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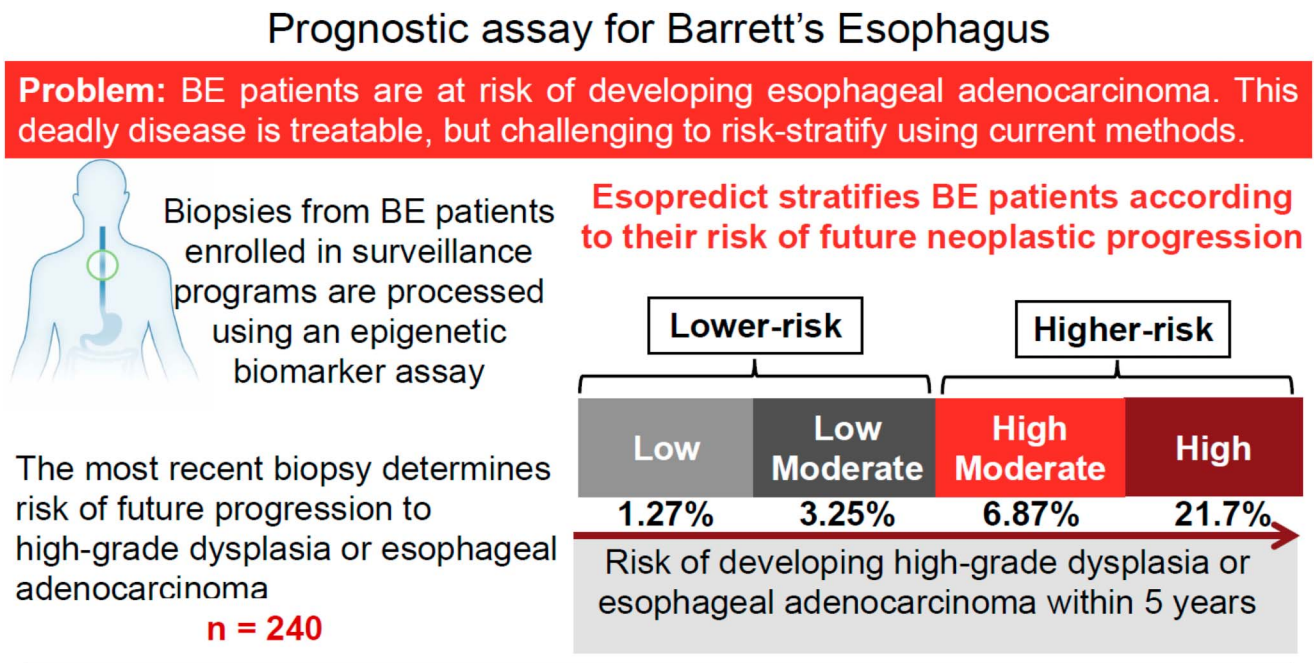
# Validation of an Epigenetic Prognostic Assay to Accurately Risk-Stratify Patients With Barrett Esophagus

Sarah E. Laun, PhD[1], Lisa Kann, PhD[1], Jerome Braun, PhD[1], Stacey Gilbert, MPH, MBA[1], Daniel Lunz, MBA[1], Francia Pierre, MPH[1], Andrew Kalra, MD[2], Ke Ma, MD[2], Hua-Ling Tsai, PhD[3,4], Hao Wang, PhD[3,4], Simran Jit, MD[2], Yulan Cheng, PhD[2], Yousra Ahmed, MD[2], Kenneth K. Wang, MD, FACG[5], Cadman L. Leggett, MD[5], Ashley Cellini, PA[6], Olga B. Ioffe, MD[6], Ali H. Zaidi, MD[7], Ashten N. Omstead, MS[7], Blair Jobe, MD[8,9], Louis Korman, MD[10], Drew Cornish, MD[10], Pauline Zellenrath, BS, PhD[11], Manon Spaander, MD, PhD[11], Ernst Kuipers, MD[11], Lorrie Perpetua, BS[12], Bruce D. Greenwald, MD[13], Tara Maddala, PhD[1] and Stephen J. Meltzer, MD[2,3]

INTRODUCTION: **Esophageal adenocarcinoma (EAC) is the second-most lethal cancer in the United States, with Barrett esophagus (BE) being the strongest risk factor. Assessing the future risk of neoplastic progression in patients with BE is difficult; however, high-grade dysplasia (HGD) and early EAC are treatable by endoscopic eradication therapy (EET), with survival rates of 90%. Thus, it would be beneficial to develop a molecular assay to identify high-risk patients, who merit more frequent endoscopic surveillance or EET, as well as low-risk patients, who can avoid EET and undergo less frequent surveillance.**

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[1]Previse, Baltimore, Maryland, USA; [2]Division of Gastroenterology and Hepatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [3]Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [4]Division of Biostatistics, Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [5]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA; [6]Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland, USA; [7]Esophageal Institute, Allegheny Health Network Cancer Institute, Allegheny Health Network, Pittsburgh, Pennsylvania, USA; [8]Department of Surgery, Esophageal Institute, Allegheny Health Network, Pittsburgh, Pennsylvania, USA; [9]Department of Surgery, Drexel University, Philadelphia, Pennsylvania, USA; [10]Capital Digestive Care, Chevy Chase, Maryland, USA; [11]Department of Gastroenterology & Hepatology, Erasmus MC University Medical Center, Rotterdam, the Netherlands; [12]Research Tissue Biorepository Core Facility, University of Connecticut, Storrs, Connecticut, USA; [13]Division of Gastroenterology and Hepatology, University of Maryland School of Medicine, Baltimore, Maryland, USA. **Correspondence:** Stephen J. Meltzer, MD. E-mail: smeltzer@jhmi.edu.
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METHODS: **Deidentified endoscopic biopsies were acquired from 240 patients with BE at 6 centers and confirmed as future progressors or nonprogressors. Tissues were analyzed by a set of methylation-specific biomarker assays. Test performance was assessed in an independent validation set using 4 stratification levels: low risks, low-moderate risks, high-moderate risks, and high risks.**

RESULTS: **Relative to patients in the low-risk group, high-risk patients were 15.2 times more likely to progress within 5 years to HGD or EAC. For patients in the high-risk category, the average risk of progressing to HGD or EAC within 5 years was 21.5%, 4-fold the BE population prevalence within 5 years, whereas low-risk patients had a progression risk of only 1.85%.**

DISCUSSION: **This clinical assay, Esopredict, stratifies future neoplastic progression risk to identify higher-risk patients with BE who can benefit from EET or more frequent surveillance and lower-risk patients who can benefit from reduced surveillance.**



**KEYWORDS:** esophageal cancer; personomics; clinical decisions; predictive biomarkers; epigenetics

**SUPPLEMENTARY MATERIAL** accompanies this paper at http://links.lww.com/AJG/D379

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## INTRODUCTION

Patients with Barrett esophagus (BE), relative to the general population, are at a 10-fold to 50-fold increased risk for developing esophageal adenocarcinoma (EAC), the second-most lethal cancer in the United States, with a 5-year survival of only 21% (1,2,4–8). Therefore, patients with BE customarily undergo esophagogastroduodenoscopic surveillance to determine whether there is no dysplasia (i.e., nondysplastic BE, NDBE), if dysplasia is present as low-grade dysplasia (LGD) high-grade dysplasia (HGD), or indeterminate (i.e., indefinite for dysplasia, IND) (1,2,3,5,6,9). Endoscopic surveillance programs seek to improve patient survival by detecting cancerous or precancerous changes early, while tissues can still be curatively treated. When HGD or early EAC is identified, endoscopic eradication therapies (EET) have high success rates, with 91% of patients achieving complete remission of dysplasia and 78% attaining complete elimination of underlying NDBE (10,11). Patients with NDBE, who comprise 90% of all patients with BE, typically undergo endoscopic surveillance once every 3–5 years (7,8,12–15). However, among patients who develop HGD or EAC, up to 25% actually had progressed before their next interval surveillance EGD (16,17). Conversely, since most patients with NDBE do not progress to HGD or EAC, medical resources and patient productivity, time, and peace of mind are casualties of surveillance. Thus, if a very low-risk subgroup of patients with NDBE could have their surveillance frequency reduced, while high-risk patients could be better identified for potential intervention, these disadvantages would be substantially mitigated.

Esopredict is a prognostic assay based on DNA methylation levels that stratified future progression risk in patients with BE using biopsies already obtained during surveillance esophagogastroduodenoscopy. This assay uses DNA methylation biomarkers plus age, including the genes RUNX3, p16, HPP1, and FBN1, which were previously established in studies performed at The Johns Hopkins University School of Medicine and then further developed and validated at the Previse Clinical Laboratory Improvement Amendments (CLIA) laboratory (CLIA: 21D2256153) (Table 1) (18–30). This assay measures the level of methylation of each biomarker. Altered methylation often occurs early, before significant shifts in clinical phenotype, representing an important advantage favoring early detection and prognostication (31–34). The goal of this study was to clinically validate Esopredict to support the management of patients with BE by defining the risk of progression to HGD or EAC within 5 years. We hypothesized that methylation algorithm outputs would correlate with risk of future progression in patients with BE, enabling us to stratify patients with BE according to their probability of neoplastic progression within 5 years.

## METHODS

### Setting

Retrospectively collected biopsies from patients with known BE were collected between May 2021 and January 2023 from 6 independent collaborating sites: Allegheny Health Network, Capital Digestive Health, Johns Hopkins University, Mayo Clinic, University of Maryland, and University of Connecticut. Diagnoses of dysplasia and other relevant clinical metrics were recorded, including age and sex (Table 2). There were no detectable differences in quality control metrics between the oldest biopsies collected 32 years ago (1991) and the newest biopsies collected 4 years ago (2020).

### Study design

In this case-control study, biopsies from patients with BE meeting inclusion criteria were received from collaborating sites (see below, Patient selection). Samples were collected and processed from all 6 sites; the first 99 patients received comprised the training set, which was analyzed first. Subsequently, after the model algorithm had been locked, the final 110 patients received were analyzed as the validation set. Within each data set (Training or Validation), samples were processed in random order, so that different enrollment sites and biopsy years were represented equally among different run batches.

### Patient selection

We accepted all available patients from each center who met the following inclusion criteria: (i) index biopsies (i.e., the earliest biopsy from each patient with a histological diagnosis of NDBE, IND, or LGD) made by an expert gastrointestinal pathologist at each institution and (ii) follow-up histological results for patients were required for all patients. For those who did not progress to HGD or EAC (i.e., non-progressors), follow-up of 5 years or more was

 

**Table 1. Biomarkers of Esopredict**

**A. Esopredict biomarkers**

| Biomarker gene | Official full name | Role(s) |
|---|---|---|
| P16/CDKN2A | Cyclin-dependent kinase inhibitor 2A | Cell cycle regulation, G1 control, tumor suppressor |
| RUNX3 | RUNX family transcription factor 3 | Transcription factor, tumor suppressor |
| HPP1 | Hyperpigmentation, progressive 1 | Potential tumor suppressor, transmembrane protein |
| FNB1 | Fibrillin 1 | Extracellular matrix component, glycoprotein |

**B. References for Esopredict biomarkers**

| Title | Year | Biomarkers | N | Reference number |
|---|---|---|---|---|
| Inactivation of p16, RUNX3, and HPP1 occurs early in Barrett-associated neoplastic progression and predicts progression risk (manuscript) | 2005 | P16, RUNX3, HPP1 | 53 | (24) |
| Three-tiered risk stratification model to predict progression in Barrett esophagus using epigenetic and clinical features (manuscript) | 2008 | P16, RUNX3, HPP1 | 62 | (25) |
| A multicenter, double-blinded validation study of methylation biomarkers for progression prediction in Barrett esophagus (manuscript) | 2009 | P16, RUNX3, HPP1 | 195 | (20) |
| Analytical validation of a novel multigene assay for patients with Barrett esophagus (Poster abstract) | 2014 | P16, RUNX3, HPP1 | N/A (analytical) | (29) |
| Methylation biomarker panel performance in EsophaCap cytology samples for diagnosis Barrett esophagus: A prospective validation study (manuscript) | 2019 | P16, RUNX3, HPP1 | 80 | (27) |
| Analytical validation of a DNA methylation-based prognostic assay for risk stratification of patients with Barrett esophagus (Poster Abstract) | 2022 | P16, RUNX3, HPP1, FBN1 | N/A (analytical) | (19) |
| Validation of a DNA methylation-based prognostic assay for risk stratification of patients with Barrett esophagus (Poster Abstract) | 2022 | P16, RUNX3, HPP1, FBN1 | 63 | (28) |
| A clinically applicable prognostic assay for risk stratification of patients with Barrett esophagus (Presentation Abstract) | 2023 | P16, RUNX3, HPP1, FBN1 | 115 | (18) |
| Independent validation of Esopredict, a prognostic assay to risk-stratify patients with Barrett esophagus across multiple spatial and temporal biopsies (Poster Abstract) | 2023 | P16, RUNX3, HPP1, FBN1 | 224 | (30) |

required (Figure 1b). These index (i.e., baseline) biopsies were the samples analyzed in this study by the molecular assay and subsequent algorithm. Among 209 patients, 78 progressed to HGD/EAC within 5 years (progressors), while 131 had no progression at final followup intervals of ≥5 years (nonprogressors) (Figure 1). To test our algorithm on patients who progressed at followup interval latter than 5 years, an additional cohort of 31 progressors was independently tested (Figure 1).

### Biopsy procurement and pathologic confirmation

Eight consecutive sections were cut from formalin-fixed paraffin-embedded tissue blocks containing esophageal biopsies from 240 patients with BE (Figure 1). Histological diagnoses were recorded for both index (i.e, assayed) biopsies with ND, IND, or LGD and outcome biopsies (i.e., the most recent follow-up biopsy) for patients who developed HGD or EAC. In addition, patient age, sex, date of biopsies, and other clinical variables including body mass

**Table 2. Baseline demographics and characteristics of patients**

| | Training (n = 99) | Validation (n = 110) | *P* value |
|---|---|---|---|
| Age (year) | | | |
| Mean (SD) | 64.6 (11.2) | 61.1 (11.5) | 0.027 |
| Median [min, max] | 64.0 [39.0, 93.0] | 61.5 [21.0, 82.0] | |
| Sex (n) | | | |
| Female | 17 (17.2%) | 22 (20.0%) | 0.729 |
| Male | 82 (82.8%) | 88 (80.0%) | |
| Index biopsy (year) | | | |
| 1991–2000 | 7 (7.1%) | 6 (5.5%) | 0.172 |
| 2001–2010 | 57 (57.6%) | 51 (46.6%) | |
| 2011–2020 | 35 (35.4%) | 53 (48.2%) | |
| Index biopsy, dysplasia (n) | | | |
| Nondysplastic | 50 (50.5%) | 93 (84.5%) | <0.001 |
| Indefinite for dysplasia | 15 (15.2%) | 3 (2.7%) | |
| Low-grade dysplasia | 34 (34.3%) | 14 (12.7%) | |
| Progression status based on outcome biopsy (n) | | | |
| Nonprogressor | 61 (61.6%) | 70 (63.6%) | 0.874 |
| Progresso | 38 (38.4%) | 40 (36.4%) | |
| Interval between index and outcome biopsies (yr) | | | |
| Mean (SD) | 6.43 (4.28) | 5.19 (2.84) | 0.0158 |
| Median [min, max] | 5.70 [0.252, 19.2] | 5.05 [0.0521, 13.3] | |
| Segment length (n) | | | |
| Short (<3 cm) | 20 (20.0%) | 34 (30.9%) | 0.150 |
| Long (>3 cm) | 34 (34.0%) | 27 (24.5%) | |
| Unknown | 45 (45.0%) | 49 (44.5%) | |
| Smoking status (n) | | | |
| Current | 8 (8.1%) | 5 (4.6%) | 0.131 |
| Former | 21 (21.2%) | 36 (32.7%) | |
| Never | 41 (41.4%) | 39 (35.5%) | |
| Unknown | 29 (29.3%) | 30 (27.3%) | |

index, segment length, and smoking status were recorded for each patient.

### Assay

Esopredict consists of 4 biomarkers (p16, HPP1, RUNX3, and FBN1) plus age, which were selected based on prior studies as described in the introduction and Table 1. Refer to Supplementary Methods (Supplementary Digital Content 1, http://links.lww.com/AJG/D379) for more details on sample processing and analysis.

### Training cohort, model development, and final locked model

Clinical samples meeting the specified inclusion criteria were used for biomarker selection (Table 1 and Supplementary Methods, Supplementary Digital Content 1, http://links.lww.com/AJG/D379) and previous versions of the model development (18–20,24,25,27–30). During the model development phase, we applied several methods, including machine learning (random forest and XGBoost); however, these methods did not perform as well as statistical regression (18,19). We therefore chose the best-performing model to move forward as our final locked algorithm reported and validated in this article. For the final model, data conventions were revised using the same parameters for biomarker selection when no amplification was detected (zero) or below the lower limit of quantification (0.0008). As previously done during model development, normalized methylation value (NMV) of each gene was evaluated for performance. In this final model, the functional form was assessed for each marker (18,19). Owing to the high correlation between HPP1 and FBN1, an equally weighted average of their NMVs was used to combine the 2 markers (Figure 2a). Since p16 showed a biphasic relationship, this marker had a threshold placed at 0.25. Runx3 was not transformed before inclusion in the model. Finally, approximate linearity was achieved for all 3 predictors through the square root transformation (Figure 2b). Using the transformed NMV for the 4 genes, a final model was locked using the 4 genes and age.

### Validation cohort

Validation was performed by assessing the relationship between the risk score and corresponding category and risk level with progression. To obtain confidence intervals for prediction, a logistic model was fitted to the validation data using the risk score and adjusted for population prevalence as described below (35–40).

 

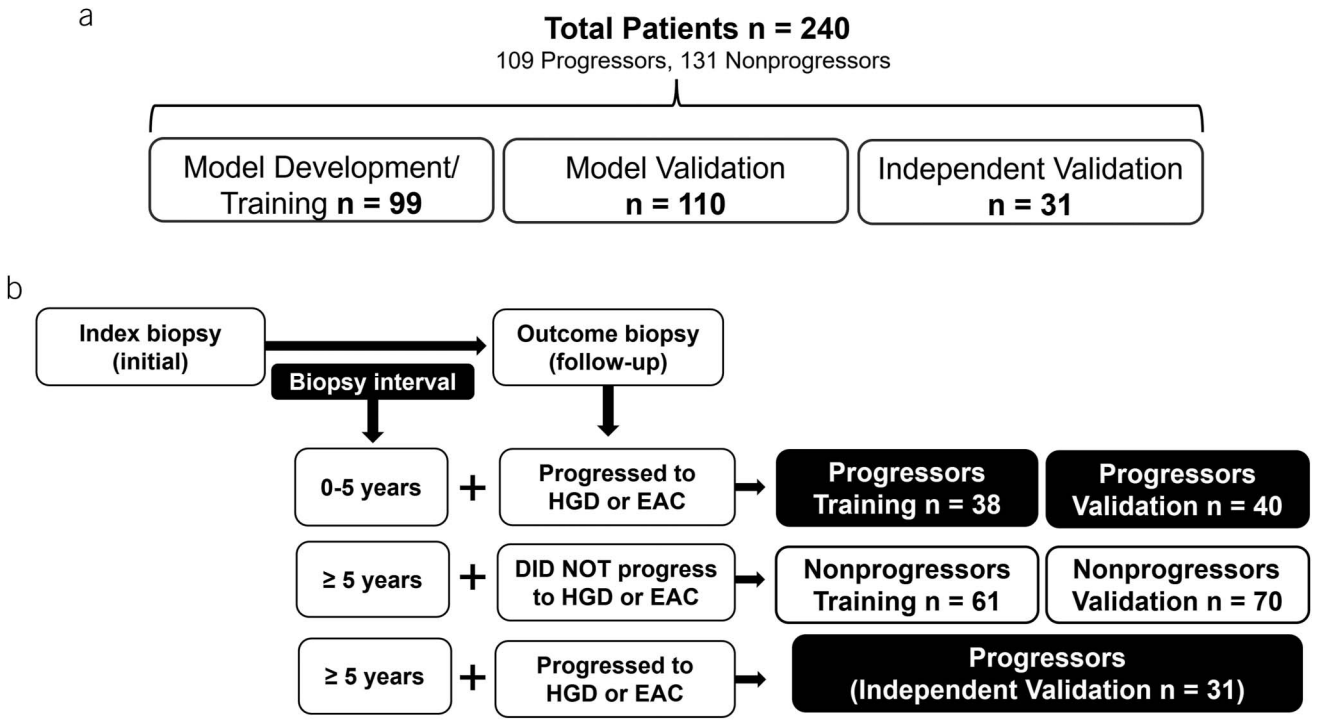


**Figure 1.** Study enrollment cohorts and inclusion criteria. (**a**) Diagram describing the retrospective patient collection cohorts of training, validation, and independent validation. (**b**) The inclusion criteria are based on biopsy interval years and progression status. EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia.

### Statistics

In addition to the changes in our final model (discussed above in the training cohort, model development, and final locked model), a new statistical method not used in prior published models was used to estimate the prevalence-adjusted probability of progression, and the intercept term was adjusted using the log odds of the population prevalence (18,19). To approximate a predictiveness curve from the training data for the overall population, the sample was assumed to be representative, and nonprogressors were repeated to nearly match population prevalence (35–40). Under this assumption, the population-adjusted percentiles approximate the risk at each observed score value. Cut points were placed to estimate patients with a lower-than-average risk of progression based on prevalence (*lower-risk* category) vs patients with higher-than-average risk (*higher-risk* category). These cut points were chosen after a visual inspection of the predictiveness curve plotting the risk percentile vs the predictive probability. Our goal was for the *lower-risk* category to identify a significant number of patients with a clinically meaningful low probability of progression within 5 years. Equally, this logic was applied to have a *higher-risk* category with a clinically meaningful high probability of progression within 5 years. We further refined these categories into 2 risk levels per category using the same logic. For the *lower-risk* category, we targeted approximately 27.5% of patients as low risk, and 42% as low-moderate risk. Similarly, for the *higher-risk* category, we targeted 17.5% as high-moderate risk and 12.5% as high risk. The score was rescaled to the interval [0, 100], and the cut points were rounded to the nearest value to form the Esopredict score.

### Ethical statement

All histologic tissue sections were collected from patients diagnosed with Barrett's esophagus (BE) . The tissue samples were prepared at the time of endoscopy for clinical indications, and were not collected specifically for this present study. Archival tissue samples were completely anonymized and deidentified, with no possibility of linking them back to patients. The specimens were prepared and provided by personnel without any role in this research study except for providing the tissue specimens. The study was approved by review by the institutional ethics committee of Johns Hopkins University, Institutional Review Board NA_0000436.

## RESULTS

### Development of the classification algorithm

Among 240 patients, 209 met our inclusion criteria (described in Methods, Patient selection) and were collected as model training (n = 99) and subsequently collected as model validation (n = 110) cohort from the same 6 collaborating sites. An additional independent validation (n = 31) included patients who progressed but were outside our patient inclusion criteria (>5 years as a progressor) (Figures 1 and 5). Biomarker and clinical variables were assessed and selected using the Least Absolute Shrinkage and Selection Operator method in a logistic regression setting. Besides age, other clinical covariates (e.g., sex, clinical site, smoking, proton-pump inhibitor use, body mass index) were either not predictive of progression or not consistently collected, and therefore not included in the final analysis (Supplementary Methods, Supplementary Digital Content 1, http://links.lww.com/AJG/D379).

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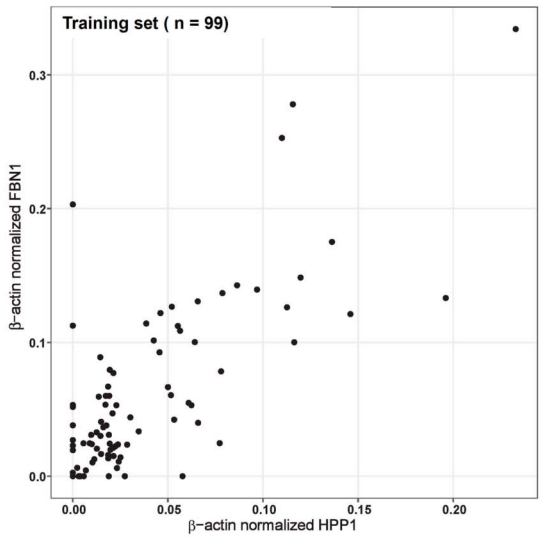


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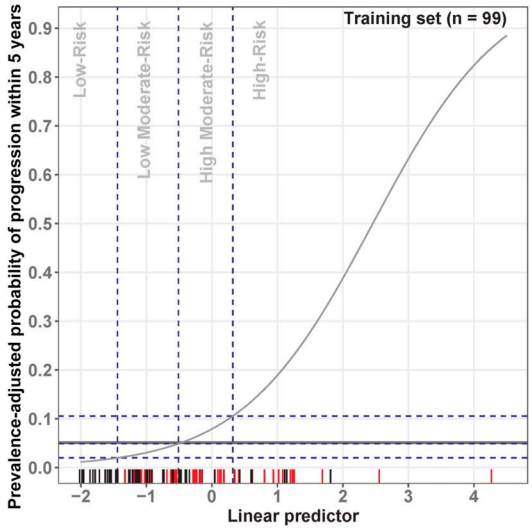


b

*Training set (n = 99)*

| Parameter (transformed) | Coefficient | SE | CI (low) | CI (high) | z | p |
|---|---|---|---|---|---|---|
| (Intercept) | -0.5119 | 0.24 | -0.98 | -0.05 | -2.18 | 0.0295 |
| Age | 0.3710 | 0.24 | -0.08 | 0.85 | 1.58 | 0.1149 |
| HPP1+FBN1 NMV | 0.6225 | 0.28 | 0.09 | 1.21 | 2.22 | 0.0264 |
| P16 NMV | 0.4956 | 0.38 | -0.12 | 1.42 | 1.32 | 0.1884 |
| RUNX3 NMV | 0.1001 | 0.30 | -0.49 | 0.68 | 0.34 | 0.7354 |

d

*Training set (n = 99)*

| Risk Category | Risk Level | Population adjusted (n) | Population adjusted (%) | Average prevalence adjusted risk (%) |
|---|---|---|---|---|
| Lower-risk | Low | 205 | 26.62 | 1.53 |
| | Low-moderate | 325 | 42.21 | 2.98 |
| Higher-risk | High-moderate | 143 | 18.57 | 6.51 |
| | High | 97 | 12.60 | 19.14 |

**Figure 2.** Model development and training. All of these data represent the training set (n = 99). (**a**) Bivariate plot of biomarkers HPP1 and FBN1 with the x-axis showing normalized methylation values of HPP1 and the y-axis showing normalized methylation values of FBN1. Normalized to the internal control β-Actin. (**b**) Coefficients and low and high confidence intervals (CI) of fitting multivariate logistic regression models to the data with standardized predictors including SE and z-score (z). (**c**) Predictiveness curve with prevalence-adjusted probability compared with the model score with cut points chosen represented by dashed vertical lines indicating risk levels. The bold gray line represents the average probability of progression based on prevalence within 5 years. The rug plot across the x-axis shows lines representing patient scores. The red lines indicate a patient that progressed to high-grade dysplasia or esophageal adenocarcinoma, and the black lines indicate a nonprogressor (n = 99). (**d**) Table reflecting population-adjusted average risk, and estimated number (n) and percent (%) of population-adjusted patients in each risk category and risk level. To adjust for prevalence, the number of nonprogressors in this cohort was multiplied by a factor of 12 (n = 99). NMV, normalized methylation value.

A formula containing the 4 biomarkers plus age was established, and classification accuracy was evaluated using receiver-operator characteristic curves. The area under the ROC curve for this prognostic assay in predicting progression to HGD or EAC was 0.76 in the training set, vs 0.73 in the validation set. Age is known to be correlated with both risk of developing EAC and increased methylation levels, so we compared biomarker assay results with those based on age alone (area under the ROC curve = 0.62). The prevalence-adjusted curve of predicted probability within 5 years for progression to HGD or EAC for the training set is illustrated in Figure 2c, with the corresponding data table in Figure 2d.

### Predictive performance of the algorithm

The predicted probability of the validation (n = 110) is shown after adjusting for prevalence and population, with each Esopredict score (X-axis) correlating with a specific risk of progression (Figure 3a). The averages of these parameters within each risk category/level are shown in Figure 3b. Overall, the odds of progression within 5 years of the *higher-risk* category (i.e., risk levels high-moderate and high), comprising patients who would likely benefit from improved care management, was 6.4 times higher than the progression odds of the *lower-risk* category (i.e., risk levels low and low-moderate) (Figure 3c). Similar trends were observed in the further refined 4 risk levels comparing the low risk with the other risk levels, including the high-risk level 15.2 (lowest confidence level 2.7, upper confidence level 84.2) times more likely to progress than the low-risk level (Figure 3c).

The percentage of patients that progress was increased in the *higher-risk* category (i.e., risk levels high moderate, and high), while the percentage of nonprogressors was increased in the *lower-risk* category (low and low-moderate risk levels) (Figure 4a). This trend was consistently observed comparing the full validation set with the subset of patients with index NDBE biopsies (n = 93) (Figure 4a). In addition, across risk levels, the population-adjusted percentage of NDBE-only patients shifted slightly, with similar average percent risk and population-adjusted percentages (Figure 4b) compared with the full validation cohort (Figure 3b). In this validation cohort, 93 patients (85%) had index biopsies with a diagnosis of NDBE, aligning closely with the NDBE prevalence observed in the general BE population. The remaining 17 patients of the validation cohort (15%) had index (i.e., baseline) biopsies diagnosed with LGD or IND. Of these 17, 11 patients (65%) were categorized in the *higher-risk category* (i.e., risk levels high-moderate and high). Nevertheless, the relatively small size of this subgroup was too small to draw statistically significant conclusions. An additional

 

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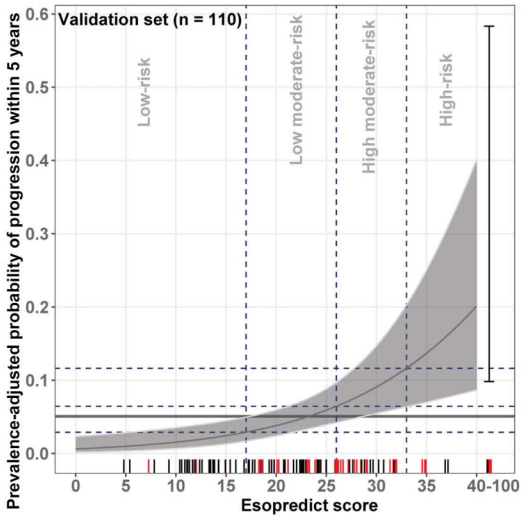


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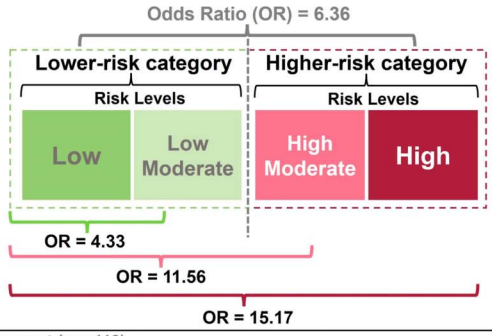



*Validation set (n = 110)*

| Risk Category | Odds Ratio | LCL | UCL |
|---|---|---|---|
| **Lower-risk vs. Higher-risk** | **6.36** | **2.37** | **17.09** |
| **Risk Level** | **Odds Ratio** | **LCL** | **UCL** |
| **Low to Low Moderate** | 4.33 | 1.12 | 16.82 |
| **Low to High Moderate** | 11.56 | 2.82 | 47.34 |
| **Low to High** | 15.17 | 2.73 | 84.18 |

b

*Validation set (n = 110)*

| Risk Category | Risk Level | Population adjusted (n) | Population adjusted (%) | Average prevalence adjusted risk (%) |
|---|---|---|---|---|
| **Lower-risk** | Low | 289 | 35.68 | 1.85 |
| | Low-moderate | 311 | 38.40 | 4.37 |
| **Higher-risk** | High-moderate | 159 | 19.63 | 8.12 |
| | High | 51 | 6.30 | 21.46 |

**Figure 3.** Validation of model. All of these data represent the validation set (n = 110). (**a**) Predictiveness curve with prevalence-adjusted probability compared with the model score with locked cut points, represented as dashed lines. The bold gray line represents the average probability of progression based on prevalence in 5 years. The rug plot across the x-axis shows lines that represent patient scores, the red lines indicate a patient that progressed to high-grade dysplasia or esophageal adenocarcinoma, and the black lines indicate a nonprogressor (n = 110). The bold black vertical line in the high-risk level represents a 95% confidence interval, included 5 patients with scores ranging from 43 to 56, with 3 progressors and 2 nonprogressors. (**B**) A table reflecting population-adjusted average risk, and estimated number (n) and percent (%) of population-adjusted patients in each risk category and risk level. To adjust for prevalence, the number of nonprogressors in this cohort was multiplied by a factor of 12 (n = 110). (**c**) Estimate the likelihood of progression, i.e., OR, within each risk category. *Top figure and table: lower-risk* category (i.e., risk levels low and low-moderate) compared with *higher-risk* category (i.e., risk levels high-moderate and high). *Bottom table:* Comparing all risk levels to the low-risk level, including LCL and UCL. Owing to prevalence, the number of nonprogressors in this cohort was represented by a multiplication of 12 (n = 110). LCL, lowest confidence level; OR, odds ratio; UCL, upper confidence level.

a

| **1.1 Validation set (All patients, n = 110)** | | | | | |
|---|---|---|---|---|---|
| **Risk level** | **Low (n = 29)** | **Low Moderate (n = 42)** | **High Moderate (n = 28)** | **High (n = 11)** | **Overall (n = 110)** |
| **Nonprogressor** | 26 (89.7%) | 28 (66.7) | 12 (42.9%) | 4 (36.4%) | 70 (63.6%) |
| **Progressor** | 3 (10.3%) | 14 (33.3%) | 16 (15.1%) | 7 (63.6%) | 40 (36.4%) |
| **1.2 Validation set (NDBE patients only, n = 93)** | | | | | |
| **Risk level** | **Low (n = 29)** | **Low Moderate (n = 36)** | **High Moderate (n = 20)** | **High (n = 8)** | **Overall (n = 93)** |
| **Nonprogressor** | 26 (89.7%) | 27 (75.0%) | 10 (50.0%) | 4 (50.0%) | 67 (72.0%) |
| **Progressor** | 3 (10.3%) | 9 (25.0%) | 10 (50.0%) | 4 (50.0%) | 26 (28.0%) |

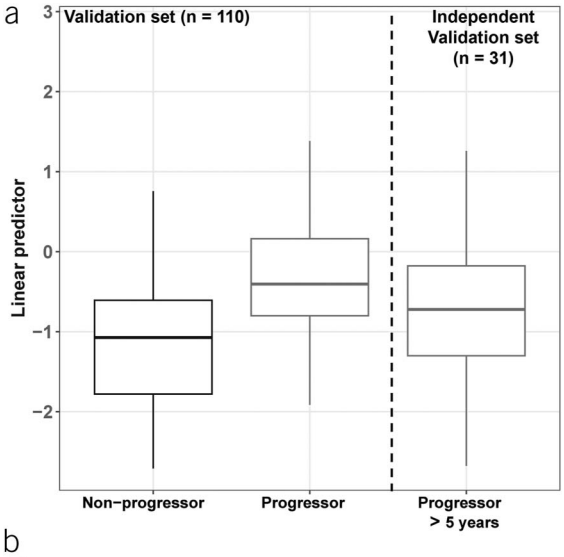
b

*Validation set NDBE only (n = 93)*

| Risk Category | Risk Level | Population adjusted (n) | Population adjusted (%) | Average prevalence adjusted risk (%) |
|---|---|---|---|---|
| **Lower-risk** | Low | 289 | 35.68 | 1.27 |
| | Low-moderate | 306 | 37.78 | 3.37 |
| **Higher-risk** | High-moderate | 120 | 14.81 | 6.79 |
| | High | 48 | 5.93 | 21.25 |

**Figure 4.** Performance of Esopredict. All of these data represent the validation set (n = 110). (**a**) Table with the number of patients (n) in each risk level and overall separated by nonprogressor and progressor. **1.1** Includes all patients in the validation cohort (n = 110) and **1.2** includes only patients with an index biopsy of NDBE in the validation cohort (n = 93). (**b**) Includes only patients who had an index biopsy (i.e., assayed) of NDBE, and table with the number of patients (n), population-adjusted percent of patients, and the average prevalence-adjusted risk percent across each risk category and risk level. NDBE, nondysplastic Barrett esophagus.

a




b

*Validation set (n = 110) + Independent Validation set (n = 31)*

| Term | Sum Sq | Df | F value | PR (>F) |
|---|---|---|---|---|
| Category | 12.44 | 2 | 8.30 | 0.0004 |
| Residuals | 103.35 | 138 | | |

**Figure 5.** Performance in an independent validation cohort. (**a**) Boxplots of the Esopredict scores (y-axis) of nonprogressor (black, n = 70) and progressor patients in the first validation (gray, n = 40) for the 2 left plots, the right plot (represents independent validation patients that progressed >5 years [n = 31]). The bold line represents the median score, and the box represents the first and third quartiles. (**b**) Analysis of variance of the 3 patient populations: non-progressor (n = 70), progressor (n = 40) from the validation, and progressions with outcome biopsies >5 years (n = 31).

validation set included 31 progressors whose outcome was > 5 years, with a mean of 6.5 years (5.2–17.8). There was a similar overall trend in increased scores compared with nonprogressor patients (Figure 5), indicating that regardless that progression occurred much longer than a typical surveillance interval (3–5 years), the performance of this assay was comparable with those with follow-up within 5 years, $P = 0.0004$ (Figure 5b).

In addition to a histological diagnosis of NDBE, IND, or LGD, additional clinical variables are also strongly considered by clinicians in assessing patients with BE for risk stratification. Conversely, with molecular assays like Esopredict, some predictive models focus solely on clinical factors: for example, the Progression in Barrett (PIB) score system considers cigarette smoking, confirmed LGD at baseline, male sex, and BE segment length (41–43). We conducted a subset analysis from our validation data set on patients with sufficient PIB data (n = 54) and compared results with Esopredict in the same patients (Supplemental methods, Supplementary Digital Content 1, http://links.lww.com/AJG/D379). The results of this comparative analysis are shown in Supplemental Figure 1A, Supplementary Digital Content 1, http://links.lww.com/AJG/D379. However, considering potential sampling bias, this subset analysis is considered exploratory. In addition, the average percent risk of progression per year was compared between Esopredict and PIB and showed that these are not comparable. For example, the high-risk level for Esopredict has an average of 4.3% per year compared with 1.1% per year for PIB (Supplemental Figure 1B, Supplementary Digital Content 1, http://links.lww.com/AJG/D379). In the future, collecting clinical variables to evaluate the predictive value of Esopredict better relative to clinical factors will be valuable.

## DISCUSSION

As demonstrated by this retrospective, multicenter, 240-patient study comprising 110 patients in primary validation and 31 in an independent second validation set, Esopredict provides simplified clinically useful information by stratifying patients as either *lower-risk* category (further refined into low-risk and low-moderate-risk levels) or *higher-risk* category (further refined into high-moderate-risk and high-risk levels). The OR comparing the *lower-risk* category to the *higher-risk* category indicates patients in the latter category are 6.4 times more likely to progress to HGD or EAC within 5 years. By further stratifying into 4 risk levels, we gain deeper insights for surveillance and treatment considerations, whose clinically relevant levels are defined as (i) low risk, with a 4 times *below-average* risk of progression (1.85% average); (ii) low-moderate risk, with a *slightly lower-than-average* risk of progression (4.47%); (iii) high-moderate risk, with a *slightly-higher-than-average* risk of progression (8.12%); and (iv) high risk, with more than 4 times *above-than-average* risk of progression (21.46%) (Figure 3c, and Table 3) (35–40). Our study results demonstrated that compared with low-risk patients, high-risk patients had 15.2 times higher odds of progression to HGD or EAC within 5 years.

Although progression to HGD or EAC is rare in patients enrolled in BE surveillance programs, almost one-quarter of patients who progress do so within 1 year of a negative endoscopy, representing missed opportunities for early intervention (17). Indeed, 9 patients in our validation (n = 110) had an outcome biopsy showing progression <1 year after their index biopsy. Of these patients, 6 were predicted in *the higher-risk* category

**Table 3. Risk and potential beneficial change in care**

| Risk category | Risk level | Compared with average risk of BE patients | % Risk range | Potential beneficial change in care |
|---|---|---|---|---|
| Lower-risk | Low | 2.7 times lower | 0.6–2.8 | Reduced EGD surveillance |
| | Low-moderate | 1.2 times lower | 2.9–6.2 | Continued surveillance schedule |
| Higher-risk | High-moderate | 1.6 times higher | 6.3–11.2 | Increased EGD surveillance |
| | High | ≥2–4 times higher | 11.3–≥20 | Increased surveillance or treatment |

Table listing different risk categories and risk levels showing the associated risk compared with the average risk of patients with BE, the percent risk range, and finally a potential beneficial change in care.
BE, Barrett esophagus; EGD, esophagogastroduodenoscopy.

(i.e., risk levels high-moderate and high). In our validation cohort (n = 110), 85% of patients had an index biopsy of NDBE; among these patients with NDBE, 62 had a last-known follow-up biopsy with NDBE—i.e., no change in nondysplastic status at follow-up intervals ranging from 5 years to 18 years. Esopredict classified 85.0% (n = 50) of these 62 patients in the *lower-risk* category (i.e., risk levels low or low-moderate), with 26 patients being in the low-risk level (i.e., yielding an negative predictive value of 99%), indicating a potential opportunity to decrease surveillance. Among 26 patients with NDBE who had progressed based on outcome biopsy within 0–5 years, 14 (57.7%) would have been classified by Esopredict into the *higher-risk* category (risk levels high moderate, or high), indicating the potential benefit for increased surveillance frequency or perform preventative EET. Today, these patients with NDBE would likely be overlooked based on existing standard-of-care methods. Current evidence suggests that treatment of patients with LGD and EET can be a successful preventative measure; however, concern about the over diagnosis of LGD and care management of the LGD patient population has been controversial (44–46). Our validation cohort included 17 patients (15%) with either IND or LGD index biopsies. Of these patients, 0 had a follow-up biopsy of NDBE, and 0 returned low-risk level Esopredict scores. Among these patients, Esopredict classified 11 (64.7%) in the *higher-risk* category (risk levels high-moderate or high risk) who had either progressed or remained IND or LGD at the time of outcome biopsy. These results suggest potential clinically relevant use in managing patient care in BE patients with IND or LGD, warranting additional follow-up studies.

Prospective studies are challenging to achieve with prognostic assays in a timely manner for a disease with low occurrence. Furthermore, due to this very low prevalence of progression among patients with BE, our study used a case-control design, enriching for patients who progressed to HGD/EAC compared with the general population. Methods were used to adjust for this enrichment to generalize to the population. BE occurs predominantly in White patients. We received patients from collaborating sites without specific racial criteria; however, most patients were White. Future studies should include patients of different races and ethnicities. Another limitation is that instead of a central pathology review, our study design relied on the pathological diagnosis from each clinical center (both index and outcome), which could affect the variability of histological diagnosis. However, this use of the local pathologist's review mimics the real-world use case of Esopredict, which is intended to supplement the pathological reports from different pathologists at different centers. Future studies will incorporate the use of local and centralized pathology reviews with different samples and spatial samples taken during the biopsy histology review including hematoxylin and eosin staining, and other histological features. It will be critical to assess the performance of Esopredict with these additional variables in future studies to compare both spatial samples (biopsies from the same endoscopic surgery) and longitudinal biopsies (same patient but biopsies from different endoscopic surgeries). Finally, our study encountered constraints due to the small subset of patients with LGD or IND index biopsies. Future research on these subsets, as well as additional patients with NDBE, will be pivotal in determining the functionality of this assay across varying stages of dysplasia.

Endoscopic surveillance with histopathologic analysis of biopsy samples is the current standard-of-care method to determine the risk of future neoplasia in patients with BE. However, compliance with these programs is not consistently high, with adherence to established guidelines at only 50% (47–54). Moreover, while underutilization of surveillance may allow preventable cancers to develop, overutilization contributes to higher healthcare costs and inefficient resource utilization. One recent study suggests that excess surveillance endoscopies increase costs by ≥50% without significant increases in life expectancy or quality-adjusted life years (55). An advantage of the Esopredict assay is that it adds complementary value to the current standard of care, incorporating epigenetic data without the need for additional biopsies to advance the personalized management of patients with BE. More patients who are high-risk and would benefit from preventative EET or increased surveillance can be identified beyond the current method while reducing biopsies in patients at low risk for progression. The low cost, high throughput, and repeatable consistent performance of the biomarkers across multiple development studies make Esopredict an ideal technology for BE surveillance.

Esopredict provides critical information for guiding preventative treatment decisions. Indeed, in a study of 100 practicing gastroenterologists, 89 patients reported an increased confidence in making treatment decisions with Esopredict than clinical factors alone (56,57). It is understood that as patients with BE are diagnosed and managed, they incur higher ongoing costs related to inpatient and outpatient visits, ER visits, and medications compared with people without a BE diagnosis. A 2023 claims-based analysis of a large US administrative claims database suggests that direct medical costs of patients with NDBE are as high as a mean of $8,473 per patient annually and $145,302 for patients with EAC (58).

Patients in BE surveillance programs also face multiple hurdles, including but not limited to lost productivity due to time off needed to attend appointments and procedures, lost wages (when time off with pay is not available), insufficient childcare support, the need to obtain a driver to travel to and from endoscopy appointments, and issues related to a lack of reliable phone, computer, lack of transportation, or other support. Clinicians will be able to use the risk stratification system of Esopredict with an individualized probability of progression score to determine the most appropriate management for their patients with BE, to lengthen future endoscopic surveillance intervals and avoid EET (low risk), build confidence around current care management (low-moderate risk), or consider increasing surveillance or EET to prevent the development of one of the most lethal cancers in patients at higher risk.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Stephen J. Meltzer, MD.
**Specific author contributions:** S.E.L.: designed and conducted the study; provided administrative, technical, and material support; acquired, analyzed, and interpreted the data; drafted, reviewed, and revised the manuscript; and approved the final draft submitted. L.K and D.L.: designed and conducted the study; provided administrative, technical, and material support; analyzed and interpreted the data; reviewed and revised the manuscript; and approved the final draft submitted. J.B., H.L.T., H.W.: analyzed and interpreted the data; drafted, reviewed, and revised the manuscript; and approved the final draft submitted. S.G. and A.K.: reviewed and revised the manuscript and approved the final draft submitted. F.P.: acquired and analyzed data, reviewed the manuscript, and approved the final draft submitted. K.M. and Y.C.:

provided material support, reviewed the manuscript, and approved the final draft submitted. S.J., Y.A., K.K.W., C.L.L., A.C., O.B.I., B.D.G., A.H.Z., A.N.O., B.J., L.K., D.C., P.Z., M.S., E.K., L.P.: provided material support, reviewed the manuscript, and approved the final draft submitted. T.M., S.J.M.: designed and conducted the study; supervised the study; provided administrative, technical, and material support; analyzed and interpreted the data; reviewed and revised the manuscript; and approved the final draft submitted.
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## Study Highlights

### WHAT IS KNOWN

- ✓ Barrett's Esophagus (BE) is the only known precursor to Esophageal Adenocarcinoma (EAC).
- ✓ EAC is the second most lethal cancer in the United States, with rates increasing.
- ✓ EAC is treatable and preventable, yet current risk assessment is subjective and imprecise.

### WHAT IS NEW HERE

- ✓ Our epigenetic biomarker assay predicts progression to high-grade dysplasia or EAC within 5 years.
- ✓ High-risk patients had a 22% risk of progressing, 4 times the average risk for BE.
- ✓ Validation of a risk-stratification tool that informs clinical decision-making for patients with BE.

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