Annals of Gastroenterology (2026) **39,** 1-10

Clinical utility of the tissue systems pathology test for risk-aligned management of Barrett's esophagus: a decision modeling study

Lucas C. Duits[a†], Amir M. Khoshiwal[a†], Jon M. Davison[b], Prashanthi N. Thota[c], John R. Goldblum[c], David L. Diehl[d], Harshit S. Khara[d], Gary W. Falk[e], Christian M. Smolko[f], Jennifer J. Siegel[f], Rebecca J. Critchley-Thorne[f]*, Jacques J.G.H.M. Bergman[a]*

Amsterdam University Medical Centers, The Netherlands; University of Pittsburgh School of Medicine, PA, USA; Cleveland Clinic, Ohio, USA; Geisinger Medical Center, Danville, PA, USA; Perelman School of Medicine University of Pennsylvania, Philadelphia, PA, USA; Castle Biosciences, Inc., Pittsburgh, PA, USA

Abstract

Background Barrett's esophagus (BE) is the precursor to esophageal adenocarcinoma (EAC). Guidelines recommend endoscopic surveillance for BE patients to enable early detection and treatment of dysplasia and EAC. The tissue systems pathology test (TissueCypher, TSP-9) has been validated for the risk stratification of BE patients for progression to high-grade dysplasia (HGD)/EAC. The purpose of this study was to use decision modeling to evaluate the utility of the TSP-9 test to enable risk-aligned clinical management for patients with BE.

Methods Patients diagnosed with BE who had known progression outcomes were evaluated, including 392 patients with diagnoses of non-dysplastic BE (NDBE), 63 patients indefinite for dysplasia, and 244 with low-grade dysplasia. Patient management decisions were simulated based on clinical practice, with or without guidance from TSP-9 risk results. Appropriate management decisions were calculated based on known progression outcomes.

Results TSP-9-guided management resulted in a significant increase in appropriate management for patients with BE, including patients with NDBE and short-segment BE who are considered clinically to be at lower risk (P<0.001). In patients with NDBE who progressed to HGD/EAC, the use of TSP-9 increased the percentage of patients receiving short-interval surveillance or endoscopic eradication therapy (EET) from 30.4% (95% confidence interval [CI] 22-40) to 56.9% (95%CI 47-67; P<0.001).

Conclusions TSP-9-guided management significantly improved the likelihood of receiving appropriate management for patients with NDBE. TSP-9 demonstrated significant clinical utility, enabling more progressors to be appropriately managed with short-interval surveillance or EET, which are highly effective strategies to improve patient health outcomes for patients with BE.

Keywords Barrett's esophagus, esophageal adenocarcinoma, risk stratification, tissue systems pathology test (TSP-9), TissueCypher

Ann Gastroenterol 2026; 39 (XX): 1-10

Correspondence to: Rebecca J. Critchley-Thorne, PhD, Castle Biosciences, Inc., 100 S Commons, Pittsburgh, PA 15212, USA, e-mail: rthorne@castlebiosciences.com

Jacques J.G.H.M. Bergman, MD, PhD, Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, Academic Medical Center, Meibergdreef 9, Amsterdam 1105 AZ, The Netherlands; j.j.bergman@amc.uva.n

Received 2 December 2025; accepted 13 June 2026; published online 23 July 2023

DOI: https://doi.org/10.20524/aog.2026.1100

Introduction

Barrett's esophagus (BE) is a pre-malignant condition that can progress to esophageal adenocarcinoma (EAC) [1]. Despite extensive BE surveillance programs and the availability of endoscopic eradication therapy (EET), which is highly effective at eradicating BE and preventing EAC, there has been no significant reduction in the incidence or mortality of EAC in decades. The histologic grading of biopsies taken during endoscopy is the main factor used in making clinical management decisions for patients with BE. The grades are non-dysplastic BE (NDBE), indefinite for dysplasia (IND) and low-grade dysplasia (LGD), and have population-based progression rates to high-grade dysplasia (HGD)/EAC of 0.63%, 1.5% and 1.73% per year, respectively [2-4]. However,

risk assessment based on histopathology alone is known to miss many patients with BE who harbor high-risk biology that cannot be observed on histology slides, and there is significant interobserver variation among pathologists in the histologic grading of BE [5,6]. This uncertainty about progression risk can lead to significant variability in management decisions for patients with BE, as well as the overuse of endoscopy and EET [7,8].

Clinicopathologic factors have limited ability to predict which patients with BE will progress to EAC, and patients with clinically lower risk factors, such as NDBE, short-segment BE or female sex, can progress to HGD/EAC during guideline-recommended surveillance intervals. Furthermore, up to 25% of EACs are missed at the initial endoscopy from which BE is diagnosed, delaying diagnosis and treatment [9,10]. To identify high-risk patients who will benefit from intervention to reduce the incidence and mortality of EAC, a risk stratification test is needed for patients with BE. The tissue systems pathology test (TissueCypher, TSP-9) is a commercially available test that analyzes esophageal tissue biopsies obtained from patients diagnosed with NDBE, IND or LGD to predict a patient's risk of progression to HGD/EAC. The test integrates quantitative data from 15 spatialomic features derived from 9 protein biomarkers, together with nuclear morphology, into a locked risk-prediction algorithm that generates a risk report containing a patient's risk score (0.0-10.0), risk class (low, intermediate, high), and 5-year probability of progressing to HGD/EAC.

The TSP-9 test has been validated in multiple clinical studies to objectively predict the progression of BE to HGD/EAC, independently of clinical and pathology variables [11-18]. These studies have shown that the TSP-9 test identifies a subset of high-risk patients with NDBE who progress at similar rates to patients with confirmed LGD, for whom guidelines recommend intervention with short-interval surveillance or EET. These findings are clinically impactful as these high-risk patients with NDBE are missed by the current standard of care, and due to the size of the NDBE population, may represent at least half of the patients who develop EAC during guideline-recommended surveillance intervals each year in the US.

The clinical utility of the TSP-9 test in guiding risk-aligned management decisions for patients with BE with community-based diagnoses of LGD has recently been reported [19]. However, the impact of the test in guiding risk-aligned management decisions has not yet been modeled in the broader BE population. This study evaluated the clinical utility of the TSP-9 test using clinical decision modeling in all patients for whom the test is intended (patients with NDBE, IND or LGD) to assess the utility of TSP-9 to escalate management decisions to short-interval surveillance or EET for patients with BE who are at high risk for progression, and to reduce the overuse of care in patients with BE at low risk for progression, in a large, diverse cohort of patients with known clinical outcomes.

Patients and methods

Study design

Patients with BE who had known progression/non-progression outcomes (n=699) from 5 independent clinical validation studies [11-15] were evaluated; these included 392 patients with an original diagnosis of NDBE, 63 patients with IND and 244 with LGD (Table 1, Supplementary Tables 1,2). The original diagnoses, provided by a mix of generalist and expert gastrointestinal (GI) pathologists at 5 clinical centers in the United States (US) and Europe, based on biopsies from the baseline endoscopy, were abstracted from electronic health records. The same specimens were independently reviewed in a blinded manner by expert GI pathologists as a component of the original research studies. Each specimen was also tested using TSP-9. All data were derived from datasets reported in open access, peer-reviewed, published studies, which had been approved by the relevant institutional review boards at each institution [11-14], or were exempted from review [15] by the relevant institutional ethics committee.

TSP-9 testing

The TSP-9 test was run on each specimen in a blinded manner at Castle Biosciences' Clinical Laboratory Improvement Amendments-certified College of American Pathologists-accredited laboratory (Pittsburgh, PA, USA). All test parameters, including the 9 biomarkers, image analysis features, risk prediction algorithm and cut points, were prespecified and locked, as previously defined [11]. The TSP-9 test results were reported as a continuous risk score (0-10), a categorical risk class (low-, intermediate-, high-risk), and probability for progression to HGD/EAC within 5 years.

[†]These authors *contributed equally* to this work and share *first authorship*

[a]Amsterdam University Medical Center, The Netherlands; [b]University of Pittsburgh School of Medicine, PA, USA; [c]Cleveland Clinic, OH, USA; [d]Geisinger Medical Center, PA, USA; [e]Perelman School of Medicine University of Pennsylvania, PA, USA; [f]Castle Biosciences, Inc., PA, USA. (Christian M. Smolko, Jennifer J. Siegel, Rebecca J. Critchley-Thorne)

Conflict of Interest: LCD and AMK disclose no conflicts. JMD has received consulting income from Castle Biosciences and Cernostics, Inc.[‡] PNT received research funding via a sub-award from an NIH grant awarded to Cernostics, Inc.[‡] JRG has received consulting fees for research work from Cernostics, Inc[‡]. DLD is a consultant for Castle Biosciences, Inc. HSK is a consultant for Castle Biosciences, Inc. GWF has received research funding and consulting income from Castle Biosciences, Inc. and Cernostics, Inc.[‡], research funding and consulting income from Lucid Diagnostics, Inc., and consulting income from CDx Diagnostics and Exact Sciences. RJCT is a full-time employee of, and holds stock and stock options in Castle Biosciences, Inc., and is an inventor on patents on the TissueCypher Barrett's Esophagus test. CMS and JJS are full-time employees of and hold stock and stock options in Castle Biosciences, Inc. JJB has received research funding from Cernostics, Inc.[‡], CDx Diagnostics, and Lucid Diagnostics. [‡]Cernostics, Inc. is a wholly owned subsidiary of Castle Biosciences, Inc.

Funding: This study was funded by Castle Biosciences, Inc.

Table 1 Patient characteristics

Characteristic	Non-progressors[1]	Progressors[2]	All patients
n (%)	509 (72.8)	190 (27.2)	699
Age, median (IQR)	61 (53-69)	63.0 (56.0-69.1)	61.0 (53.1-69.1)
HGD/EAC-free surveillance time, median years[3] (IQR)	6.7 (5-9)	2.6 (1.2-4.2)	5.8 (3.5-8.2)
Sex, n (%)			
Male	385 (75.6)	164 (86.3)	549 (78.5)
Female	124 (24.4)	26 (13.7)	150 (21.5)
Segment length, n (%)			
Long (≥3 cm)	311 (61.1)	148 (77.9%)	459 (65.7)
Short (<3 cm)	148 (29.1)	36 (18.9%)	184 (26.3)
Unknown	50 (9.8)	6 (3.2%)	56 (8.0)
Original[4] diagnosis, n (%)			
NDBE	290 (57.0)	102 (53.7)	392 (56.1)
IND	51 (10.0)	12 (6.3)	63 (9.0)
LGD	168 (33.0)	76 (40.0)	244 (34.9)
TSP-9 risk class, n (%)			
High-risk	32 (6.3)	80 (42.1)	112 (16.0)
Intermediate-risk	61 (12.0)	35 (18.4)	96 (13.7)
Low-risk	416 (81.7)	75 (39.5)	491 (70.2)

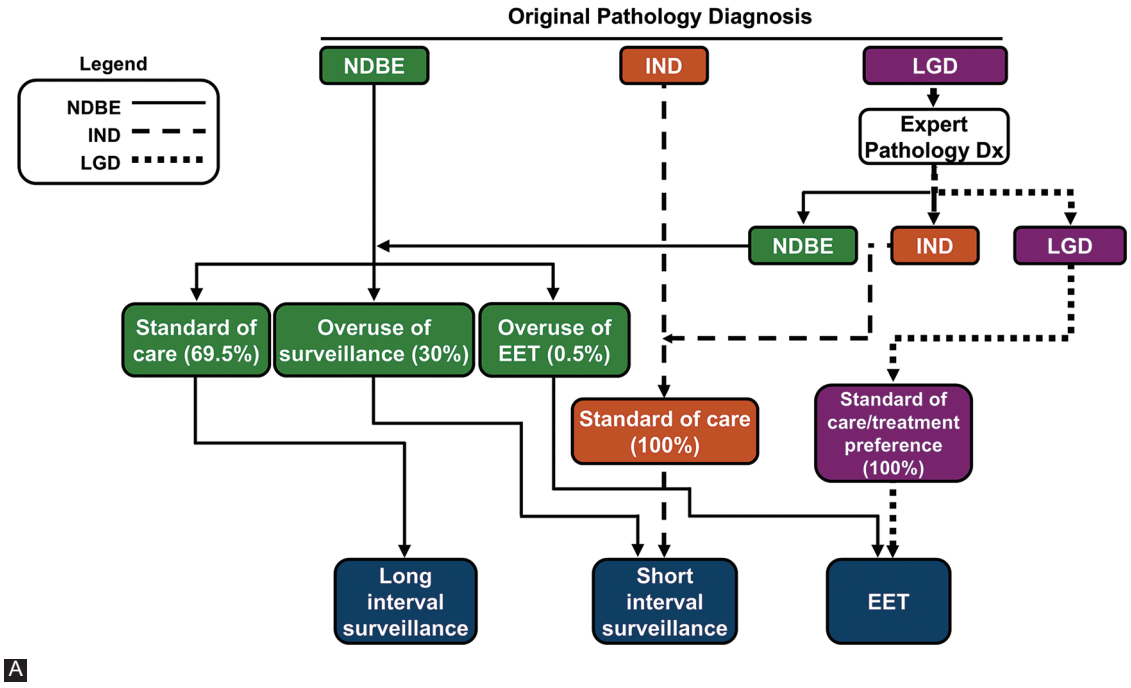
[1]Patients without progression to HGD/EAC during follow-up period
[2]Patients who received a diagnosis of HGD/EAC during follow-up period
[3]Time to subsequent diagnosis of HGD/EAC (for progressors) or last follow-up (for non-progressors)
[4]Original pathology diagnosis abstracted from electronic health records
EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; IND, indefinite for dysplasia; IQR, interquartile range; LGD, low-grade dysplasia; NDBE, non-dysplastic Barrett's esophagus; TSP-9, tissue systems pathology test

Clinical decision models and management simulations

A decision-tree model was used to simulate the clinical course of patient care and outcomes, with and without the use of TSP-9 results in BE disease management decisions, using known patient progression outcomes data from 5 clinical validation studies. For both simulations (with and without TSP-9), appropriate management for each patient was determined based on alignment between the management decision (long-interval surveillance in 3-5 years, short-interval surveillance within 1 year, or EET) and disease progression. Short-interval surveillance (i.e., surveillance within 1 year) or EET was considered appropriate if a patient had documented progression to HGD/EAC, and long-interval surveillance was considered appropriate if available outcome data showed no progression to HGD/EAC. The HGD/EAC-free surveillance time for this model was defined as the time between the endoscopy at which biopsies were tested with TSP-9, and either the subsequent diagnosis of HGD/EAC (for progressors) or last follow-up (for non-progressors).

For simulated management without TSP-9 testing, management decisions depended on the original and/or expert pathological diagnosis (Fig. 1A). Patients with an original pathology diagnosis of NDBE were managed with long-interval surveillance, while patients with a diagnosis of IND were managed with short-interval surveillance. Patients with an original pathology diagnosis of LGD or higher were assumed to have their specimen reviewed by an expert pathologist per guidelines. Patients with an expert pathology diagnosis of NDBE were managed with long-interval surveillance, while a diagnosis of IND was managed with short-interval surveillance. If the expert pathologist diagnosis was LGD or higher, the patient underwent EET, in accordance with guidelines that suggest EET over surveillance for management of confirmed LGD [1,20]. The simulation included an additional clause, given the documented overtreatment of patients with NDBE reported in the clinical setting [21-24]. Wani *et al* reported that 30% of patients with NDBE received a surveillance endoscopy earlier than the long-interval 3-year time point [22]. Additionally, the use of EET has been reported in patients with NDBE (0.5%), according to commercial claims and encounters databases and peer-reviewed literature [25-27]. Therefore, in the simulated management, 30% of patients with an original pathology diagnosis of NDBE received short-interval surveillance, while 0.5% underwent EET (Fig. 1A, Supplementary Tables 3,4).

For simulated management that included TSP-9 testing and guidance, management decisions depended on a combination of original and/or expert pathological diagnosis and the TSP-9 result (Fig. 1B). If the original diagnosis was NDBE or IND, and the TSP-9 result was low-risk, management was long-interval surveillance. If the original diagnosis was LGD, it was assumed that slides were reviewed by an expert pathologist. If the expert pathology diagnosis was NDBE, management was long-interval surveillance if the TSP-9 result was low-risk, and short-interval surveillance if the TSP-9 result was intermediate/high-risk. If the expert pathology diagnosis was IND, management was long-interval surveillance for patients with a TSP-9 low-risk



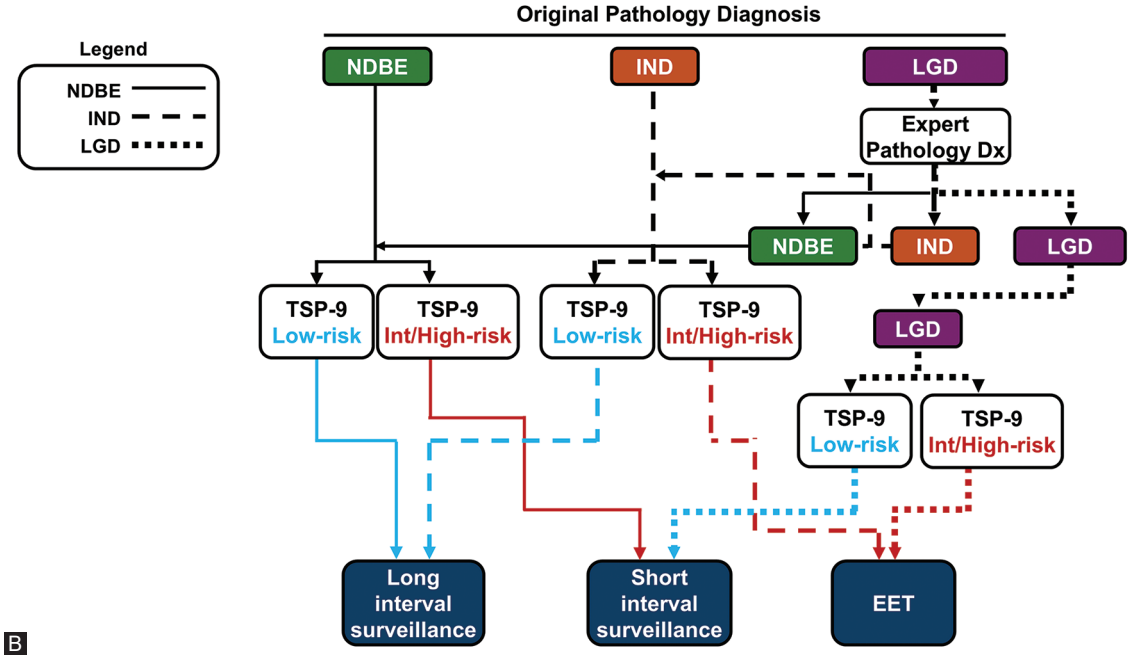


Figure 1 (A and B) Clinical decision model and management simulation scheme, with and without TSP-9-guided risk stratification. A decision-tree model was used to simulate the clinical course of patient care and outcomes with and without including TSP-9 results in BE management. Management decisions depended on the original and/or expert pathology diagnoses, with consideration of real-world over-surveillance and overuse of EET incorporated into the model for patients with NDBE. Within the simulation model, appropriate management for each patient was determined based on alignment between the management decision (long-interval surveillance in 3-5 years, short-interval surveillance in 1 year, or EET) and progression to HGD/EAC, or lack of progression, during follow-up. Short-interval surveillance or EET was considered appropriate if a given patient had documented progression to HGD/EAC, and long-interval surveillance was considered appropriate if no progression to HGD/EAC was reported during available follow-up

BE, Barrett's esophagus; EET, endoscopic eradication therapy; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; NDBE, non-dysplastic Barrett's esophagus; TSP-9, tissue systems pathology test

result, and EET for patients with intermediate-/high-risk TSP9 results. Finally, if the expert pathology diagnosis was LGD, management was short-interval surveillance if the TSP9 result was low-risk, and EET if intermediate-/high-risk (Fig. 1B, Supplementary Tables 3,4). The intermediate- and high-risk classes were combined in the model, based on the previously reported finding that both risk classes are at statistically significantly higher risk of developing HGD/EAC compared to patients with low-risk results (hazard ratio [HR] 7.1, 95% confidence interval [CI] 4.8-11.2 for high- vs. low-risk, P<0.001, and HR 2.6, 95%CI 1.3-4.7, P=0.003 for intermediate- vs. low-risk).

While additional factors, such as patient preferences and physician/site-specific practices, can factor into management decisions, these were not evaluated in this model, since the aim was to evaluate the impact of TSP-9 guidance on risk-aligned management decisions for patients with BE; hence these other factors were kept constant. This study was reported in alignment with guidelines provided by the Standards for Quality Improvement Reporting Excellence 2.0 (Supplementary Table 5) [28].

Statistical analysis

Appropriate or inappropriate management for each patient was determined based on alignment between clinical management and the known progression outcomes. Short-interval surveillance or EET was considered appropriate if a given patient had documented disease progression to HGD/EAC, and long-interval surveillance was considered appropriate if no disease progression to HGD/EAC was reported during the available follow-up. The primary measure of interest was the percentage of appropriately managed patients for each simulation (TSP-9 guided and unguided) for all patients, and for each clinically-relevant subset of patients. Confidence intervals (95%CIs, 2-tailed) were calculated for the percentage of management decisions that were scored as appropriate per the known patient outcomes for each simulation for each subset of interest, by bootstrap resampling the final management results (with replacement ×10,000 iterations to maximize the precision of P-values, and no constraints placed on the proportion of progressors or non-progressors for resampling). Non-overlapping CIs between TSP-9 guided and unguided simulations indicate a significant difference in patient management (α=0.05/number of family-wise comparisons). P-values for bootstrap tested data were determined by the empirical cumulative distribution function method. Family-wise alpha was adjusted when progressors and non-progressors were tested separately using the conservative Bonferroni method (α=0.05/2 = 0.025). All clinical management simulations and statistical analyses were performed using custom-written software and open-source packages in R v4.1.3. Independent oversight and verification of the data were carried out by the lead author (LCD), who had full access to the raw data and analysis code and reports no conflicts of interest.

Results

Patient characteristics

Six hundred ninety-nine patients with BE from 5 published clinical validation studies were included, of whom 190 (27.2%) were subsequently diagnosed with HGD/EAC, whereas 509 (72.8%) did not progress to HGD/EAC during follow-up [11-15] (Table 1, Supplementary Tables 1,2). The median age of patients in this cohort was 61 years (interquartile range [IQR] 53.1-69.1), while the majority of patients were male (78.5%) and had long-segment BE (65.7%). In this cohort of patients with BE, 392 patients had an original diagnosis of NDBE, 63 had IND and 244 had LGD.

TSP-9 and appropriate management

To evaluate the utility of TSP-9 in guiding clinical management decisions for patients with BE, the percentage of appropriate management decisions was calculated with and without guidance from the TSP-9 risk results. Management decision simulations showed that use of the TSP-9 test results in combination with pathology diagnoses significantly increased the percentage of patients who received appropriate management from 59.8% (95%CI 56-63%) to 75.3% (95%CI 72-78%) (P<0.001) (Fig. 2A). In patients with BE who progressed to HGD/EAC, use of the TSP-9 test significantly increased the percentage of patients receiving EET or short-interval surveillance from 50.5% (95%CI 43-58%) to 66.3% (95%CI 59-73%) (P=0.008) (Fig. 2A). Overall, use of the TSP-9 test led to a 31.9% decrease in the undertreatment of progressors (P=0.008) and a 41.7% decrease in the overtreatment of non-progressors (P<0.001) (Fig. 2B,C). These results demonstrate the clinical utility of the TSP-9 test in increasing early detection of progressors, enabling escalation of management to prevent progression to HGD/EAC.

TSP-9 in patients who progress from NDBE to HGD/EAC

Of the 392 patients with original diagnoses of NDBE, 102 (26.0%) were subsequently diagnosed with HGD/EAC, while 290 (74.0%) did not progress to HGD/EAC during follow-up (Table 1). HGD/EAC-free surveillance times in progressors had a median of 3.3 years (IQR 2-5) after the baseline endoscopy, whereas non-progressors had a median HGD/EAC-free follow-up of 6.4 years (IQR 5-9). Additional baseline demographic features can be found in Supplementary Table 1. The median age of patients with NDBE was 61 years (IQR 53-69), 40.8% of patients were ≥65 years of age (eligible for Medicare), 77.8% of patients were males, and 69.1% had long-segment BE (≥3 cm). Eighty-six of 102 progressors (84.3%) and 219 of 290 non-progressors (75.5%) were males, and 82.4% of progressors had long-segment BE (≥3 cm), compared to 64.5% of non-progressors. The TSP-9 test scored 26.3% of patients with NDBE as intermediate/high-risk for progression, and 73.7% as low-risk for progression to HGD/

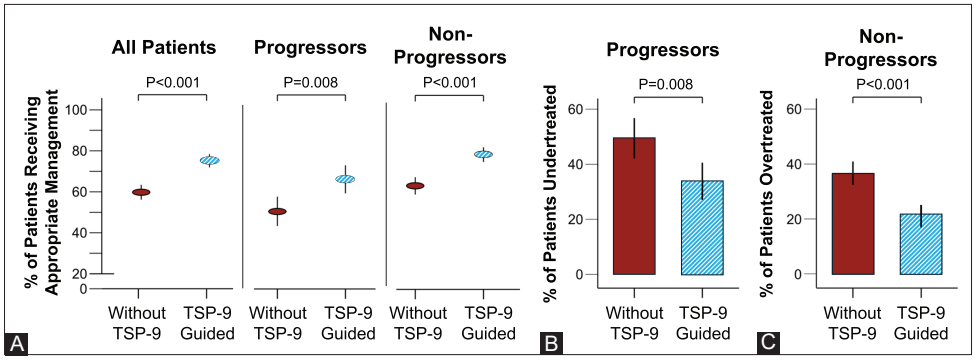


Figure 2 TSP-9-guided management increases the likelihood of appropriate management decisions in patients with BE. Likelihood of receiving appropriate management per known progression/non-progression outcome using BE management without TSP-9 vs. TSP-9-guided management. (A) All patients with BE (NDBE, IND and LGD, n=699), patients with BE who were subsequently diagnosed with HGD/EAC (progressors, n=190), or patients with BE without progression (non-progressors, n=509). (B) Percentage of progressors who received management decisions resulting in undertreatment, considering the known clinical outcome. (C) Percentage of non-progressors who received management decisions resulting in overtreatment, considering the known clinical outcome. Error bars indicate 2-tailed 95% confidence intervals. Comparisons between progressors and non-progressors used a family-wise alpha of 0.05/2 tests = 0.025

BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; IND, indefinite for dysplasia; LGD, low-grade dysplasia; NDBE, non-dysplastic Barrett's esophagus; TSP-9, tissue systems pathology test

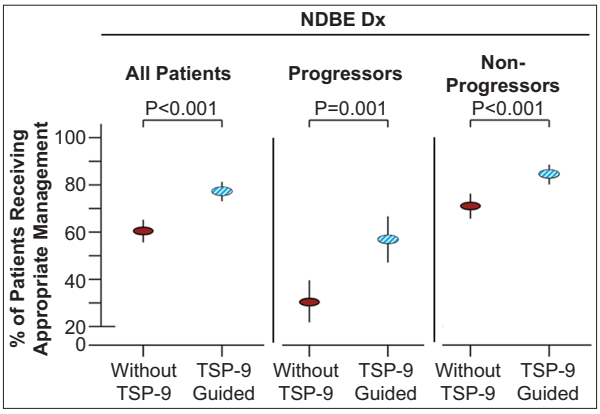


Figure 3 TSP-9-guided management increases the likelihood of appropriate management decisions in patients with pathology diagnoses of NDBE. Likelihood of receiving appropriate management per known progression/non-progression outcome using BE management without TSP-9 vs. TSP-9-guided management in patients with original pathology diagnosis of NDBE (n=392), patients with original pathology diagnosis of NDBE who progressed to HGD/EAC (n=102), and patients with original pathology diagnosis of NDBE without progression (n=290). Original pathology diagnoses were abstracted from electronic health records, which were provided by a mix of generalists and expert gastrointestinal pathologists at 5 sites. Error bars indicate 2-tailed 95% confidence intervals. Comparisons between progressors and non-progressors used a family-wise alpha of 0.05/2 tests = 0.025

BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; NDBE, non-dysplastic Barrett's esophagus; TSP-9, tissue systems pathology test

EAC within 5 years. Of the patients with NDBE who were subsequently diagnosed with HGD/EAC during follow-up, 56.9% were scored as intermediate/high-risk for progression by the TSP-9 test, while 84.5% of patients with NDBE who did not progress to HGD/EAC during follow-up scored low-risk by TSP-9.

The clinical utility of the TSP-9 test was further evaluated in the subsets of patients with pathology diagnoses of NDBE (Fig. 3), who represent approximately 89% of the BE surveillance population in the US. The highest overall clinical utility of the TSP-9 test was observed in patients with an NDBE diagnosis who progressed; in these patients the use of TSP-9 significantly increased the percentage receiving surveillance within 1 year or EET from 30.4% (95%CI 22-40%) to 56.9% (95%CI 47-67%; P=0.001, Fig. 3). A statistically significant increase in appropriate management was also observed in patients with NDBE who did not progress, from 71% (95%CI 66-76%) to 84.5% (95%CI 80-89%) when TSP-9 results were used to guide the management decisions, a significant reduction in the overtreatment of non-progressors (P<0.001, Fig. 3). These results demonstrate the clinical utility of the TSP-9 test in detecting the majority of progressors at the NDBE stage, enabling escalation of management to prevent progression to HGD/EAC, while also preventing overuse of care in patients who do not progress.

TSP-9 test in higher and lower risk patient subsets

The clinical utility of the TSP-9 test results was evaluated in subsets of patients with NDBE stratified by BE segment length, which is a known clinical risk factor in patients diagnosed with BE. Use of the TSP-9 test results significantly increased the percentage of patients receiving appropriate management in the subsets with short- and long-segment BE (Fig. 4). A significant improvement in appropriate management was observed for patients who had NDBE with long-segment BE, from 57.9% (95%CI 52-64%) to 74.9% (95%CI 70-80%, P<0.001) when TSP-9 results were used to guide management decisions (Fig. 4). A similar improvement in appropriate management was observed for patients with NDBE with short-segment BE, which are considered to be clinically lower-risk patients: 66% (95%CI 57-75%) of those patients received appropriate

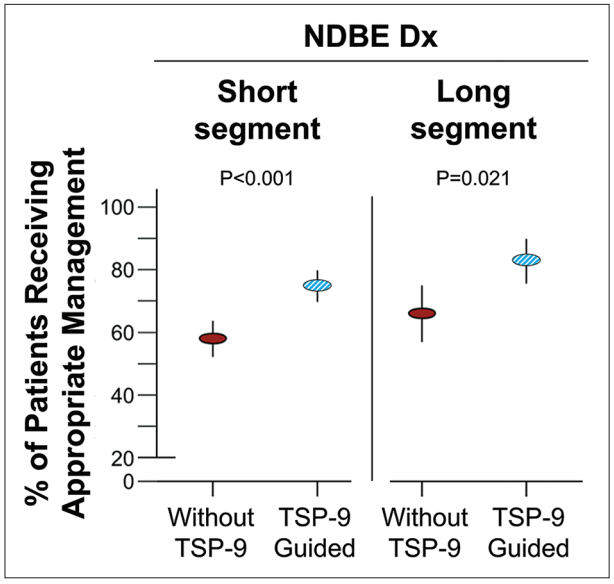


Figure 4 TSP-9-guided management increases the likelihood of appropriate management decisions in clinically relevant subsets of patients with NDBE. Likelihood of receiving appropriate management per known progression/non-progression outcome using BE management without TSP-9 vs. TSP-9-guided management in the subset of patients with NDBE with long-segment BE (n=271), and in patients with NDBE with short-segment BE (n=106). Error bars indicate 2-tailed 95% confidence intervals. Comparisons depending on segment length used a family-wise alpha of 0.05/2 tests = 0.025
BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; NDBE, non-dysplastic Barrett's esophagus; TSP-9, tissue systems pathology test

management without TSP-9, compared to 83% (95%CI 76-90%, P=0.021) when TSP-9 results were used (Fig. 4).

TSP-9-guided management in patients with IND or LGD

Of the 307 patients with IND/LGD, 88 (28.7%) were subsequently diagnosed with HGD/EAC, whereas 219 (71.3%) did not progress to HGD/EAC during follow-up (Supplementary Table 1). HGD/EAC-free surveillance times were a median of 1.9 years (IQR 1-3) after the baseline endoscopy for progressors, while non-progressors had a median HGD/EAC-free follow-up of 7.1 years (IQR 5-10). The median age was 62 years (IQR 55-70), 79.5% of patients were male, and 61.2% had long-segment BE (≥3 cm). The TSP-9 test scored 34.2% of IND/LGD patients as intermediate/high-risk and 65.8% as low-risk for progression to HGD/EAC within 5 years. Of the IND/LGD patients subsequently diagnosed with HGD/EAC during follow-up, 64.8% were scored as TSP-9 intermediate/high-risk, while 78.1% of IND/LGD patients who did not progress to HGD/EAC during follow-up were scored as TSP-9 low-risk.

A statistically significant improvement in appropriate management was also observed in the subset of patients with a pathology diagnosis of IND/LGD when TSP-9 results were included to guide management decisions. This was due to an increase in the percentage of non-progressors receiving appropriate management, from 53.0% (95%CI 46-60%) to 70.8% (95%CI 65-77%) (P<0.001), while the use of TSP-9 results did not lead to undertreatment of patients who progressed to HGD/EAC (Supplementary Fig. 1).

Discussion

This study used decision-tree simulations to evaluate the utility of the TSP-9 test to enable risk-aligned clinical management for patients with BE. The results showed that, when the TSP-9 test was used to guide management, there was a significant increase in the percentage of patients with BE leading to HGD/EAC who received appropriate management through short-interval surveillance or EET. The use of TSP-9 results, compared to current clinical practices, significantly reduced the undertreatment of patients who progressed to HGD/EAC, without leading to overtreatment of patients who did not progress during surveillance. The highest clinical utility of the TSP-9 test was observed in patients with NDBE who progressed to HGD/EAC; this is a critical finding, as these patients can be missed by current clinical practices. Patients with NDBE who progressed to HGD/EAC were significantly more likely to receive short-interval surveillance or EET when the TSP-9 test results were used to guide management decisions, compared to BE management without TSP-9 that was primarily driven by the pathology diagnosis. In patients with NDBE who did not progress during surveillance, TSP-guided management significantly reduced the overuse of endoscopy and EET. Similar clinical utility of the TSP-9 test was observed in NDBE patients with short- and long-segment BE, demonstrating the broad utility of the test in guiding management for patients with NDBE. Collectively, these findings indicate that the TSP-9 test has clinical utility to enable risk-aligned management for patients with BE, thereby allowing more patients at high risk for progression to be detected early and managed with short-interval surveillance or EET, which are highly effective approaches to reduce the incidence of EAC and to improve patient health outcomes [29-31].

Current guidelines recommend endoscopic surveillance with biopsies every 3-5 years for patients with a pathology diagnosis of NDBE, given the low overall rate of progression to HGD/EAC in this group of patients (0.63%/year) [1,4,32,33]. However, patients with NDBE represent 89% of the approximately 450,000 patients who undergo surveillance for BE each year in the US [34]. Thus, the NDBE subset of patients includes approximately 50% of the patients who progress to HGD/EAC. These patients can be missed, and hence undertreated by the current standard of care. Despite current limitations within many health plan medical policies that restrict the use of short-interval surveillance and EET for patients with NDBE, regardless of risk factors, current practice patterns still show considerable use of EET in patients with NDBE [25,31]. However, it is not clear that these EET procedures are being directed to patients with the highest risk of progression within the NDBE population. Early identification of patients with NDBE who are at high risk of progression, coupled with escalated management including EET, could significantly reduce the incidence of EAC, since EET is more effective when

used at earlier stages [25]. Furthermore, real-world evidence from the analysis of electronic health record-derived data suggests that patients with NDBE may require fewer sessions of EET to achieve complete eradication of BE and, therefore, may have a lower likelihood of EET-associated adverse events than patients with dysplasia or EAC, indicating that earlier detection of high-risk patients may optimize the allocation of healthcare resources and improve patient health outcomes [25].

Identification of patients with NDBE at high risk for progression by TSP-9 indicates that there is a subset of patients in surveillance for NDBE who can benefit from similar management to those with LGD with the goal of preventing malignant progression. In clinical practice, TSP-9 identifies approximately 15% of patients with NDBE as intermediate/high-risk for progression, with a predicted progression risk similar to that in patients with LGD [35]. The clinical utility reported here indicates that use of the TSP-9 test can guide escalation of care for patients with NDBE who are at high risk for progression, enabling either short-interval surveillance, or potentially consideration of intervention with EET, after ruling out missed prevalent HGD/EAC. Short-interval surveillance can be an effective management strategy to enable the early detection and treatment of dysplasia and EAC [29]. EET, such as radiofrequency ablation, is 92-99% effective in eradicating BE and preventing progression to EAC, leading to better health outcomes [30,36].

While guidelines recommend 3-5-year surveillance intervals for patients with NDBE, there is variation in adherence to this recommendation: endoscopy is over-utilized in 30-65% of patients with NDBE and EET is used in a subset of patients with NDBE [7,22,34,37]. This overuse of procedures is likely due to uncertainty regarding the risk of progression, and to patient anxiety about the potential for development of EAC [38]. Our model conservatively accounted for this overutilization by assigning 30% of patients with NDBE to short-interval surveillance. A key finding of this study was that when TSP-9 test results were incorporated into simulated management of BE based on real-world data, use of the test reduced the overuse of procedures in patients with NDBE who did not progress to HGD/EAC.

These findings have clinical implications, as they indicate that risk stratification using the TSP-9 test may provide confidence in adhering to the 3-5-year surveillance intervals recommended by guidelines in the majority of patients with NDBE who score low risk, thereby enhancing quality of life and improving efficient utilization of healthcare resources. These findings are supported by peer-reviewed data, including a randomized controlled trial demonstrating that TSP-9 results increased physician adherence to published GI guideline-recommended management strategies [39], and a study by Diehl *et al*, which reported that 33.4% of patients had management plans de-escalated to a surveillance-only approach, based on a low-risk TSP-9 result, irrespective of the original pathological diagnosis [40]. Further illustrating the utility of the test is the number of patients in the population who would need to be tested to identify a patient who will be diagnosed with HGD/EAC within 5 years (prevalence-adjusted number needed to predict; NNP_{adj}). The NNP_{adj} is 32 for a TSP9 intermediate-/high-risk result, which is less than half of the calculated NNP_{adj} when risk is assessed based on an expert pathological diagnosis (NNP_{adj}=70) [17]. This demonstrates the robust nature of the test in comparison to histopathological evaluation alone. Recent findings from the Barrett's Oesophagus Surveillance versus endoscopy at need Study indicated that surveillance at-large did not impact cancer-specific mortality in BE in the United Kingdom [41]. The clinical implications of our decision modeling study suggest that the use of risk stratification tools like the TSP-9 test may be a promising strategy to improve the effectiveness of surveillance practices for managing patients with BE, by targeting short-interval surveillance or EET at patients with the highest risk of progressing to HGD/EAC, while extending surveillance intervals for patients with the lowest risk of progression.

The main strength of this study includes modeling of management decisions in patients with BE using results from 5 independent clinical validation studies, in which each patient had a pathology diagnosis abstracted from medical records, clinical factors, known progression/non-progression outcome data, and TSP-9 risk results. The patient cohorts included were from a broad geographic area (North America, Europe) and were managed by physicians at multiple types of care centers, increasing confidence in the validity and utility of the test for all patients with diagnoses of BE. The large, diverse cohort, representing the Barrett's population with available outcome data, enabled evaluation of the utility of the TSP-9 test in the cohort as a whole, and within clinically relevant subsets of patients (Table 1, Supplementary Tables 1,2). Because of the case–control design of the majority of the utilized studies, 27.2% of the cohort were progressors, which is higher than the expected rate of progression in the general BE population. However, the subset of patients who were progressors had a sufficient sample size to evaluate the utility of the TSP-9 test results in both progressors and non-progressors. The non-progressors had a median progression-free surveillance time of 6.4 years, which exceeds the maximum surveillance interval recommended by guidelines and provided confidence in the non-progression status of these patients. While the study utilized a simulation-based approach, the study modeled use of the TSP-9 test where various generalist and expert GI pathologists reviewed histology slides as a part of clinical practice, and also used expert GI pathology review diagnoses to simulate tertiary care settings where BE biopsy slides with initial diagnoses of LGD are reviewed by expert GI pathologists. As complete adherence to the society guidelines is difficult to achieve in real-world clinical settings, TSP-guided management was compared to BE management without TSP-9, where overuse of both surveillance endoscopy and EET occurs in patients with NDBE [22,34,37].

This study defined what constitutes risk-aligned appropriate management in the context of our model, based on GI society guidelines [1,33,42,43], real world evidence from commercial claims and encounters databases in the US, and the published literature [25,31]. These definitions are intended to illustrate how risk stratification provided by TSP-9 can guide management in patients with BE, and may differ depending on management practices, including surveillance frequencies and

EET usage in settings outside of the US, patient preferences, or other factors that impact patient care including family history of BE/EAC. Additionally, risk factors such as obesity, duration of acid reflux, reflux esophagitis and family history were not available to include in the decision simulation. Prior analyses of these pooled data have shown that TSP-9 outperforms clinical risk factors, including age, sex, segment length and hiatal hernia, in risk-stratifying patients with BE [16], supporting the modeling of TSP-9-guided simulations without clinical factors.

In conclusion, this decision simulation study demonstrated that the TSP-9 test has significant clinical utility in patients with BE, including those with NDBE, where the use of TSP-9 enabled significantly more progressors to be appropriately managed with short-interval surveillance to detect and treat dysplasia and cancer early, or EET to prevent malignant progression. Both escalation approaches are highly effective in improving patient health outcomes, by reducing the incidence and mortality of EAC. Use of the TSP-9 test in conjunction with current clinical practices may enable risk-aligned management, in which care is escalated for patients at high risk for malignant progression, while low-risk TSP-9 results may reduce the overuse of endoscopy and provide confidence in a surveillance-only approach at intervals consistent with guidelines.

Summary Box

What is already known:

- Population-based approaches to risk assessment do not adequately predict whether patients with Barrett's esophagus (BE) will progress to high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC)
- The lack of objective risk stratification tools can result in both over- and undertreatment of patients with BE
- The tissue systems pathology test (TSP-9; TissueCypher) has been validated to predict a patient's personalized 5-year risk of progression to HGD/EAC

What the new findings are:

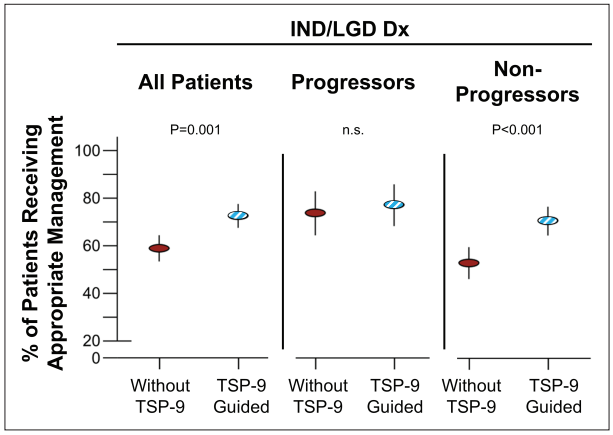
- TSP-9 can enable significantly more progressors to be appropriately managed with short-interval surveillance to detect and treat dysplasia and cancer early, or EET to prevent malignant progression
- TSP-9 test results can reduce the overuse of procedures in patients with NDBE who do not progress to HGD/EAC
- These data add to the growing body of evidence supporting the utility of the TSP-9 test, and support its adoption in clinical practice to improve health outcomes for patients with BE

References

1. Shaheen NJ, Falk GW, Iyer PG, et al. Diagnosis and management of Barrett's esophagus: an updated ACG guideline. *Am J Gastroenterol* 2022;**117**:559-587.
2. Singh S, Manickam P, Amin AV, et al. Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis. *Gastrointest Endosc* 2014;**79**:897-909.
3. Krishnamoorthi R, Mohan BP, Jayaraj M, et al. Risk of progression in Barrett's esophagus indefinite for dysplasia: a systematic review and meta-analysis. *Gastrointest Endosc* 2020;**91**:3-10.
4. Wani S, Falk G, Hall M, et al. Patients with nondysplastic Barrett's esophagus have low risks for developing dysplasia or esophageal adenocarcinoma. *Clin Gastroenterol Hepatol* 2011;**9**:220-227; quiz e26.
5. Kerkhof M, van Dekken H, Steyerberg EW, et al; CYBAR study group. Grading of dysplasia in Barrett's oesophagus: substantial interobserver variation between general and gastrointestinal pathologists. *Histopathology* 2007;**50**:920-927.
6. Montgomery E, Bronner MP, Goldblum JR, et al. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. *Hum Pathol* 2001;**32**:368-378.
7. Cruz JD, Paculdo D, Ganesan D, et al. Clinical variation in surveillance and management of Barrett's esophagus: a cross-sectional study of gastroenterologists and gastrointestinal surgeons. *Medicine (Baltimore)* 2022;**101**:e32187.
8. Abrams JA, Kapel RC, Lindberg GM, et al. Adherence to biopsy guidelines for Barrett's esophagus surveillance in the community setting in the United States. *Clin Gastroenterol Hepatol* 2009;**7**:736-742.
9. Visrodia K, Singh S, Krishnamoorthi R, et al. Magnitude of missed esophageal adenocarcinoma after Barrett's esophagus diagnosis: a systematic review and meta-analysis. *Gastroenterology* 2016;**150**:599-607.
10. Wani S, Holmberg D, Santoni G, et al. Magnitude and time-trends of post-endoscopy esophageal adenocarcinoma and post-endoscopy esophageal neoplasia in a population-based cohort study: the Nordic Barrett's esophagus study. *Gastroenterology* 2023;**165**:909-919.
11. 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;**25**:958-968.
12. 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;**26**:240-248.
13. Davison JM, Goldblum J, Grewal US, et al. Independent blinded validation of a tissue systems pathology test to predict progression in patients with Barrett's esophagus. *Am J Gastroenterol* 2020;**115**:843-852.
14. Frei NF, Konte K, Bossart EA, et al. Independent validation of a tissue systems pathology assay to predict future progression in nondysplastic Barrett's esophagus: a spatial-temporal analysis. *Clin Transl Gastroenterol* 2020;**11**:e00244.
15. 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;**116**:675-682.
16. 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;**20**:2772-2779.
17. 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**:e00631.
18. Khoshiwal AM, Frei NF, Pouw RE, et al; TissueCypher SURF LGD

Study Pathologists Consortium. The tissue systems pathology test outperforms pathology review in risk stratifying patients with low-grade dysplasia. *Gastroenterology* 2023;**165**:1168-1179.
19. Duits LC, Khoshiwal AM, Frei NF, et al; Barrett's SURF LGD Study Pathologists Consortium. 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**:2025-2032.
20. Wani S, Zhou MJ, Sawas T, et al. AGA clinical practice guideline on surveillance of Barrett's esophagus. *Gastroenterology* 2025;**169**:1184-1231.
21. Desai TK, Krishnan K, Samala N, et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. *Gut* 2012;**61**:970-976.
22. Wani S, Williams JL, Komanduri S, et al. Over-utilization of repeat upper endoscopy in patients with non-dysplastic Barrett's esophagus: a quality registry study. *Am J Gastroenterol* 2019;**114**:1256-1264.
23. Peters Y, Honing J, Kievit W, et al. Incidence of progression of persistent nondysplastic Barrett's esophagus to malignancy. *Clin Gastroenterol Hepatol* 2019;**17**:869-877.
24. Thrift AP, Kunzmann AT. Time to tailor surveillance intervals of nondysplastic Barrett's esophagus according to segment length and persistence over multiple endoscopies. *Clin Gastroenterol Hepatol* 2019;**17**:832-834.
25. Smith ZL, Thorgerson AM, Dawson AZ, et al. Incidence of esophageal adenocarcinoma, mortality, and esophagectomy in Barrett's esophagus patients undergoing endoscopic eradication therapy. *Dig Dis Sci* 2023;**68**:4439-4448.
26. Zhang Q, Li M, Jin X, et al. Comparison of interventions for Barrett's esophagus: A network meta-analysis. *PLoS One* 2024;**19**:e0302204.
27. Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for Barrett's Esophagus: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2013;**11**:1245-1255.
28. Ogrinc G, Davies L, Goodman D, et al. SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process. *BMJ Qual Saf* 2016;**25**:986-992.
29. Codipilly DC, Chandar AK, Singh S, et al. The effect of endoscopic surveillance in patients with Barrett's esophagus: a systematic review and meta-analysis. *Gastroenterology* 2018;**154**:2068-2086.
30. Qumseya BJ, Wani S, Gendy S, et al. Disease progression in Barrett's low-grade dysplasia with radiofrequency ablation compared with surveillance: systematic review and meta-analysis. *Am J Gastroenterol* 2017;**112**:849-865.
31. Wolf WA, Pasricha S, Cotton C, et al. Incidence of esophageal adenocarcinoma and causes of mortality after radiofrequency ablation of Barrett's esophagus. *Gastroenterology* 2015;**149**:1752-1761.
32. Muthusamy VR, Wani S, Gyawali CP, Komanduri S; CGIT Barrett's Esophagus Consensus Conference Participants. AGA clinical practice update on new technology and innovation for surveillance and screening in Barrett's esophagus: expert review. *Clin Gastroenterol Hepatol* 2022;**20**:2696-2706.
33. Rubenstein JH, Sawas T, Wani S, et al. AGA clinical practice guideline on endoscopic eradication therapy of Barrett's esophagus and related neoplasia. *Gastroenterology* 2024;**166**:1020-1055.
34. Truven Health Analytics. United States MarketScan Commercial Claims and Encounters Database 2023. Ann Arbor, United States of America: Truven Health Analytics.
35. 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* 2025;**59**:531-536.
36. Cotton CC, Wolf WA, Overholt BF, et al; AIM Dysplasia Trial Group. Late recurrence of Barrett's esophagus after complete eradication of intestinal metaplasia is rare: final report from ablation in intestinal metaplasia containing dysplasia trial. *Gastroenterology* 2017;**153**:681-688.
37. Crockett SD, Lipkus IM, Bright SD, et al. Overutilization of endoscopic surveillance in nondysplastic Barrett's esophagus: a multicenter study. *Gastrointest Endosc* 2012;**75**:23-31.
38. Stier MW, Lodhia N, Jacobs J, et al. Perceptions of risk and therapy among patients with Barrett's esophagus: a patient survey study. *Dis Esophagus* 2018;**31**:dox109.
39. 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**:e00644.
40. Diehl DL, Khara HS, Akhtar N, et al. TissueCypher Barrett's esophagus assay impacts clinical decisions in the management of patients with Barrett's esophagus. *Endosc Int Open* 2021;**9**:E348-E355.
41. Old O, Jankowski J, Attwood S, et al; BOSS Trial Team. Barrett's oesophagus surveillance versus endoscopy at need study (BOSS): a randomized controlled trial. *Gastroenterology* 2025;**169**:1233-1243.
42. Qumseya B, Sultan S, Bain P, et al; ASGE Standards of Practice Committee Chair. ASGE guideline on screening and surveillance of Barrett's esophagus. *Gastrointest Endosc* 2019;**90**:335-359.
43. Wani S, Qumseya B, Sultan S, et al; Standards of Practice Committee. Endoscopic eradication therapy for patients with Barrett's esophagus-associated dysplasia and intramucosal cancer. *Gastrointest Endosc* 2018;**87**:907-931.

Supplementary material



Supplementary Figure 1 TSP-9-guided management increases the likelihood of appropriate management decisions in patients with pathology diagnoses of IND/LGD. Likelihood of receiving appropriate management per known progression/non-progression outcome using BE management without TSP-9 vs. TSP-9-guided management in patients with original pathology diagnosis of IND/LGD (n=307), patients with original pathology diagnosis of IND/LGD who were subsequently diagnosed with HGD/EAC (n=88), and patients with original pathology diagnosis of IND/LGD without progression (n=219). Original pathology diagnoses were abstracted from electronic health records, which were provided by a mix of generalists and expert gastrointestinal pathologists at 5 sites. Error bars indicate 2-tailed 95% confidence intervals

EAC, esophageal adenocarcinoma; Dx, diagnosis; HGD, high-grade dysplasia; IND, indefinite for dysplasia; IQR, interquartile range; LGD, low-grade dysplasia; NDBE, non-dysplastic Barrett's esophagus; TSP-9, tissue systems pathology test

Supplementary Table 1 Characteristics of subsets of patients with pathology diagnoses of NDBE and IND/LGD

Characteristic	NDBE patients[1] without progression during follow-up	NDBE patients[1] with subsequent diagnosis of HGD/EAC during follow-up	IND/LGD patients[1] without progression during follow-up	IND/LGD patients[1] with subsequent diagnosis of HGD/EAC during follow-up
n (%)	290 (74.0)	102 (26.0)	219 (71.3)	88 (28.7)
Age, median (IQR)	60.4 (52-69)	63.5 (54-70)	62.0 (54-71)	62.0 (57-69)
HGD/EAC-free surveillance time, median years[2] (IQR)	6.4 (5-9)	3.3 (2-5)	7.1 (5.0-9.7)	1.9 (0.6-3.1)
Sex, n (%)				
Male	219 (75.5)	86 (84.3)	166 (75.8)	78 (88.6)
Female	71 (24.5)	16 (15.7)	53 (24.2)	10 (11.4)
Segment length, n (%)				
Long (≥3 cm)	187 (64.5)	84 (82.4)	124 (56.6)	64 (72.7)
Short (<3 cm)	92 (31.7)	14 (13.7)	56 (25.6)	22 (25.0)
Unknown	11 (3.8)	4 (3.9)	39 (17.8)	2 (2.3)
TSP-9 risk class, n (%)				
High-risk	11 (3.8)	42 (41.2)	21 (9.6)	38 (43.2)
Intermediate-risk	34 (11.7)	16 (15.7)	27 (12.3)	19 (21.6)
Low-risk	245 (84.5)	44 (43.1)	171 (78.1)	31 (35.2)

[1]Original pathology diagnosis abstracted from electronic health records

[2]Time to subsequent diagnosis of HGD/EAC or last follow-up

EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; IND, indefinite for dysplasia; IQR, interquartile range; LGD, low-grade dysplasia; NDBE, non-dysplastic Barrett's esophagus; TSP-9, tissue systems pathology test

Supplementary Table 2 Patient data sources

Study (PMID)[‡]	Study design	Patients per country		Total (n)
		United States (n)	The Netherlands (n)	
27197290	Case–control	77	106	183
27729357*	Case–control	125	50	175
32079863	Case–control	268	0	268
33108124[†]	Case–control	0	76	76
33982936	Retrospective cohort study	0	155	155

[‡]The data from 699 patients were derived from previously published studies (PMIDs: 27197290, 27729357, 32079863, 33108124, 33982936) affiliated with institutions/medical centers in the US and Europe. Only unique patients were included (n = 699)
*same non-progressor patients (n = 145) as 27197290
[†]overlap of progressor patients (n = 13) with 27197290
PMID, PubMed Identifier

Supplementary Table 3 Clinical decision simulation models for patients with pathology diagnosis of NDBE

Model	Pathology diagnosis and/or TSP-9 result	Clinical management decision
BE management without TSP-9	NDBE	Surveillance in 3-5 years for 70% of patients Surveillance in 1 year for 30% of patients EET for 0.5% of patients
TSP-9-guided management	NDBE & low-risk	Surveillance in 3-5 years
	NDBE & intermediate/high-risk	Surveillance in <1 year or EET
Appropriate management per known outcome	Non-progressor	Progressor
Surveillance in 3-5 years	Appropriate	Not appropriate
Surveillance in <1 year or EET	Not appropriate	Appropriate

BE, Barrett's esophagus; EET, endoscopic eradication therapy; NDBE, non-dysplastic Barrett's esophagus; TSP-9, tissue systems pathology test

Supplementary Table 4 Clinical decision simulation models for patients with pathology diagnoses of IND/LGD

Model	Pathology diagnosis and/or TSP-9 result	Clinical management decision
BE management without TSP-9	IND	Surveillance in <1 year
	LGD[1]	EET
TSP-9-guided management	IND & low-risk	Surveillance in 3-5 years
	LGD[1] & low-risk	Surveillance in <1 year
	IND/LGD[1] intermediate/high-risk	EET

[1]Specimen slides from patients with a diagnosis of LGD were reviewed by an expert GI pathologist
BE, Barrett's esophagus; EET, endoscopic eradication therapy; IND, indefinite for dysplasia; LGD, low-grade dysplasia; TSP-9, tissue systems pathology test

Supplementary Table 5 Standards for quality improvement reporting excellence 2.0 checklist

Title and abstract		Component(s) added	Location in manuscript
1. Title	Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patient-centeredness, timeliness, cost, efficiency, and equity of healthcare)	Complete	Title/abstract
2. Abstract	a. Provide adequate information to aid in searching and indexing b. Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions	a, b	Abstract
Introduction		**Component(s) added**	**Location in Manuscript**
3. Problem description	Nature and significance of the local problem	Complete	Introduction
4. Available knowledge	Summary of what is currently known about the problem, including relevant previous studies	Complete	Introduction
5. Rationale	Informal or formal frameworks, models, concepts, and/or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s), and reasons why the intervention(s) was expected to work	Complete	Introduction
6. Specific aims	Purpose of the project and of this report	Complete	Introduction
Methods		**Component(s) added**	**Location in Manuscript**
7. Context	Contextual elements considered important at the outset of introducing the intervention(s)	Complete	Methods; Study Design
8. Intervention(s)	a. Description of the intervention(s) in sufficient detail that others could reproduce it b. Specifics of the team involved in the work	a	Methods; Tissue systems pathology-9 (TSP-9) testing & Clinical decision models and management simulations
9. Study of the intervention(s)	a. Approach chosen for assessing the impact of the intervention(s) b. Approach used to establish whether the observed outcomes were due to the intervention(s)	a, b	Methods; Clinical decision models and management simulations; Statistical Analysis
10. Measures	a. Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability b. Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost c. Methods employed for assessing completeness and accuracy of data	a, c	Methods; Statistical Analysis
11. Analysis	a. Qualitative and quantitative methods used to draw inferences from the data b. Methods for understanding variation within the data, including the effects of time as a variable	a, b	Methods; Statistical Analysis
12. Ethical Considerations	Ethical aspects of implementing and studying the interventions and how they were addressed, including but not limited to, formal ethics review, and potential conflicts of interest	Complete	Disclosures/conflicts of interest

(*Contd...*)

Supplementary Table 5 (*Continued*)

Results		Component(s) added	Location in Manuscript
13. Results	a. Initial steps of the intervention(s) and their evolution over time (e.g., time-line diagram, flow chart, or table), including modifications made to the intervention during the project b. details of the process measures and outcome c. Contextual elements that interacted with the interventions d. Observed associations between outcomes, interventions, and relevant contextual elements e. Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s). f. Details about missing data	a, b, c, d	Results; Fig. 1-4; Supplementary files
Discussion		Component(s) added	Location in Manuscript
14. Summary	a. Key findings, including relevance to the rationale and specific aims b. Particular strengths of the project	a, b	Discussion
15. Interpretation	a. Nature of the association between the interventions and the outcomes b. Comparison of results with findings from other publications c. Impact of the project on people and systems d. Reasons for any differences between observed and anticipated outcomes, including the influence of context e. Costs and strategic trade-offs, including opportunity costs	a, c, e	Discussion
16. Limitations	a. Limits to the generalizability of the work b. Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis c. Efforts made to minimize and adjust for limitations	a, b, c	Discussion
17. Conclusions	a. Usefulness of the work b. Sustainability c. Potential for spread to other contexts d. Implications for practice and for further study in the field e. Suggested next steps	a, d	Discussion
Other information		Component(s) added	Location in manuscript
18. Funding	Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting	Complete	Statements & declarations; “Funding”