writing to both physicians and patients that patients will not incur any financial risk. A clear framework for private practices and healthcare systems would benefit implementation.

Improving Workflow Integration

Embedding TissueCypher into electronic health record systems for streamlined ordering, result acquisition and interpretation. Ideally lab results would be present under pathology or standard laboratory section.

Identify early adopters at the specific institution to champion the use of TissueCypher and refine workflow best practices.

Implement clinical decision support prompts to guide physicians on how to act based on test results.

Utilizing AI algorithms to enhance predictive accuracy and provide actionable recommendations.

5. Implementing TissueCypher into Clinical Practice

Understanding the value for the patient

Objective Risk Assessment

The provision of objective data defining risk for Barrett's Esophagus and potential progression to EAC is very impactful for management and quality of care. Making sure patients and primary care physicians understand that we finally have an objective tool to define and personalize the risk of EAC for patients.

TissueCypher High Risk

The use of high-risk results to offer endoscopic eradication therapy provides a much more streamlined and thoughtful path for treating high-risk patients than the use of current standards (clinical risk based on histopathology and patient preference).

TissueCypher Low Risk

For patients with NDBE, indefinite for dysplasia or even LGD a low-risk result can eliminate unnecessary anxiety and avoid overuse of endoscopic therapy where it is not needed or where risk outweighs benefits. Furthermore, for short segment disease this should allow the endoscopist to extend surveillance intervals to 5 years without reservation.

Clinical Workflow and Reimbursement

Clinical Workflow

01

Ensure your partners in practice, referring physicians, and primary care doctors understand the value of TC and your practice with it. Educating those around you will increase the value of its use and help others understand your TC based management of the patient.

02

As you roll this out in practice make sure your staff, pathology staff, and the pathologists understand how you want this to be done. This can be an algorithm predefining the patients who should get TC or a simple process whereby the MD forwards a BE result and asks for TC and staff can make this happen behind the scenes.

03

It is essential that the result is uploaded into the EHR (Future integration is needed).

Reimbursement Considerations

Patient Cost

The Cost to the patient at current time is zero.

Personalized Risk Model

Personalize risk stratification and prevention of cancer is relatively novel for gastroenterologists and a model we must embrace moving forward.

Cost vs. Outcomes

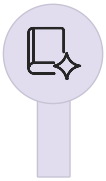
The use of TC for personalized risk stratification will help reduce costs to the practice over time. However, the key to this is consistent use and standardized results-based practice. Offering EET to high-risk patients will avoid the future development of a few EACs that would deplete the system, while increasing interval or eliminating surveillance for low risk will reduce unnecessary procedures and improve overall access.

Coverage for EET

Coverage for EET in those patients with NDBE/Indefinite for Dysplasia but are "high risk" based on TC needs to be addressed. It may be worth researching this as a supportive point for clinical integration or as a possible barrier to adoption that still needs to be addressed.

6. Future Directions

Long-Term Goals



Educating all gastroenterologists with this CPM

Conducting multicenter studies to validate findings across diverse practice settings.

Exploring the integration of TissueCypher with other emerging technologies, such as AI-assisted endoscopy.

Improving coverage

Anticipated Outcomes

Reduction in unnecessary interventions for low-risk patients.

Improved detection of high-risk cases, leading to timely and appropriate treatment.

Enhanced patient satisfaction through personalized risk assessments and care plans.

Advancing the field by introducing and establishing the predictive analytics paradigm in modern day Barretts practice.

Accurate risk stratification for most cases which are non-dysplastic Barrett's esophagus will promote expanded screening opportunities that increase the pool of potential patients.

Key Recommendations

The Message

Ensuring All Stakeholders understand the value add for Personalized Risk Stratification for patients with Barrett's Esophagus

Patient Selection

Discussing with your practice where you feel TC can provide value for your patients (e.g. IND, NDBE)

Workflows

Establishing a simple, burden-free pathway for your staff and pathology to scale the use of TC in your practice

Standardization of Results Based Practice

The success of risk stratification is contingent on a standardized practice based on the results. Whether it is offering EET or increasing surveillance intervals, a best practices concept should be established for your practice.

Reimbursement and Cost Reduction

It is important to emphasize to the patient they will bear no cost for this added value to their care. It is equally critical for the practice to understand the downstream savings TC brings.