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### Eosinophilic Esophagitis: Stricture Risk and Molecular Diagnosis

The incidence of eosinophilic esophagitis (EoE), a chronic immune-mediated esophageal disorder characterized by esophageal dysfunction, primarily dysphagia leading to food impaction, and eosinophil-predominant inflammation on biopsy, has significantly increased since its initial description over 2 decades ago. In this issue of Gastroenterology (accompanied by an editorial), 2 studies address the diagnosis and natural history of this emerging yet still enigmatic disorder.

The diagnosis of EoE currently rests on the histologic analysis of esophageal biopsies in concert with clinical symptoms of esophageal dysfunction. However, esophageal eosinophilia is not specific to EoE. Taking advantage of the discovery of a uniquely conserved gene expression profile in patients with EoE, Wen et al developed a molecular EoE diagnostic panel (EDP) using a quantitative polymerase chain reaction array of 94 representative EoE genes and 2 housekeeping controls to better diagnose EoE. This EDP identified pediatric and adult patients with EoE with high sensitivity (~96%) and specificity (~98%; Figure 1). The EDP also discriminated between patients with EoE in remission from normal controls. Furthermore, in patients with <15 eosinophils/high-power field, the EDP identified a subset of patients at risk for developing active EoE. Finally, the EDP distinguished patients with EoE from patients with gastroesophageal reflux disease and nonerosive reflux disease. Comparable results were obtained whether fresh or formalin-fixed paraffin-embedded tissue was used. These findings provide proof of principle for the use of a tissue-based molecular test in the diagnosis of EoE and highlight the advantages of such techniques over histologic analysis.

The endoscopic features of EoE have been categorized as either inflammatory, characterized by whitish exudates, edema, and linear furrows, or fibrotic, characterized by rings, strictures, and crepe paper esophagus, although most patients present with an overlap of these features. Schoepfer et al perform a retrospective analysis of the relationship between the duration of untreated disease and the risk of stricture formation in 200 patients with EoE. The median diagnostic delay (time from first symptoms to diagnosis) was 6 years and was longest in patients ≤20 years old, and decreased with increasing age. Inflammatory features were present in 79.5%, fibrotic features in 60%, and strictures in 37.5% of patients at the time of EoE diagnosis. The prevalence of fibrotic features at the time of EoE diagnosis with or without inflammatory features increased with increasing duration of diagnostic delay from 46.5% in patients with a diagnostic delay of ≤2 years compared with 87.5% in patients with a diagnostic delay of >20 years. In addition, the prevalence of esophageal strictures correlated with the presence of fibrotic features and the duration of diagnostic delay, with a prevalence of strictures of 17.2% in patients with a diagnostic delay of ≤2 years compared with 70.8% in patients with a diagnostic delay of >20 years. The duration of diagnostic delay was the only risk factor associated with the presence of strictures at the time of EoE diagnosis. In contrast, the prevalence of inflammatory features alone decreased with increasing duration of diagnostic delay. These findings help to define the natural history of untreated EoE and support measures to reduce the diagnostic delay in patients with this chronic esophageal disorder.

**See 1230 and 1289; editorial on page 1186.**

### IBS: Emotional Learning and Rome III Criteria Validation

Irritable bowel syndrome (IBS) is commonly seen in gastroenterology practices with a global prevalence of about 20%. It is characterized by abdominal pain with changes in stool consistency and frequency. IBS is a functional bowel disorder whose diagnosis can be established only when other organic gastrointestinal diseases are absent. As a result, patient evaluation commonly employs costly diagnostic interventions such as colonoscopy, esophagoduodenoscopy, and imaging studies. The overlap of IBS symptoms with those of other organic gastrointestinal diseases contributes to the associated high costs of a diagnostic evaluation. Thus, symptom-based criteria have been developed for the purpose of differentiating patients with IBS from those with organic diseases. These have included the Manning, Rome I, Rome II, and Rome III criteria. A missing element underlying many of the criteria is the absence of adequate clinical validation. In this issue of Gastroenterology, Ford et al studied 1848 adult patients from 2 hospitals in Hamilton, Canada. The Rome III questionnaire was applied to the patients, followed by a colonoscopy with biopsies. If the patients' celiac disease serologies were positive, an upper endoscopy was also performed. The criteria used for IBS in this study consisted of lower abdominal pain at least once a week, altered bowel habits, and the absence of evidence for organic disease on endoscopy and pathology.

The results indicated that Rome III performed less well than either the Rome I and II criteria (Table 1). All

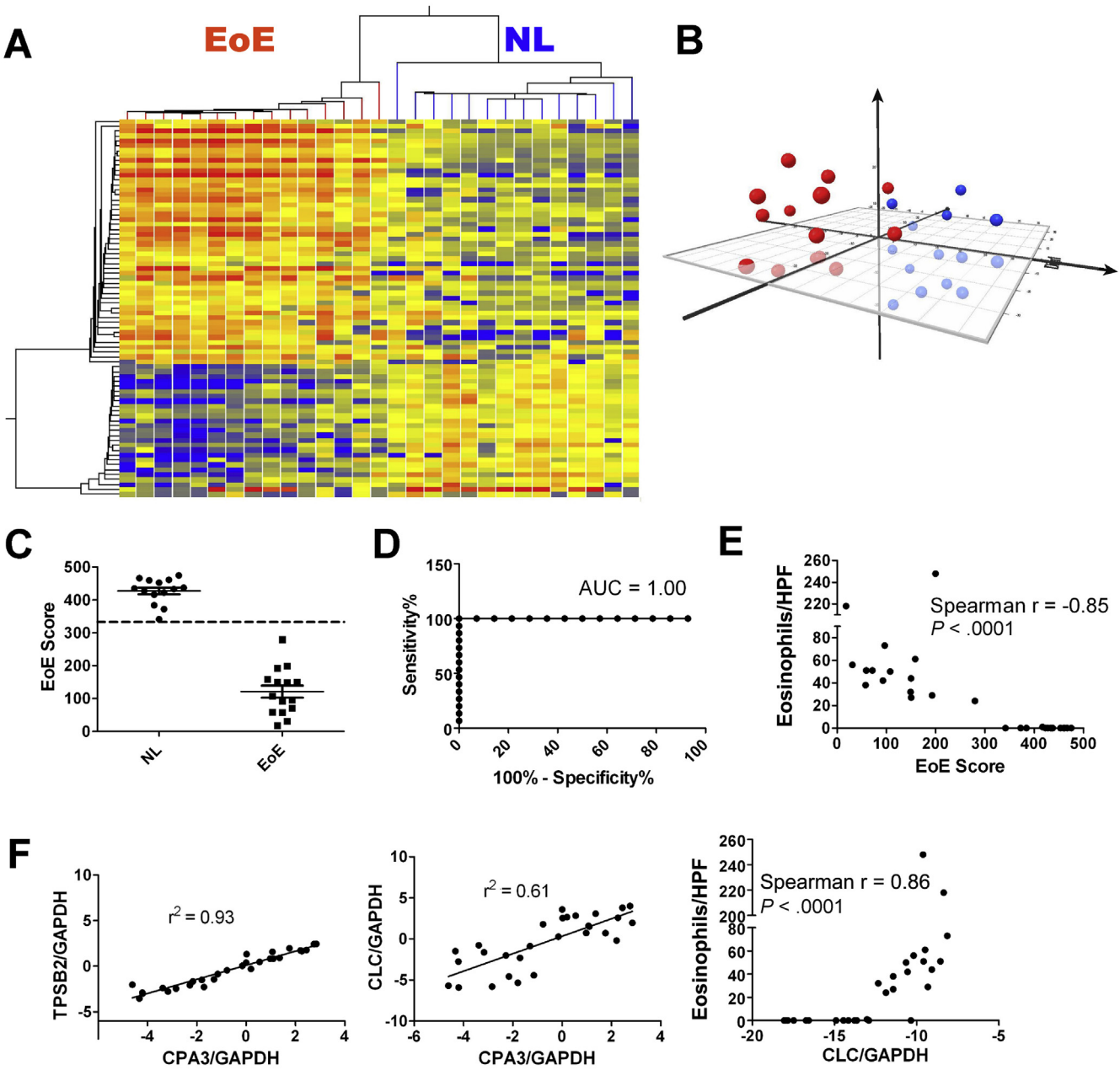


**Figure 1.** Dual EDP algorithms for molecular diagnosis of EoE. (*A*) For the 94 EoE genes embedded, a statistical screening was performed between the 14 normal (NL) patients (*blue branch*) and 15 patients with EoE (*red branch*), resulting in 77 genes with false discovery rate_corrected $P < .05$ and fold change >2.0. Based on these 77 core genes, a heat map (*red*: up-regulated) was created, with the hierarchical tree (*dendrogram*) established on both gene entities and sample conditions. On the *x-axis*, the first branch of the top tree is utilized to predict EoE vs NL. (*B*) The 77-gene/dimension expression data on 14 NL controls (*blue*) and 15 patients with EoE (*red*) were reduced to 3-dimensional presentation by multidimensional scaling analysis for visual presentation of the expression distance between samples. *Lighter colors* indicate positions under the plane. (*C*) An EoE score was developed based on dimensionality reduction to distinguish EoE vs NL and quantify EoE disease severity. A diagnosis cut-off at EoE score = 333 (*dashed line*) was derived from later, larger-scale studies by ROC analysis. (*D*) ROC curve based on *panel C* and the EoE score = 333 cut-off, with an AUC of 1.0. (*E*) A linear correlation between eosinophils/HPF and EoE score, with Spearman r and *P* values shown. (*F*) To demonstrate gene amplification accuracy, representative linear regressions regarding mast cell gene intra-correlation (*carboxypeptidase A3* [*CPA3*] vs tryptase [*TPSB2*]), mast cell gene/eosinophil gene inter-correlation (*CPA3* vs *CLC*), and eosinophil gene/eosinophilia correlation (*CLC* vs eosinophils/HPF) are shown in the *left, middle,* and *right panels*, respectively. All scatter plots were graphed as mean ± SEM. GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

criteria studied to date, however, exhibit positive predictive values of <50%, which underscores the need for developing diagnostic strategies for IBS that are without the risk and expense of current approaches.

In a second paper in this issue of Gastroenterology, Labus et al performed a single-center, randomized,