

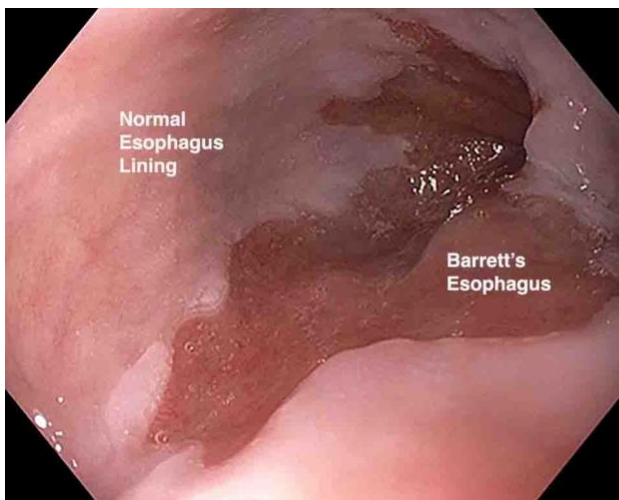
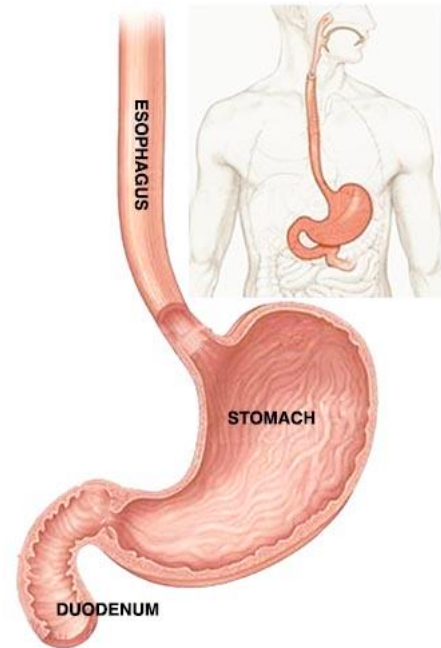


TissueCypher: A New Way to Assess Risk in Barrett's Esophagus

If you or someone you know has been diagnosed with Barrett's Esophagus, you may already be aware of the increased risk it poses for developing esophageal cancer. Assessing this risk has challenged doctors for years, as traditional methods often fail to provide a complete picture. Recently, however, a revolutionary technology called TissueCypher has emerged. Using artificial intelligence (AI) and advanced biomarker analysis, TissueCypher offers a more accurate, personalized way to predict the likelihood of cancer development in patients with Barrett's Esophagus. This article will explain what TissueCypher is, how it works, and how it could benefit you as a patient.

What is Barrett's Esophagus?

Barrett's Esophagus is a condition that affects the lining of the esophagus, the tube that carries food and liquids from your throat to your stomach. In individuals with chronic acid reflux (also known as gastroesophageal reflux disease, or GERD), the acid can cause damage to the cells lining the esophagus. Over time, this can change the lining, where the normal squamous cells are replaced with cells that resemble the intestinal lining. (see below) This process, known as "*intestinal metaplasia*," is the body's response to long-term irritation from stomach acid.



Barrett's Esophagus

This is a photograph taken in the lower esophagus during an upper endoscopy examination. You can see where chronic acid reflux has splashed up and damaged the lower esophagus, transforming the normal esophagus cells into discolored areas of *intestinal metaplasia* or Barrett's Esophagus.

The condition is named after Australian thoracic surgeon Norman Barrett (1903–1979), even though it was initially described by Philip Rowland Allison in 1946. The incidence of Barrett's Esophagus among Caucasian men in the United States is eight times the rate among Caucasian women and five times greater than that among African American men. Overall, the male-to-female ratio of Barrett's esophagus is 10:1.

While Barrett's Esophagus itself is not cancerous, it is considered a precancerous condition. This means that people with Barrett's Esophagus have a higher risk of developing esophageal adenocarcinoma, a dangerous type of cancer that often goes undetected until its later stages. The risk of esophageal cancer in people with Barrett's Esophagus is estimated to be about 30 times higher than in the general population. This underscores the importance of regular monitoring and effective risk assessment.

Challenges with Traditional Risk Assessment

Traditionally, doctors assess cancer risk in patients with Barrett's Esophagus through a process called dysplasia grading. This involves taking a biopsy (a small tissue sample) from the esophagus and examining it under a microscope for signs of abnormal cell growth or dysplasia. *Dysplasia is categorized into different grades: no dysplasia (normal cells), low-grade dysplasia (mildly abnormal cells), and high-grade dysplasia (more seriously abnormal cells with a higher risk of becoming cancerous).*

However, dysplasia grading has its limitations. The process can be highly subjective, with different pathologists sometimes reaching different conclusions based on the same biopsy sample. This can result in misclassification, where some patients with a high risk of cancer are labeled as low risk and vice versa. Moreover, dysplasia grading does not account for individual patient differences, such as genetic factors and other unique biological markers, affecting their cancer risk. TissueCypher was developed to address these limitations and provide a more precise, individualized approach to assessing cancer risk.

What is TissueCypher? [PODCAST LINK](#)

TissueCypher is a groundbreaking diagnostic tool designed specifically for patients with Barrett's Esophagus. *It utilizes artificial intelligence and spatialomics technology to analyze biopsy samples from the esophagus, allowing doctors to obtain a more precise, personalized risk assessment for each patient.* By examining specific protein biomarkers within the biopsy sample, TissueCypher generates a "risk score" that reflects the likelihood of a patient developing high-grade dysplasia or esophageal cancer.

How TissueCypher Benefits Patients

TissueCypher provides a level of precision and individualization that was previously unavailable with traditional methods. This tool is especially helpful for patients who fall into the "gray area" of Barrett's Esophagus – those who don't show obvious signs of high-grade dysplasia but may still be at risk of cancer. By analyzing various biomarkers and considering their spatial arrangement within the tissue sample, TissueCypher provides a detailed picture of each patient's unique cancer risk. This enables doctors to make more informed decisions about

monitoring and treatment, ensuring that high-risk patients receive the care they need while low-risk patients avoid unnecessary procedures.

How Does TissueCypher Work?

The TissueCypher Process Step-by-Step

The TissueCypher test begins with a routine biopsy taken during an upper endoscopy. An upper endoscopy is a procedure in which a thin, flexible tube with a camera on the end is passed through the mouth and into the esophagus, allowing doctors to examine the esophageal lining. If any areas of concern are found, the doctor takes a small tissue sample or biopsy, which is then sent to a specialized lab in Pittsburgh, PA, for analysis with TissueCypher. Biopsy samples come from all over the world to be processed there.

1. **Staining the Biopsy Sample:** Once the biopsy sample arrives at the TissueCypher lab, it is carefully prepared and stained with fluorescent antibodies. These antibodies are designed to bind to specific protein biomarkers within the tissue, effectively "lighting up" certain sample features associated with cancer risk.
2. **High-Resolution Imaging:** The stained tissue sample is then scanned using high-resolution imaging technology. This process produces detailed images of the sample, capturing data on the presence and arrangement of multiple biomarkers.
3. **Spatialomics Analysis:** TissueCypher uses spatialomics technology, which allows it to examine not only the presence of biomarkers but also their spatial organization within the tissue. This is similar to studying traffic patterns in a city; instead of just counting cars, you would look at how they're moving, where they're going, and what routes they're taking. Understanding the spatial arrangement of biomarkers provides a more complete picture of cancer risk.
4. **AI-Driven Analysis of Data Points:** The images are analyzed by sophisticated AI algorithms that process millions of data points. The AI identifies 15 specific features within the tissue that have been shown to correlate with cancer progression. This in-depth analysis produces a "risk score" for the patient, which doctors can use to guide their treatment plan.

Key Biomarkers Assessed by TissueCypher

TissueCypher evaluates nine protein biomarkers, each of which plays a unique role in cancer development:

- **p53:** Often called the "guardian of the genome," this protein helps prevent cells from growing uncontrollably. If p53 malfunctions, cells can proliferate unchecked, a warning sign for cancer risk.
- **p16:** This biomarker helps regulate cell division. Loss of p16 can lead to rapid cell growth, increasing cancer risk.
- **COX2:** COX2 is an enzyme involved in inflammation, and chronic inflammation can create an environment that fosters cancer development.

- HIF-1 alpha: When tissues lack oxygen, they can become more cancer-prone. HIF-1 alpha is a marker of low oxygen levels (hypoxia), often indicating aggressive tumor growth.

These biomarkers and others like AMACR, HER2, CD68, and CD45RO are examined to give doctors a comprehensive view of each patient's cancer risk. By understanding these biomarkers' precise arrangement and levels, TissueCypher offers insight that traditional methods can't match.

The Testing Process for TissueCypher

For patients with Barrett's Esophagus, the TissueCypher test can be an important tool in managing their condition. Here is what the process generally looks like:

1. Initial Consultation: Start by discussing your options with your gastroenterologist. They will review your medical history, symptoms, and prior test results to determine if TissueCypher is suitable.
2. Undergoing an Upper Endoscopy: If TissueCypher testing is recommended, the next step is an upper endoscopy to obtain a biopsy sample. This procedure allows the doctor to visually examine the esophagus and take tissue samples from areas that look abnormal or concerning.
3. Biopsy Analysis in the Lab: The biopsy is sent to the TissueCypher lab for processing. The sample goes through the staining, imaging, and AI analysis process described earlier.
4. Receiving the Results: TissueCypher results are usually available within a few weeks. The AI-driven image analysis is reported as a risk score from 0 to 10, a risk class of LOW, INTERMEDIATE, or HIGH risk, and an associated personalized 5-year risk of progression to high-grade dysplasia or esophageal cancer. Your doctor will review the risk score with you and discuss what it means for your care.

Insurance and Accessibility

TissueCypher is covered by most insurance plans, which makes it widely accessible to patients. This means that individuals who could benefit from this testing may be able to do so without significant financial burden. If you're considering this test, ask your doctor or insurance provider to verify coverage so you know what to expect regarding cost.

Benefits of TissueCypher for Patients and Doctors

Early Detection and Tailored Treatment

One of the primary advantages of TissueCypher is its ability to enable early detection of cancer risk. This can mean more frequent screenings or proactive treatments like ablation therapy (a procedure that destroys abnormal tissue) for high-risk patients. By identifying cancer risk at an earlier stage, TissueCypher helps prevent the progression of Barrett's Esophagus to esophageal cancer, which can make a significant difference in patient outcomes.

Reducing Anxiety for Low-Risk Patients

Not all patients with Barrett's Esophagus are at high risk of cancer. The test can provide peace of mind for those whose TissueCypher results indicate a low risk. Instead of undergoing frequent and potentially unnecessary procedures, low-risk patients may only need routine monitoring, reducing the physical and emotional burden of managing their condition.

Advancing Personalized Medicine

TissueCypher is an example of personalized medicine, a healthcare approach that tailors treatment to the individual rather than applying a "one-size-fits-all" solution. By assessing each patient's unique risk profile, TissueCypher allows doctors to make treatment decisions based on each individual's specific needs and risks. This personalized approach leads to more effective care and better outcomes for patients.

Conclusion

If you have Barrett's Esophagus, the TissueCypher test offers a powerful tool for assessing your cancer risk. Using advanced AI and biomarker analysis, TissueCypher provides doctors with a personalized risk score, enabling earlier detection and more tailored treatment options. Covered by most insurance plans, this test is widely accessible, helping ensure that patients receive the individualized care they deserve.

Understanding your risk and discussing the latest options with your doctor can be crucial for better health. Remember, knowledge is power. With technologies like TissueCypher and promising future advancements, there has never been a better time to take control of your digestive health.

Robert Fusco MD
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The Center for Digestive Health & Nutrition is a private medical practice comprised of experienced Gastroenterologists, Nurse Practitioners, and staff members dedicated to preventing and treating digestive disorders. Our physicians have been serving the needs of those in Western Pennsylvania and surrounding areas since 1977, having cared for tens of thousands of individuals with digestive problems. Our mission is to deliver high-quality gastroenterology services efficiently and cost-consciously. We realize the very sensitive nature of GI illness and understand the necessity of providing our services in an environment that stresses patient privacy and confidentiality and where patient satisfaction is the goal. Appointments can be conveniently scheduled online via our website above. Learn more about digestive issues on Instagram @thedigestivetract

DISCLAIMER: The information on this website is provided for general information. It does NOT reflect definitive medical advice, and self-diagnoses should not be made based on information obtained online. It is essential to consult a physician for a consultation and examination regarding any symptoms or signs, as they may signify a serious illness or condition. A qualified doctor should only make an accurate diagnosis and treatment plan to exclude a serious condition.

FINAL REPORT

Patient:
Sex: Male
DOB:
Client: Center For Digestive Health & Nutrition
Provider: Robert D. Fusco, MD

Specimen ID: CD24-02882
Collected: 09/20/2024
Received: 09/26/2024
Reported: 10/08/2024
Specimen Type: FFPE Tissue

Here is an example of TissueCypher report. This patient's traditional biopsy did NOT show dysplasia, but TissueCypher analysis shows a high risk of high-grade dysplasia or cancer in the next 5 years. More aggressive treatment was advised.

TISSUECYPHER® RISK CLASS AND RISK SCORE

Risk Class*

HIGH

Risk Score

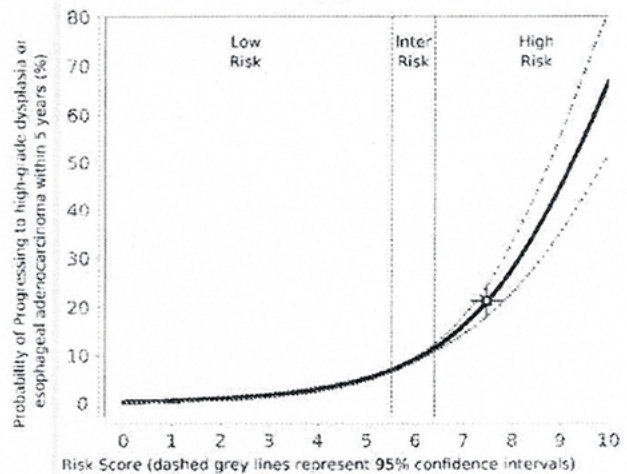
7.5

5-year Probability
of Progression**

21%

(95% C.I. 18,25)

5-year probability of progression as a function of the Risk Score



* 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 (Zeiss Axioscan) 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

This test was developed, and its performance characteristics validated, by Castle Biosciences, Inc. It has not been cleared or approved by the FDA. The laboratory is registered under CLIA as qualified to perform high complexity testing. This test is used for clinical purposes. It should not be regarded as a substitute for standard of care or for any other. Patient counseling.