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The Tissue Systems Pathology Test Objectively Risk-Stratifies Patients With Barrett's Esophagus

Results From a Multicenter US Clinical Experience Study

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Background: Barrett's esophagus (BE) is a diagnosis of esophageal intestinal metaplasia, which can progress to esophageal adenocarcinoma (EAC), and guidelines recommend endoscopic surveillance for early detection and treatment of EAC. However, current practices have limited effectiveness in risk-stratifying patients with BE.

Aim: This study aimed to evaluate use of the TSP-9 test in risk-stratifying clinically relevant subsets of patients with BE in clinical practice.

Methods: TSP-9 results for tests ordered by 891 physicians for 8080 patients with BE with clinicopathologic data were evaluated. Orders were from nonacademic (94.3%) and academic (5.7%) settings for nondysplastic BE (NDBE; n = 7586; 93.9%), indefinite for dysplasia (IND, n = 312, 3.9%), and low-grade dysplasia (LGD, n = 182, 2.3%).

Results: The TSP-9 test scored 83.2% of patients with low risk, 10.6% intermediate risk, and 6.2% high risk, respectively, for progression to HGD/EAC within 5 years. TSP-9 provided significant risk-stratification independently of clinicopathologic features, within NDBE, IND, and LGD subsets, male and female, and short- and long-segment subsets of patients. TSP-9 identified 15.3% of patients with NDBE as intermediate/high-risk for progression, which was 6.4 times more than patients with a pathology diagnosis of LGD. Patients with NDBE who scored intermediate or high risk had a predicted 5-year progression risk of 8.1% and 15.3%, respectively, which are similar to and higher than published progression rates in patients with BE with confirmed LGD.

Conclusions: The TSP-9 test identified a high-risk subset of patients with NDBE who were predicted to progress at a higher rate than confirmed LGD, enabling early detection of patients requiring management escalation to reduce the incidence of EAC. TSP-9 scored the majority of patients with NDBE as low risk, providing support to adhere to 3- to 5-year surveillance per guidelines.

Key Words: Barrett's esophagus, esophageal adenocarcinoma, tissuecypher, tissue systems pathology test (TSP-9)

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Barrett's esophagus (BE) is characterized by the presence of intestinal metaplasia in the esophagus that can progress to esophageal adenocarcinoma (EAC) in some patients, which has a 5-year survival rate of approximately 21%.[1] Gastroenterology Society guidelines recommend endoscopic surveillance of BE with biopsies and pathology review to identify dysplasia at an early treatable stage. Diagnostic grading of dysplasia is the main criterion used to make clinical management decisions in BE. However, the interobserver variability among pathologists is significant and can lead to variability in management decisions and health outcomes.[2,3] In addition to diagnostic grade, clinical variables such as segment length and sex have been associated with progression risk.[4,5] However, both pathology review and clinical variables have limited effectiveness to guide risk-aligned management as patients with low-risk clinicopathologic features, such as nondysplastic BE (NDBE), short-segment BE, and female sex, can still harbor prevalent high-grade dysplasia (HGD) or EAC, or progress to HGD/EAC during their surveillance interval. The average risk of progression is low (0.6% per year) in patients with NDBE and this diagnosis does not confer a substantial concern for prevalent HGD/EAC at the time of diagnosis or for development of incident HGD/EAC during the 3- to 5-year surveillance intervals that guidelines recommend for patients with NDBE.[6,7] However, the patients with NDBE represent approximately 89% of the patients in surveillance for BE, indicating that the majority of progression events may occur in patients diagnosed as NDBE at their most recent endoscopy.[7,8]

Endoscopic eradication therapy (EET) is highly effective to halt the progression of BE to HGD or EAC.

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Given this fact, improved risk stratification to enable better identification of patients who are at high risk for progression can help direct effective therapeutic intervention that has been proven to improve outcomes. In addition, identification of patients with lower progression risk who can be effectively managed by a tailored surveillance-only approach would be expected to improve health outcomes. The tissue systems pathology test (TissueCypher, also known as TSP-9, Castle Biosciences, Inc.) is available commercially and has been extensively validated to predict progression of BE to HGD/EAC within 5 years.[9–18] This test uses a spatialomics-based multiplexed fluorescent imaging platform that quantifies nine protein-based markers and quantitative image analysis linked to a risk prediction algorithm that integrates 15 quantitative image analysis features to produce a risk score that ranges from 0 to 10 and a risk class of low, intermediate, or high risk for progression to HGD/EAC within 5 years.[9] The aim of this study was to evaluate the use of TSP-9 to risk-stratify clinically relevant subsets of patients with BE in clinical practice.

MATERIALS AND METHODS

Study Design and Patients

The study cohort included 8080 patients with BE with clinicopathologic data for whom TSP-9 tests were ordered from June 2016 to July 2023 by 891 physicians in the United States. Ordering sites were categorized as academic medical centers, which were defined as practices associated with universities or nonacademics that included private practices, community hospitals, and integrated healthcare systems. Patient age, sex (male vs. female), BE segment length [long ($\geq$3 cm) vs. short ($<$3 cm)], and pathology diagnoses (LGD, IND, and NDBE) were abstracted from health records. Pathology diagnoses of patients with BE (n = 142) that were not clearly categorized as NDBE, IND, or LGD on the report from the submitting pathology laboratory were excluded from analysis. The TSP-9 risk classes (high, intermediate, and low) and probability of progression to HGD/EAC within 5 years predicted by the TSP-9 were evaluated in all patients and subsets of patients defined by clinical features and pathology diagnoses. The study was approved by Advarra's Institutional Review Board.

Tissue System Pathology (TSP-9) Testing

The TissueCypher Barrett's Esophagus Test (TSP-9) was run on sections from each specimen at Castle Biosciences' CLIA-certified laboratory (Pittsburgh, PA), as previously described.[10] Test results were reported to ordering physicians that included the TSP-9 continuous risk score (0 to 10), risk class (low, intermediate, or high) for progression to HGD/EAC within 5 years, as well as the probability of progression to HGD/EAC within 5 years associated with the reported continuous risk score. The probability of progression predicted by TSP-9 was based on progression rates in a published clinical validation study with progression outcomes.[17]

Statistical Analysis

Chi-square test was used to compare the percentage of patients scoring low, intermediate, and high from academic centers versus nonacademic centers and in clinically relevant subsets of patients defined by clinical features (sex, age, and segment length) and pathology diagnoses (NDBE, IND, and LGD). Pairwise Wilcoxon tests with the Holm adjustment were used to compare the 5-year risk of progression predicted by the TSP-9 in subsets of patients defined by pathology diagnoses. One sample bootstrap test was used to evaluate risk stratification in patient subsets with the null hypothesis that patients with NDBE, female patients, patients who were $<$65 years of age, and short-segment BE would score low risk for progression to HGD/EAC.

RESULTS

Patient Characteristics

The clinical characteristics of the patient cohort are summarized in Table 1. Eight thousand eighty patients with BE were evaluated from 36 academic centers and 469 nonacademic centers. Orders were received from a total of 891 physicians. Four hundred sixty-two (5.7%) of TSP-9 test orders were from academic medical centers, and 7618 (94.3%) patients were from nonacademic settings including private practices, community hospitals, and integrated healthcare systems. Patients managed at academic sites more often scored intermediate/high risk than patients at community sites (22.9% vs. 16.4%, $P = 0.0003$). The clinicopathologic characteristics of the patients were consistent with the published literature on the surveillance population of patients with BE in the United States.[7] The mean age of patients was 63.6 years (range, 15 to 90), 4961 (61.4%) patients were male, and 4324 patients (53.5%) were eligible for Medicare. Segment length was available for 686 patients, of which 384 (56.0%) had long-segment BE ($\geq$3 cm), consistent with recent published literature on BE segment length.[19,20]

Pathology reports submitted with test orders showed that 7586 (93.9%) patients had a pathology diagnosis of NDBE, 312 (3.9%) had IND, and 182 (2.3%) had LGD, and 1036 (12.8%) had biopsies from multiple endoscopic levels

TABLE 1. Patient Characteristics

	Patients with BE (n = 8080)
Age*, range, y (mean ± SD)	15–90 (63.6 ± 12.6)
Medicare eligible (65+ y), n (%)	4324 (53.5)
Sex, n (%)†	
Male	4961 (61.4)
Female	3115 (38.6)
Practice setting, n (%)	
Academic medical center‡	462 (5.7)
Nonacademic	7618 (94.3)
Diagnoses, n (%)	
NDBE	7,586 (93.9)
IND	312 (3.9)
LGD	182 (2.3)
Segment Length, n (%)§	
Short ($<$3 cm)	302 (44.0)
Long ($\geq$3 cm)	384 (56.0)
TissueCypher (TSP-9) test results, n (%) (all patients)	
Low risk	6,725 (83.2)
Intermediate risk	855 (10.6)
High risk	500 (6.2)

*Age of patients 90 and over were recoded to 90 to protect patient identifying information.

†Four patients did not have a recorded sex.

‡Academic centers were defined as practices associated with universities.

§Segment length was only available for 686 of 8080 patients.

submitted for testing. Because 94.3% of test orders were placed by physicians at community practice sites, the majority of the diagnoses were likely rendered by generalist pathologists, although information on the subspeciality training and experience of pathologists was not available. The median predicted 5-year rates of progression to HGD/EAC in the diagnostic subsets (without TSP-9 risk stratification) were 3.4% (IQR 2.1 to 5.4) for NDBE, 4.4% (IQR 2.5 to 8.1) for IND, and 6.3% (IQR 3.0 to 14.5) for LGD ($P < 0.004$ for all pairwise comparisons, Fig. 1), which are similar to published rates of progression associated with these pathology diagnoses in the community practice setting.[6,21,22] The TSP-9 scored 6.2% of patients as high risk, 10.6% as intermediate risk, and 83.2% as low risk for progression to HGD/EAC within 5 years.

TSP-9 Test Provided Clinically Impactful Risk Stratification in the Diagnostic Subsets of BE

Risk stratification provided by the TSP-9 was evaluated in the diagnostic subsets of patients. In patients with NDBE, the TSP-9 scored 15.3% (n = 1160) of patients as intermediate/high risk (95% CI 14.5% to 16.1%, $P < 0.0001$, Table 2, Fig. 2), with 10.2% scoring intermediate and 5.1% scoring high risk, which was 6.4 times higher than the number of patients who received a pathology diagnosis of LGD (n = 182). Intermediate risk scores in patients with NDBE predicted a 5-year risk of progression to HGD/EAC of 8.1% (IQR 7.3 to 9.1) which was similar to the risk of progression in patients with LGD in this cohort [6.3% (IQR 3.0 to 14.5) in 5 y] as well as published estimates (Fig. 1).[22] High-risk scores in patients with NDBE predicted a 5-year progression risk of 15.3% (IQR 12.9 to 22.5), which is higher than published estimates of progression in expert pathologist-confirmed LGD and HGD.[23] Low-risk scores in patients with diagnoses of NDBE predicted a 5-year progression risk of 2.8% (IQR 1.8 to 4.3), or 0.56% per year.

TSP-9 risk stratification results were also evaluated in the subset of patients with IND and LGD. Intermediate/high-risk TSP-9 results were obtained in 34% of patients with IND and 49% of patients with LGD, providing an objective result to enable confidence in an escalation of management in these subsets (Fig. 2). TSP-9 testing scored 66.3% of patients with IND and 50.5% of patients with LGD as low risk for progression to HGD/EAC in 5 years,

TABLE 2. TSP-9 Risk Stratification

	Patients with BE
TSP-9 test results, n (%) (by site type)	
Academic centers*	
Low risk	356 (77.1)
Intermediate risk	59 (12.8)
High risk	47 (10.2)
Nonacademic centers	
Low risk	6369 (83.6)
Intermediate risk	796 (10.4)
High risk	453 (6.0)
	Probability of progression to HGD/EAC within 5 y (median [IQR])†
All patients	
Low risk	3.0% [1.8–4.3]
Intermediate risk	8.1% [7.3–9.1]
High risk	16.2% [12.9–23.7]
All patients with NDBE (without risk stratification)	3.4% [2.1–5.4]
NDBE risk-stratified by TSP-9	
Low risk	2.8% [1.8–4.3]
Intermediate risk	8.1% [7.3–9.1]
High risk	15.3% [12.9–22.5]
All IND patients (without risk stratification)	4.4% [2.5–8.1]
IND risk-stratified by TSP-9	
Low risk	3.2% [1.8–4.3]
Intermediate risk	8.1% [7.3–9.1]
High risk	18.1% [14.5–26.3]
All LGD patients (without risk stratification)	6.3% [3.0–14.5]
LGD risk-stratified by TSP-9	
Low risk	3.0% [1.7–4.8]
Intermediate risk	9.4% [8.4–10.3]
High risk	21.3% [14.7–33.1]

*Academic centers were defined as practices associated with universities.
†Probability of progression within 5 years is provided on the TissueCypher (TSP-9) clinical report and is based on progression rates in a published clinical validation study.[17]

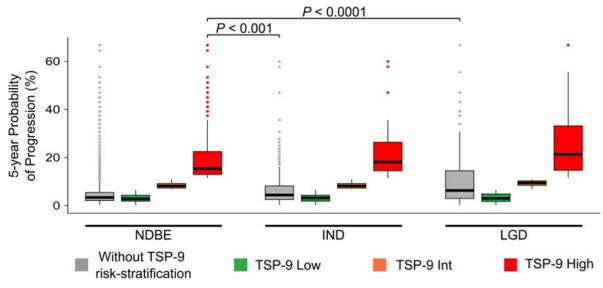

FIGURE 1. Probability of progression to HGD/EAC within 5 years. Predicted probability of progression to HGD/EAC within 5 years in patients with pathology diagnoses of nondysplastic BE (NDBE, n = 7,586), indefinite for dysplasia (IND, n = 312) and low-grade dysplasia (LGD, n = 182) without TSP-9 (gray) and with TSP-9 risk classes of low (green), intermediate (orange) and high risk (red). The probability of progression predicted by TSP-9 is based on progression rates in a published clinical validation study with progression outcomes.[17]

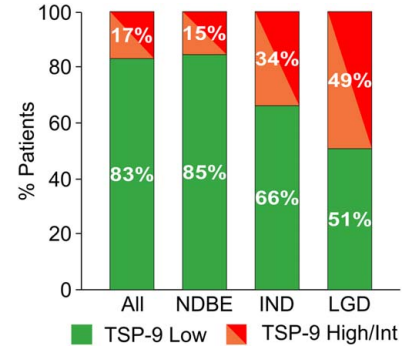

FIGURE 2. TSP-9 risk stratification results in the diagnostic subsets of BE. Percentage of patients scoring TSP-9 low (green) and intermediate or high risk, that is, nonlow risk (orange/red) in patients with BE without dysplasia (NDBE), indefinite for dysplasia (IND), and low-grade dysplasia (LGD). Diagnoses were abstracted from pathology reports and segment length was abstracted from endoscopy reports. Intermediate- and high-risk classes were combined, as both have been associated with significantly increased risk of progression to HGD/EAC in patients with BE.

with predicted 5-year progression risks of 3.2% (IQR 1.8 to 4.3) and 3.0% (IQR 1.7 to 4.8), respectively (Table 2, Fig. 1). This indicates there are low-risk cohorts of patients within the subsets of IND and LGD that can be identified by TSP-9, enabling confidence in a surveillance approach instead of therapy.

TSP-9 Test Provided Objective Risk Stratification in Clinically High-Risk and Clinically Low-Risk Subsets of Patients With BE

TSP-9 results were evaluated in subsets of patients stratified by sex and segment length, which are known clinical risk factors in patients with BE. In females and patients with short-segment BE, which are considered to be clinically low risk, the TSP-9 detected 15.2% (95% CI 14.1% to 16.6%, $P < 0.0001$) and 14.6% (95% CI 10.9% to 18.9%, $P < 0.0001$), respectively, as intermediate/high risk with predicted 5-year progression rates of 9.1% (IQR 7.7 to 12.5) and 9.7% (IQR 8.0 to 11.5) (Fig. 3). These results indicate that there are significant subsets of clinically low-risk patients who are at increased risk for progression as determined by TSP-9. The TSP-9 scored 17.7% of male patients as intermediate/high risk with a predicted 5-year risk of HGD/EAC of 9.7% (IQR 7.7 to 14.5) (Fig. 3). The higher percentage of male versus female patients scoring intermediate/high risk ($P = 0.0039$) is consistent with published literature showing that the male BE population harbors more progressors. The test also scored a statistically significant higher percentage of long-segment patients as intermediate/high risk (25.5%) than short-segment patients (14.6%) (n = 686, $P = 0.0006$). Of the patients with segment length reported, the majority (91.1%) were from non-academic centers. The identification of intermediate/high-risk patients in all evaluated subsets of patients indicates that TSP-9 can risk stratify independent of clinical variables.

DISCUSSION

This study evaluated use of the TSP-9 test in risk-stratifying clinically relevant subsets of patients with BE in clinical practice. Clinical use of TSP-9 showed adoption that reflects the BE surveillance population in the United States with 94.3% of orders coming from nonacademic, community practice sites and 93.9% having pathology diagnoses of NDBE. In a cohort of 8080 patients from 505 clinical sites, TSP-9 risk-stratified patients with BE with high-risk clinical features including male sex, long-segment length, and diagnoses of IND or LGD, as well as low-risk clinical features, including women, patients with short-segment BE and diagnosis of NDBE. The TSP-9 identified intermediate/high-risk patients in all evaluated clinicopathologic subsets, indicating that the test has significant, independent clinical utility to improve management decisions for the BE surveillance population. In line with recommended use of the TSP-9 in the 2022 American Gastroenterological Association (AGA) BE Clinical Practice Update, the majority of patients receiving TSP-9 results had diagnoses of NDBE.[7] TSP-9 identified an intermediate/high-risk pool of patients with NDBE, predicted to progress at a higher rate (8.1% for intermediate risk and 15.3% for high-risk patients by 5 y) than patients with LGD (6.3% by 5 y).[10–14] This intermediate-/high-risk subset of patients with NDBE may benefit from escalation of management to reduce the incidence and mortality of EAC. The TSP-9 scored the majority of patients with NDBE (85%) as low risk for progression, which supports adherence to 3- to 5-year surveillance per guidelines for most patients with NDBE. Taken together these results demonstrate that risk stratification by the TSP-9 can increase early detection of progressors at the NDBE stage, enabling risk-aligned management of BE.

In this cohort of patients with BE, the TSP-9 identified 15.3% of patients with NDBE as intermediate/high risk for progression to HGD/EAC within 5 years, 6.4 times greater than the total number of patients with LGD. These patients may benefit from either close endoscopic surveillance to detect dysplasia or EAC at an early treatable stage or EET which, regardless of grade, has been shown to be safe and highly effective in eradicating dysplasia and early EAC and in preventing future malignant progression.[24,25] Close surveillance and EET have both been shown to be effective strategies to improve health outcomes for patients with BE.[24,25] Although the overall progression rate in the NDBE population is low, which has led to guideline recommendations for surveillance at 3- to 5-year intervals in these patients, these patients represent the majority of the ∽490,000 patients undergoing endoscopic surveillance for BE each year in the United States.[6,8] As such, the NDBE population may harbor the majority of progressors. Early identification of these progressors by TSP-9 coupled with escalated management including EET could significantly reduce the incidence of EAC, which is the goal of surveillance programs. Risk stratification provided by the TSP-9 can also be beneficial in identifying patients with NDBE who are at low risk for progression and can avoid unnecessary procedures. Overutilization of endoscopy has been reported in approximately 30% of patients with NDBE, which may be due to uncertainty regarding risk of progression and patient anxiety about the potential for development of EAC.[26–29] Objective risk stratification by TSP-9 may support increased adherence to 3- to 5-year surveillance intervals as recommended by guidelines in the majority of patients with NDBE who score low risk, allowing for more efficient use of healthcare resources as well as improved quality of life.

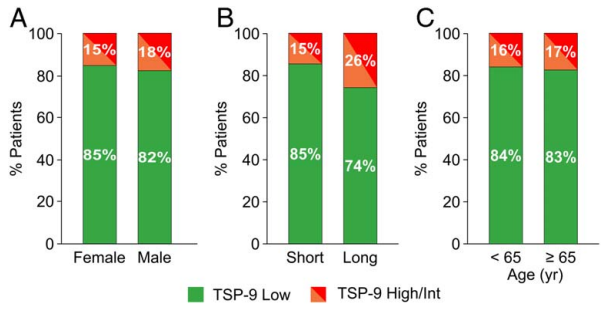

FIGURE 3. TSP-9 risk stratification results in clinically high-risk and clinically low-risk subsets of patients with BE. A, Percentage of female (n = 3115) and male (n = 4961) patients with BE scoring TSP-9 low (green) and intermediate or high risk (orange/red). B, Percentage of patients with BE with short- (n = 302) and long-segment (n = 384) BE scoring TSP-9 low and intermediate or high risk. C, Percentage of patients with BE with < 65 (n = 3756) and ≥ 65 years of age (n = 4324) scoring TSP low and intermediate or high risk. Diagnoses were abstracted from pathology reports and segment length was abstracted from endoscopy reports. Intermediate- and high-risk classes were combined, as both have been associated with significantly increased risk of progression to HGD/EAC in patients with BE.

The subset of patients with IND and LGD can be difficult to manage clinically due to the significant observer variability in the pathology diagnosis and uncertainty in the natural history.[30] There is also a clinical need to identify patients with IND/LGD who have a low risk for progression to HGD/EAC, as these patients can be effectively managed by surveillance alone instead of EET. This study demonstrated that the TSP-9 can identify a pool of low-risk patients with IND/LGD with predicted progression rates similar to patients with NDBE. Low-risk patients with IND may be effectively managed by long-interval instead of short-interval surveillance, and low-risk patients with LGD may be effectively managed by short-interval surveillance instead of EET. Objective risk stratification by TSP-9 in IND/LGD patients can enable risk-aligned decision-making, allowing the lower-risk group of patients to safely avoid overuse of endoscopy and unnecessary therapeutic interventions to improve health outcomes.[31]

Long-segment Barrett's and male sex have been associated with a higher risk of progression and the recent guidelines from the American College of Gastroenterology recommend use of segment length to guide surveillance intervals for patients with NDBE.[5,7,19,32] The TSP-9 provided objective risk stratification in both female and male subsets of patients, and the subsets with short- and long-segment BE, indicating that the test can provide risk stratification independently of clinical factors.

The main strength of this study is the evaluation of a large cohort (8080 patients from 891 physicians in 505 centers) of patients with BE who are representative of the US BE surveillance population in terms of pathology diagnoses of NDBE, IND, and LGD and predicted progression rates associated with these diagnoses. An additional strength was the availability of clinical and pathological data for such a diverse population of patients, which enabled evaluation of the TSP-9 in subsets of patients defined by clinicopathologic variables with sufficient statistical power. The limitation of this study includes a lack of follow-up data on the health outcomes of the patients. In addition, information on segment length was available for only 686 patients, the majority of which were from nonacademic centers.

In conclusion, the TSP-9 provided objective risk stratification within all clinically relevant patient subsets, including those considered to be at low risk for malignant progression based on clinicopathologic factors. Risk stratification provided by the TSP-9 can increase the early detection of patients at high risk for progression enabling escalation of management to reduce the incidence and mortality of EAC. The test also identifies patients at low risk for progression who can avoid unnecessary interventions and be effectively managed by surveillance. The risk results provided by the TSP-9 allow physicians to make risk-aligned management decisions with their patients that can lead to improved health outcomes.

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