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ORIGINAL ARTICLE

Gastroenterology: Eosinophilic Gastrointestinal Disease

EndoFLIP distensibility index correlates with histologic findings in children with eosinophilic esophagitis

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Abstract

Background and Aims: The Eosinophilic Esophagitis Histology Scoring System (EoEHSS) is useful for diagnosing and characterizing eosinophilic esophagitis (EoE). A limitation of the EoEHSS is that lamina propria fibrosis scores are infrequently determined due to challenges in sampling lamina propria. Low distensibility index (DI) measured by endoluminal functional lumen imaging probe (EndoFLIP) is associated with fibrostenotic severity in pediatric patients with EoE. We investigated the correlation between DI and the EoEHSS to understand whether EndoFLIP could be a useful complementary tool for evaluating EoE-associated remodeling in children.

Methods: We reviewed the medical records of patients <21 years of age who underwent an esophagogastroduodenoscopy (EGD) with biopsy and EndoFLIP between October 2017 and July 2023 with histologic diagnoses of normal/reactive, reflux, or EoE. EoEHSS scores and luminal parameters were compared between groups. DI measured at 30 mL inflation was compared with EoEHSS scores.

Results: One hundred twenty-six EGDs with biopsy and EndoFLIP were performed on 112 patients. There were 80 normal/reactive, 32 reflux, and 14 EoE biopsies. At 30 mL inflation, DI was lowest in the EoE group ($p = 0.03$). DI at 30 mL inflation negatively correlated with the EoEHSS overall grade score, as well as grade and stage scores for eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, and basal zone hyperplasia (all $p < 0.05$). DI at 30 mL inflation also negatively correlated with the eosinophilic inflammation stage score ($p < 0.05$).

Conclusion: DI measured by EndoFLIP at 30 mL inflation shows a negative correlation with composite EoEHSS scores and subscores, suggestive of remodeling. EndoFLIP may complement the EoEHSS in evaluating EoE-associated esophageal remodeling.

[Correction added on 26 April 2025, after the first online publication: Funding has been updated.]

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Erik Almazan and Tom Z. Liang contributed equally to this study.

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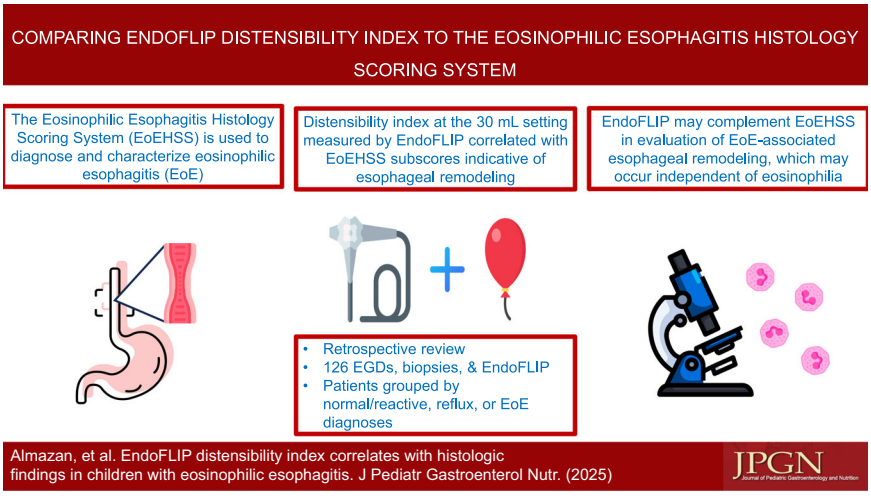

KEYWORDS

endoscopy, EoEHSS, esophagus, pathology, pediatrics

1 | INTRODUCTION

1.1 | Eosinophilic esophagitis (EoE) in the pediatric setting

EoE is an important cause of esophagitis in children and has an estimated incidence and prevalence in North American children of 8.1 cases/100,000 persons/year and 38.3 cases/100,000 persons, respectively.[1] EoE is a chronic inflammatory disease of the esophagus characterized by eosinophilic infiltration and is thought to occur as a T helper type 2 (Th2)-mediated allergic response to food-based antigens.[2,3] Patients with EoE often experience dysphagia, nausea, vomiting, abdominal pain, and/or gastroesophageal reflux-like symptoms.[4] EoE, furthermore, can have a detrimental impact on feeding and, from its progressive disease course, can lead to long-term complications such as fibrosis and strictures, making it a significant concern in the pediatric setting.[4]

Early identification of esophageal fibrosis and remodeling in EoE is important to identify subclinical disease and preemptively prevent complications from chronic, untreated EoE.[2] While the traditional method for diagnosing EoE relies primarily on the presence of suggestive esophageal symptoms combined with esophageal biopsies showing a peak eosinophil count (PEC) of ≥15 eosinophils/high-powered field (HPF), it does not formally incorporate the examination of other histological features that identify esophageal remodeling.[2,5]

1.2 | EoE and the eosinophilic esophagitis histology scoring system (EoEHSS)

The newly developed EoEHSS by Collins et al. is a highly reliable diagnostic tool that can provide more information than the gold-standard, PEC.[6] In addition to aiding in establishing a diagnosis, the EoEHSS is better able to assess disease severity following treatment, and has been shown to differentiate between patients who have received treatment for EoE and those with active disease.[6,7] The EoEHSS is comprised of eight components to address grade (severity) and stage (extent). The eight components are eosinophilic inflammation (EI), eosinophil

What is Known

- The Eosinophilic Esophagitis Histology Scoring System (EoEHSS) is useful for diagnosing eosinophilic esophagitis (EoE), characterizing disease severity, and gauging treatment response.
- Esophageal lamina propria fibrosis is challenging to assess from biopsies due to superficial sampling.
- Patients with EoE may have reduced esophageal distensibility measured by endoluminal functional lumen imaging probe (EndoFLIP).
- Esophageal distensibility inversely correlates with fibrostenotic severity in pediatric patients with EoE.

What is New

- EndoFLIP distensibility index at 30 mL inflation is lower in pediatric patients with EoE compared to those with reflux or normal/reactive diagnoses and inversely correlates with overall EoEHSS grade score and EoEHSS grade and stage subscores.

abscesses (EA), surface layering (SL), surface epithelial alteration (SEA), dyskeratotic epithelial cells (DECs), dilated intercellular spaces (DIS), basal zone hyperplasia (BZH), and lamina propria fibrosis (LPF). An important aspect of the EoEHSS is that components of the model, namely BZH and DIS, do not evaluate eosinophil inflammation, but effectively distinguish between treated and untreated patients, indicating that disease severity in EoE encompasses features beyond eosinophilia.[6] One limitation of the EoEHSS is the low intraobserver and interobserver reproducibility for components of the score, including LPF grade and stage scores.[8] There are also frequent challenges in obtaining sufficient and appropriate quality lamina propria samples from biopsies for analysis.[6,9–14] Characterizing LPF, nevertheless, is important as it is prevalent in children with EoE and is associated with dysphagia.[15]

1.3 | EoE and the endoluminal functional lumen imaging probe (EndoFLIP)

LPF is associated with decreased esophageal distensibility in children, suggesting that distensibility may be a useful proxy for fibrosis and esophageal remodeling.[12] This idea is supported by data showing that esophageal distensibility negatively correlates with eosinophil-associated proteins, which are themselves associated with biochemical markers of the epithelial–mesenchymal transition (EMT) that occurs during esophageal remodeling.[16] Distensibility measurements, furthermore, may allow for the identification of early remodeling, even in the absence of eosinophilia or endoscopic findings. In children and adults, decreased esophageal distensibility can be a marker for early fibrostenotic changes independent of eosinophil count.[17,18] Decreases in esophageal diameter and cross-sectional area, resulting in lower distensibility, have also been reported to occur independently of endoscopic findings, such as furrowing, rings, or white plaques.[19] These early changes are important, not only for diagnostic purposes, but also because of their prognostic value for characterizing EoE severity as they are associated with food impaction and the need for esophageal dilation.[18,20] EndoFLIP is a diagnostic tool that utilizes impedance technology to measure key luminal parameters and characteristics in real time during endoscopy. EndoFLIP may greatly complement the EoEHSS and provide data on early esophageal remodeling in EoE disease progression. We sought to compare the EndoFLIP and histology findings in pediatric patients who underwent an esophagogastroduodenoscopy (EGD) with biopsy.

2 | METHODS

2.1 | Study design

Electronic medical records were reviewed to identify all patients under 21 years of age who underwent an EGD with biopsy and EndoFLIP between October 2017 and July 2023 at the Johns Hopkins Children's Center, a tertiary-care, academic center.

2.2 | Ethics statement

The study was approved by the Johns Hopkins University Institutional Review Board.

2.3 | EndoFLIP procedure and parameters

EGD with biopsy and EndoFLIP were performed by one pediatric gastroenterologist (KN). All patients were sedated under general anesthesia and managed by a pediatric anesthesiologist. EGDs were performed using an Olympus gastroscope (model GIF-H180 or GIF-H190). An 8 cm EndoFLIP catheter was selected for patients under 42 in. in height, and a 16 cm catheter was used for those at least 42 in. tall. Preprocedural calibration of the FLIP computer was performed by the nurse or technician according to the manufacturer's guidelines. During each EndoFLIP procedure, the deflated EndoFLIP catheter was advanced to the lower esophageal sphincter (LES) under direct visualization via the gastroscope. A sodium chloride-based solution provided by the manufacturer was used to inflate the balloon catheter to 15 mL, and the catheter was centered at the LES. At the discretion of the endoscopist, the catheter was inflated to the 20, 30, 40, 50, and/or 60 mL settings. EndoFLIP luminal parameters, including diameter (cm), cross-sectional area (mm^2), compliance ($cm^2/cm\ H_2O$), distensibility index (DI; mm^2/mmHg), and pressure (mmHg) were recorded by the operating room staff at each setting used during the procedure.

2.4 | Electronic medical record review

Demographic, clinical, procedural, and pathology data were extracted from the electronic medical record. Procedural data included EndoFLIP parameter values after inflation to 20, 30, 40, 50, and/or 60 mL. Pathology data included the biopsy site and the original diagnosis rendered in the pathology report.

2.5 | EoEHSS

Biopsies from the distal esophagus were examined by two pathologists with subspecialty expertise in gastrointestinal pathology (JBG and TL). Histologic diagnoses were categorized as normal/reactive, reflux esophagitis, or EoE (Figure S1). For each biopsy, the PEC was quantified based on the number of eosinophils seen in an HPF (400× magnification). EI, EA, SL, SEA, DEC, DIS, BZH, and LPF were subsequently evaluated and individually scored using a 4-point scale for grade (severity) and stage (extent) according to the EoEHSS developed by Collins et al.[6] Following the EoEHSS, overall scores for grade and stage was calculated for each sample after taking the sum of the respective EI, EA, SL, SEA, DEC, DIS, BZH, and LPF scores and dividing the sum by the maximum possible score.[6]

2.6 | Statistical analysis

Median, minimum, and maximum values were reported for continuous variables, and percentages were reported for categorical variables. Demographics, histologic scores, and EndoFLIP parameters were compared between histologic cohorts using the Kruskal–Wallis test for continuous variables and Fisher's exact test for categorical variables. Spearman's rank correlation coefficient analyses were performed to compare EndoFLIP parameter values with the overall and component scores of the EoEHSS. The EndoFLIP parameter values at the 30 mL inflation setting were the only values used for comparative analyses as the 30 mL setting was the most used setting for patients in our cohort. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS version 29.0). p values < 0.05 (two-tailed) were considered significant in all analyses.

3 | RESULTS

3.1 | Patient characteristics

One hundred twenty-six EGDs with biopsy and EndoFLIP were performed on 112 patients (Table 1). Eighty biopsies were classified as normal/reactive, 32 as reflux, and 14 as EoE after subspecialist pathologist review. The median age of the entire cohort was 11.1 years (range, 0.1–20.9). The entire cohort had a slight male predominance (54.0%) and was predominately non-Hispanic (94.4%) and White (69.0%). The two most common chief complaints were dysphagia (66.7%) and emesis (18.3%). Age, sex, race, Hispanic ethnicity, and chief complaint did not differ significantly between histologic diagnoses (Table 1).

TABLE 1 Demographics.

	Normal or reactive ($n = 80$)	Reflux ($n = 32$)	Eosinophilic esophagitis (n = 14)	p
Age (years), median (range)	10.3 (0.8–20.9)	11.7 (0.1–20.8)	13.9 (2.9–19.4)	0.50
Sex, *n* (%)				0.47
Male	40 (50.0)	20 (62.5)	8 (57.1)	
Female	40 (50.0)	12 (37.5)	6 (42.9)	
Race, *n* (%)				0.72
Non-Hispanic White	54 (67.5)	24 (75.0)	9 (64.3)	
Black	17 (21.3)	7 (21.9)	4 (28.6)	
Other	9 (11.3)	1 (3.1)	1 (7.1)	
Hispanic, *n* (%)	6 (7.5)	1 (3.1)	0 (0)	0.60
Chief complaint, *n* (%)				0.26
Dysphagia	49 (61.3)	23 (71.9)	12 (85.7)	
Emesis	16 (20.0)	6 (18.8)	1 (7.1)	
Reflux	12 (15.0)	1 (3.1)	0 (0)	
Abdominal pain	1 (1.3)	1 (3.1)	1 (7.1)	
Abnormal imaging	2 (2.5)	1 (3.1)	0 (0)	

3.2 | EndoFLIP parameter comparison

The 30 mL inflation setting at the LES was used for comparison of the three groups (Table 2). At this inflation setting, the median DI was lowest in the EoE group (2.1 mm^2/mmHg) compared to the reflux group (3.3 mm^2/mmHg) and normal/reactive group (2.9 mm^2/mmHg) ($p = 0.03$). Of note, a narrower range of distensibility values was observed in the EoE group (1.2–4.4 mm^2/mmHg) compared to the normal/reactive group (0.7–11.7 mm^2/mmHg) and the reflux group (0.6–9.1 mm^2/mmHg). No differences were observed for diameter, cross-sectional area, compliance, or pressure across groups (all $p > 0.05$). There was no significant difference in distensibility based on sex, race, ethnicity, or age (all $p > 0.05$).

3.3 | EoEHSS validation

A comparison of EoEHSS scores across the histologic groups was made to validate the score for assessing EoE in our patient population (Table S1). The overall grade and stage scores were higher in the EoE group compared to the reflux and normal/reactive groups ($p < 0.001$). EI, EA, SL, SEA, DEC, DIS, BZH, and LPF grade and stage scores were also higher in the EoE group compared to the reflux and normal/reactive groups (all $p < 0.01$). LPF grade and stage could only be assessed in 75 (59.5%) cases, as lamina propria was not sampled or minimally sampled in the remainder of the cases.

3.4 | Comparison of EoEHSS and EndoFLIP distensibility data

A comparison of the DI at the 30 mL EndoFLIP inflation setting at the LES and the EoEHSS was made using Spearman's rank correlation coefficient (Table 3). An inverse relationship was observed between DI measured at the 30 mL EndoFLIP inflation setting and EoEHSS overall grade score ($p = 0.02$) (Figure S2). DI was also inversely related to grade and stage subscores for EA, SL, DIS, and BZH, and stage subscore for EI (all $p < 0.05$). Notably, DI did not meaningfully correlate with PEC ($p = 0.56$).

4 | DISCUSSION

Our study is the first to demonstrate that the DI measured by EndoFLIP correlates with the EoEHSS overall grade score, a validated score for EoE diagnosis and severity assessment. Our results also show that DI correlates with subscores of the EoEHSS grade and stage scores that may identify esophageal remodeling independent of eosinophilia. DI may, therefore, reflect EoE severity and complement the EoEHSS score in determining EoE-associated esophageal remodeling in children.

EndoFLIP has been well-studied in the adult population and found to be effective in diagnosing esophageal motility disorders.[21] In adults, reference values for a normal DI exist in addition to estimates for predicted distensibility changes in patients with EoE.[17,22] In the pediatric population, EndoFLIP has been used most commonly to characterize the esophageal lumen and evaluate for esophageal motility disorders. Yet, there are no established reference ranges for luminal parameters.[23] While DI measured by EndoFLIP has been shown to be decreased in pediatric patients with EoE, the absence of reference values limits its use as a standalone diagnostic tool.[12] Our results showing that DI correlates with a pathologic diagnosis of EoE and EoEHSS grade and stage scores, markers of severity and extent, demonstrate the potential of EndoFLIP to serve as an adjunctive tool to assess disease severity in patients with known EoE. This idea is supported by literature showing that decreased distensibility is associated with active disease, LPF, and fibrotic features on endoscopy in children with EoE.[12,18]

TABLE 2 EndoFLIP parameter values at the 30 mL setting at the lower esophageal sphincter.

	Normal or reactive ($n = 80$)	Reflux ($n = 32$)	Eosinophilic esophagitis ($n = 14$)	p
Parameters, median (range)				
Diameter (cm)	7.0 (3.7–13.9)	7.2 (4.8–13.9)	5.6 (4.7–9.2)	0.16
Compliance (cm^2/cm H_2O)	110.9 (38.2–650.2)	167.9 (22.8–558.3)	189.4 (34.8–393.6)	0.31
Cross-sectional area (mm^2)	39.0 (17.0–153.0)	42.0 (18.0–152.0)	25.0 (17.0–67.0)	0.17
Distensibility index (mm^2/mmHg)	2.9 (0.7–11.7)	3.3 (0.6–9.1)	2.1 (1.2–4.4)	**0.03**
Pressure (mmHg)	14.1 (5.0–38.1)	12.6 (5.0–52.9)	11.8 (7.6–47.8)	1.00

Note: The "Normal/Reactive" and "Reflux" cohorts did not have EndoFLIP values for all patients at the 30 mL setting. The "Normal/Reactive" cohort had 79, 76, 78, 78, and 79 values for the diameter, compliance, cross-sectional area, distensibility index, and pressure, respectively. The "Reflux" cohort had 30, 29, 30, 30, and 29 values for the diameter, compliance, cross-sectional area, distensibility index, and pressure, respectively. Bold value indicates statistically significant at $p < 0.05$.
Abbreviation: EndoFLIP, endoluminal functional lumen imaging probe.

TABLE 3 Spearman's rank correlation coefficient of distensibility index at the 30 mL setting at the lower esophageal sphincter and EoEHSS score.

	Correlation coefficient (95% confidence interval)	*p*
Overall grade score	−0.21 (−0.37 to −0.03)	**0.02**
Overall stage score	−0.17 (−0.34 to 0.02)	0.06
Eosinophilic inflammation grade	−0.07 (−0.25 to −0.11)	0.43
Eosinophilic inflammation stage	−0.21 (−0.37 to −0.02)	**0.02**
Eosinophil abscesses grade	−0.20 (−0.37 to −0.02)	**0.03**
Eosinophil abscesses stage	−0.20 (−0.37 to −0.02)	**0.03**
Surface layering grade	−0.23 (−0.40 to −0.05)	**0.01**
Surface layering stage	−0.23 (−0.40 to −0.05)	**0.01**
Surface epithelial alteration grade	−0.17 (−0.34 to 0.02)	0.07
Surface epithelial alteration stage	−0.17 (−0.34 to 0.02)	0.07
Dyskeratotic epithelial cells grade	−0.07 (−0.25 to 0.12)	0.46
Dyskeratotic epithelial cells stage	−0.07 (−0.25 to 0.12)	0.45
Dilated intercellular spaces grade	−0.23 (−0.40 to −0.05)	**0.01**
Dilated intercellular spaces stage	−0.23 (−0.40 to −0.05)	**0.01**
Basal zone hyperplasia grade	−0.27 (−0.43 to −0.09)	**<0.01**
Basal zone hyperplasia stage	−0.29 (−0.39 to −0.05)	**0.01**
Lamina propria fibrosis grade	−0.14 (−0.37 to 0.09)	0.23
Lamina propria fibrosis stage	−0.15 (−0.37 to 0.09)	0.21

Note: Bold values indicate statistically significant at $p < 0.05$.

Abbreviation: EoEHSS, Eosinophilic Esophagitis Histology Scoring System.

Our study found that DI correlated not only with EoEHSS overall grade scores, but also with DIS and BZH subscores, markers of epithelial injury and regeneration. The association between DI and both DIS and BZH, features that do not evaluate eosinophil infiltration, suggests that DI may elucidate aspects of the remodeling process in EoE independent of eosinophilia. BZH and DIS are characteristic findings in EoE. BZH reflects basal epithelial cell proliferation and delayed terminal differentiation. Impaired differentiation in this process has been associated with EMT and epithelial barrier defects, which may promote esophageal fibrosis.[24] DIS may additionally reflect damage to the barrier function of the esophageal squamous mucosa. Notably, while DIS and BZH are more pronounced in biopsy samples showing significant eosinophilia, they are also present in samples without many eosinophils.[9] While the presence of epithelial injury in the absence of eosinophilia could reflect the uneven distribution of eosinophils in biopsy samples, it is also possible that this could reflect prior mucosal injury, which would not necessarily correlate with the presence of eosinophils at the time of sampling. The observed correlation between DI and DIS and BZH, but not PEC, in addition to published data showing that DI predicts fibrostenotic severity in children, underscores the potential value of EndoFLIP as a tool for assessing fibrosis and remodeling in EoE independent of eosinophilia.[18]

A limitation of the EoEHSS score is the difficulty in determining LPF scores. Assessment of the lamina propria is important as pediatric patients with EoE are known to have increased markers associated with esophageal remodeling (TGF-β1 and nuclear phospho-SMAD2/3) and increased rates of subepithelial fibrosis.[15,25] LPF in children, furthermore, is not associated with specific endoscopic findings in patients with known EoE, which may indicate that LPF can be identified in the absence of EoE-specific changes seen during endoscopy.[15] Our study did not find a statistically significant association between DI and LPF scores, which may have been due to a lack of power. In our cohort, LPF scores could only be determined for 59.5% of cases, as the lamina propria was absent or only minimally sampled in the remainder of the biopsies. This limitation has been previously reported in the literature.[6,9–14] In a previous study at two pediatric institutions, decreased DI measured by EndoFLIP was

found to be associated with histologic LPF.[12] DI, therefore, may be a useful data point for assessing EoE fibrosis and may complement the EoEHSS, especially in cases of inadequate sampling of lamina propria. Additionally, DI may be useful in characterizing fibrosis in pediatric patients with inactive disease, where adequate lamina propria samples are less often obtained.[26]

There were several limitations to our study. First, this was a single-center retrospective study, which may limit the generalizability of our findings. Additionally, our study had a small sample size, especially of patients with EoE, which may have made it difficult for us to detect differences in other EndoFLIP luminal parameters between the three groups. The difficulty of observing differences across groups in the luminal parameters may also have been affected by using only the values from inflation to 30 mL for comparative analysis. The decision to use the values from inflation to 30 mL, however, was made because this was the most used setting in all patients and provided the most data for analysis. Data from inflation to 30 mL were likely the most available because baseline measurements were taken starting from either 20 mL or 30 mL, based on the patient's size at the endoscopist's discretion, and were increased in 10 mL increments up to a maximum of 60 mL, adapted from the clinical approach outlined in existing literature.[12] Another limitation of our study was that the Endoscopic Reference Score (EREFS), which characterizes disease severity in EoE, was not used. This was due to our institution's standard of practice and the fact that patients in our study were included irrespective of indication for EGD with biopsy and EndoFLIP. As a result, even if EREFS had been documented, it would not have been available for most patients in our study and would not have been useful for meaningful comparisons. Finally, the findings of our study are limited by the absence of normal reference values for EndoFLIP luminal parameters in the pediatric community. Although we observed that the median DI was lower and the range of DI values was narrower in patients with EoE compared to those without EoE, we note that overlapping DI values were observed between groups. Further studies with larger cohorts of patients are needed to verify our findings and to establish meaningful reference ranges for esophageal distensibility in pediatric patients with and without EoE.

5 | CONCLUSION

DI measured by EndoFLIP at 30 mL inflation is lower in patients with EoE compared to those with reflux or normal/reactive diagnoses. Furthermore, DI negatively correlates with the EoEHSS overall grade score, as well as EA, SL, DIS, and BZH grade and stage subscores, which may reflect esophageal remodeling. Therefore, DI may complement the EoEHSS in evaluating EoE-associated esophageal remodeling. Our study encourages further investigation into the use of EndoFLIP to improve the luminal characterization of EoE in pediatric patients.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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