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Review Article

Research gaps in eosinophilic esophagitis: unanswered questions and future directions

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ABSTRACT

Eosinophilic esophagitis (EoE) has emerged as a leading cause of dysphagia worldwide, yet significant knowledge gaps persist across fundamental aspects of disease management. This comprehensive narrative review examines critical research opportunities spanning five interconnected domains that collectively hamper optimal patient care.

Despite advances in understanding type 2 inflammation, EoE pathogenesis remains incompletely characterized, particularly regarding gene-environment interactions, epithelial barrier dysfunction mechanisms, and tissue remodeling pathways. The diagnosis currently relies on endoscopy with biopsies with an arbitrary eosinophil threshold of 15 eosinophils/high-power field, while molecular endotypes and non-invasive biomarkers lack validation. Treatment strategies remain largely empirical without strong evidence-based therapeutic hierarchies, comparative effectiveness data, or reliable response predictors. The lack of head-to-head comparison trials of different interventions limits evidence-based treatment selection, while combination therapy approaches remain mostly underexplored.

Challenges in defining optimal treatment targets persist, as recent eosinophil-depleting biologics achieved histologic responses without symptomatic improvement, highlighting the limitations of eosinophil-centric disease models. Disease trajectory prediction and long-term outcome monitoring lack systematic approaches, while primary prevention strategies remain undefined despite escalating global incidence.

Addressing these research gaps through coordinated multidisciplinary efforts has the potential to transform EoE management from empirical to personalized, evidence-based approaches, ultimately improving patient outcomes and potentially enabling disease prevention.

1. Introduction

Eosinophilic esophagitis (EoE) is a chronic, allergen-driven inflammatory disorder of the esophagus, characterized by type 2 immune-mediated responses that manifest as esophageal dysfunction accompanied by eosinophil-predominant tissue infiltration [1,2]. Over the past two decades, this condition has transformed from a rarely recognized entity to a leading cause of dysphagia in young adults and feeding difficulties in children worldwide. A comprehensive meta-analysis of 40 population-based studies spanning 15 countries found pooled incidence rates of 5.3 cases per 100,000 person-years and prevalence of 40.0 cases per 100,000 individuals [3]. The substantial increase in prevalence when comparing early study periods (1976–2001) to recent data (2017–2022) suggests complex interactions between environmental exposures and genetic susceptibility factors that remain incompletely understood.

Despite remarkable progress in understanding EoE pathophysiology and expanding therapeutic options, significant knowledge gaps persist across fundamental aspects of disease management, creating barriers to optimal patient care. While research has established EoE as an adaptive immune-mediated condition initiated when environmental allergens interact with epithelial barrier de-

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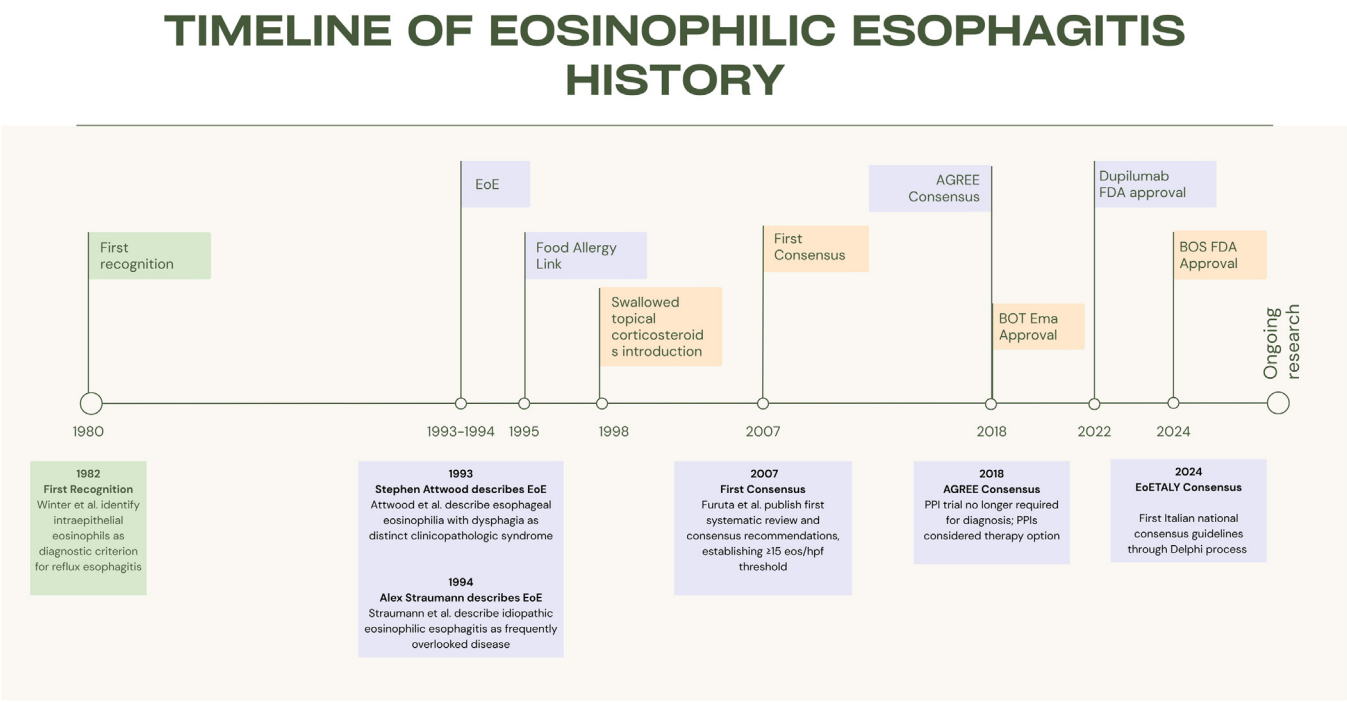

Fig. 1. Timeline of major milestones in the history of eosinophilic esophagitis from initial recognition through current therapeutic advances. Key developments include the initial description of esophageal eosinophilia (1982), recognition as a distinct clinicopathologic entity (1993–1994), establishment of food allergy connections (1995), introduction of topical corticosteroids (1998), consensus diagnostic guidelines (2007, 2018), and regulatory approvals of standardized treatments (2018–2024).
Abbreviations: AGREE, A workGroup of inteRnational Eosinophilic Esophagitis rEsearchers; BOT, budesonide orodispersible tablet; BOS, budesonide oral suspension; EMA, European Medicines Agency; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; FDA, US Food and Drug Administration; PPI, proton pump inhibitor.

fects [4–8], and has led to validated outcome measurement systems and refined diagnostic criteria [9–18], current diagnostic approaches still require invasive endoscopic procedures with arbitrary eosinophil thresholds; therapeutic strategies remain largely empirical without evidence-based treatment hierarchies; disease progression from inflammatory to fibrostenotic phenotypes lacks reliable predictive markers; and patient outcomes are compromised by diagnostic delays that directly correlate with increased complication risk [19–23]. Fig. 1 represents the timeline of EoE major milestones. Although recent therapeutic advances, including dupilumab approval, represent meaningful progress, fundamental questions regarding optimal treatment sequencing, response prediction, and personalized medicine approaches remain largely unanswered [24,25].

The clinical consequences of these knowledge gaps are substantial. Healthcare systems face challenges providing cost-effective care in the absence of comparative effectiveness data and personalized treatment approaches [1,26,27]. Patients experience significant quality of life impairment [28,29], while the lack of reliable biomarkers for disease monitoring necessitates repeated invasive procedures [30]. Table 1 summarizes the main research gaps in EoE research.

This review examines promising research directions, providing strategic guidance for researchers, clinicians, and policymakers to prioritize future investigations. By systematically pursuing these opportunities, the field is well-positioned to transform disease management, enhance therapeutic outcomes, and develop innovative prevention and treatment strategies for patients with EoE.

2. Pathophysiology

Despite substantial advances describing type 2 helper T cell-mediated inflammation, epithelial barrier dysfunction, and tissue remodeling [31], EoE pathogenesis remains incompletely understood across genetic susceptibility, environmental causation, and disease progression mechanisms [32]. Genome-wide association studies have identified reproducible variants, including those located at 5q22 (TSLP), 2p23 (CAPN14), 11q13 (LRRC32/EMSY), and 16p13 (CLEC16A/DEX1) [33–37], with recent meta-analyses expanding to include 11 additional loci including 15q23 (SMAD3) [38]. However, functional roles of CLEC16A and DEX1 in esophageal epithelial cells remain uncharacterized. Candidate gene studies have implicated variants affecting epithelial barrier function (CCL26, filaggrin, desmoplakin, desmoglein 1, SPINK5), type 2 immune responses (STAT3), and fibrosis (TGFβ1/SMAD) [39–44], yet gene-environment interactions account for only one-fifth of phenotypic variation [45] with the 2.4 % concordance rate among non-twin siblings suggests substantial environmental rather than genetic causation [46].

While epidemiological studies identify early-life risk factors including premature birth, neonatal intensive care exposure, acid suppression, antibiotic use, cesarean delivery, and maternal smoking [47–51], mechanistic pathways linking these exposures to disease development remain unclear. Recent experimental evidence demonstrating sodium dodecyl sulfate exposure in mice increases IL-33 expression, basal zone hyperplasia, and esophageal eosinophilia illustrates potential for household product ingredients to trigger disease pathways, although comprehensive human exposure studies are lacking [52]. The microbiome has been hypothesized as a potential modulator of esophageal inflammation and therefore potential marker of disease, but definitive data is lackig [53–55]. Additionally, hypothesized factors encompass farming practices, genetic food modification, packaging materials, and pollutants, as well as ultra-processed foods, yet these remain systematically understudied [56–59].

The temporal sequence of epithelial barrier dysfunction requires clarification regarding whether barrier compromise represents primary pathogenic events or secondary inflammatory consequences [60,61]. Complementing barrier dysfunction studies, ad-

Table 1
Summary of the research agenda for eosinophilic esophagitis.

Research Domain	Priority Research Need	Clinical Rationale
FUNDAMENTAL DISEASE SCIENCE		
Pathophysiology	Define proximate causes and temporal sequence of EoE initiation	Gene-environment interactions account for only ~20 % of phenotypic variability; understanding causative mechanisms could enable primary prevention
Multi-omics integration	Develop systems biology models integrating genomics, transcriptomics, proteomics, and metabolomics	Current omics studies conducted in isolation limit comprehensive disease understanding and therapeutic target identification
Microbiome research	Elucidate causal relationships between dysbiosis and pathogenesis	Recent multi-omics analyses identified microbial signatures, but causality and therapeutic targetability remain unclear
PRECISION MEDICINE & CLASSIFICATION		
Molecular endotypes	Validate and implement endotype-based treatment algorithms	Machine learning identified 3 distinct molecular endotypes with unique clinical features, but clinical utility unproven
EoE variants characterization	Define natural history and optimal management of EoE-like variants	62.2 % of EoE-like esophagitis progresses to classical EoE, but management approaches undefined
DIAGNOSTIC INNOVATION		
Non-invasive biomarkers	Develop and validate serum, salivary, and string test biomarkers	Current gold standard requires invasive endoscopy creating diagnostic barriers and delays averaging 4–10 years
AI-enhanced diagnosis	Implement artificial intelligence for histologic and endoscopic assessment	Automated eosinophil counting could address inter-observer variability; endoscopic AI could standardize EREFS scoring
Minimally invasive monitoring	Expand validation of Cytosponge and esophageal string test	Cytosponge shows 75 % sensitivity and 86 % specificity; string test demonstrates 0.83 AUC for disease activity
THERAPEUTIC OPTIMIZATION		
First-line treatment hierarchy	Establish evidence-based therapeutic algorithms through head-to-head trials	Absence of comparative effectiveness trials limits optimal treatment selection, necessitating preference-sensitive care paradigms
Combination therapy	Evaluate synergistic effects of multi-modal approaches	Limited studies suggest significant positive role for combination therapy in refractory disease
Treatment response predictors	Develop genomic, proteomic, and microbiome predictors of therapeutic response	Current predictive models show limited clinical utility; personalized therapy selection needed
Anti-fibrotic therapies	Develop targeted approaches for fibrostenotic disease	Evidence suggests fibrosis partially reversible, but dense established fibrosis remains largely untreatable
PATIENT-CENTERED OUTCOMES		
Quality of life assessment	Develop EoE-specific psychosocial intervention strategies	93.9 % of pediatric patients develop eating-related anxiety; EoE patients have lowest QoL among chronic pediatric diseases
Symptom-histology disconnect	Identify confounding factors affecting clinical-pathological correlations	Modest correlation between symptoms and histology ($\beta 1 = 0.64$) limits clinical assessment reliability
DISEASE TRAJECTORY & PREVENTION		
Natural history studies	Compare long-term outcomes in treated vs untreated patients with >10-year follow-up	Understanding disease modification potential and optimal intervention timing critical for preventing irreversible changes
Progression prediction	Identify molecular signatures predicting fibrostenotic progression	Need to determine whether early aggressive intervention can alter disease trajectory from inflammatory to fibrotic phenotypes
Primary prevention strategies	Define environmental determinants and early intervention approaches	Rising incidence suggests environmental factors play important roles, but prevention strategies remain undefined
MONITORING & SURVEILLANCE		
Optimal follow-up intervals	Determine evidence-based surveillance strategies for responsive patients	Current monitoring varies widely; gaps in care >2 years associated with increased fibrostenosis risk
Deep remission utility	Assess whether achieving comprehensive remission (symptom + endoscopic + histologic) improves long-term outcomes	Only 9.4 % achieve deep remission, but impact on preventing complications unclear
EMERGING TECHNOLOGIES		
Functional assessment standardization	Establish EndoFLIP protocols and normative values across age groups	Current distensibility thresholds require validation; age-adjusted pediatric values lacking
Digital health integration	Develop validated digital biomarkers and mobile health applications	Mobile applications could improve patient engagement and provide real-world data, but validation lacking
IMPLEMENTATION		
Healthcare delivery optimization	Define quality indicators and cost-effective care models	Healthcare systems face mounting pressure to provide coordinated care for this complex condition
Health disparities research	Address access barriers and outcome variations across populations	Limited diversity in research populations; need to understand care access and outcome disparities

Abbreviations: AI, artificial intelligence; EoE, eosinophilic esophagitis; EREFS, Endoscopic Reference Score; FLIP, functional luminal imaging probe; QoL, quality of life.

vances in understanding EoE-associated pain mechanisms reveal complex mast cell-TRPV1 nociceptor interactions that may contribute to symptom development independent of barrier compromise [54]. Perhaps most critically, the molecular basis of tissue remodeling remains poorly understood, particularly regarding the triggers that drive fibrostenotic transformation [62].

Multi-omics integration represents a critical frontier limited by analytical constraints. EoE pathogenesis complexity demands coordinated analysis combining genomic, transcriptomic, proteomic, and metabolomic data, yet current omics studies have been conducted in isolation [63].

3. Disease classification and precision medicine: beyond the eosinophil paradigm

3.1. Molecular endotypes

Disease heterogeneity and precision diagnostic approaches are still in the initial stages in EoE, particularly regarding molecular endotypes, their clinical utility, and biomarker validation. Machine learning applications to the 95-gene EoE Diagnostic Panel revealed three molecularly distinct endotypes [24,64]. The first endotype demonstrated normal esophageal morphology with pre-

served steroid sensitivity, the second manifested pronounced inflammatory alterations alongside steroid resistance, and the third exhibited fibrostenotic patterns with diminished epithelial differentiation gene expression. However, it is still unclear if such classification represent fixed disease entities or a dynamic continuum [25,65], with different therapeutic implications [66]. Long-term prospective studies examining endotype stability over time and across diverse patient populations would help clarify this step. The newly developed Index of Severity in EoE (I-SEE) scoring system represents a progress toward standardized severity assessment beyond eosinophil enumeration [17,67], but comprehensive validation across diverse populations and treatment contexts is lacking. In addition, the I-SEE does not include adaptive behaviors, which have been shown to represent a clinically meaningful disease domain [16]. Notably, patients receiving biologic therapy are automatically classified as severe under this system.

3.2. Minimally invasive diagnostic approaches and biomarkers

The diagnostic paradigm requiring endoscopic biopsy confirmation of 15 or more eosinophils per high-power field (HPF) creates substantial barriers to care access and disease monitoring [68]. This invasive requirement contributes to diagnostic delays often exceeding a decade [69], highlighting the urgent need for non-invasive alternatives, particularly given that each untreated year increases stricture risk [19,70–73].

Several minimally invasive approaches show promise for addressing these diagnostic and monitoring limitations [30]. Unsedated transnasal endoscopy has emerged as a valuable option, particularly in pediatric populations, by reducing anesthesia exposure and costs while still providing endoscopic and histologic measures for response assessment [74–78]. The Cytosponge technique, a spherical cytology brush contained in a capsule attached to a string that needs to be swallowed, allowed to expand over 5–10 min and then pulled out, demonstrates 75 % sensitivity and 86 % specificity compared to conventional biopsy and has been successfully implemented for food reintroduction protocols [79–81]. The Esophageal String Test, which uses a weighted capsule that absorbs inflammatory factors during a 1-hour esophageal residence, achieves area under the curve values of 0.83 for distinguishing active from inactive disease when measuring eotaxin-3 and major basic protein [82,83]. However, standardization of these methodologies, establishment of reference ranges, and determination of optimal implementation strategies remain incomplete for broader clinical adoption.

Despite extensive investigation of eosinophil-derived proteins including eosinophil cationic protein, eosinophil-derived neurotoxin, eosinophil peroxidase, and major basic protein, no serum biomarker has achieved clinical validation [30]. Candidate biomarkers including eosinophil cationic protein and periostin show promise but require validation in larger cohorts before clinical implementation [84–86]. The potential utility of fecal eosinophil-derived proteins as non-invasive disease activity markers represents another largely uninvestigated avenue. The overlap with other atopic conditions such as asthma further complicates biomarker interpretation [87,88]. The exploration of non-eosinophilic-derived biomarkers such as eotaxin-3, periostin, and immunoglobulin G4 remains insufficient, particularly regarding their integration into multi-marker diagnostic panels.

Interestingly, Katzka et al. demonstrated significantly elevated small intestinal permeability in active disease compared to healthy controls (lactulose:mannitol ratio 0.045 versus 0.033, $p < 0.001$), with normalization during remission [89]. This finding suggests systemic barrier dysfunction extending beyond esophageal inflammation, yet the implications for monitoring and treatment remain unexplored.

4. Diagnosis and assessment

4.1. Diagnosis

EoE diagnosis relies on a combination of clinical symptoms and histological confirmation of esophageal eosinophilia, typically requiring exclusion of secondary causes. These diagnostic requirements create research gaps by excluding patients with symptoms but subthreshold eosinophilia and those with eosinophilia but no symptoms, limiting understanding of the disease spectrum. The established diagnostic criterion of ≥15 eos/HPF, determined by 2007 expert consensus rather than evidence-based validation [90], and the expanding recognition of EoE variants presents perhaps the most complex diagnostic research frontier. EoE-like esophagitis demonstrates remarkable heterogeneity in progression patterns, with 62.2 % progressing to classical EoE over six years [63,91–94]. Furthermore, the mandatory requirement for symptoms in current diagnostic criteria presents an unresolved research question regarding whether asymptomatic patients with significant esophageal eosinophilia represent early-stage disease, subclinical EoE, or a distinct entity requiring different management approaches and the natural history, progression risk, and optimal management of these individuals remain completely undefined.

Moreover, while proton pump inhibitors (PPI) therapy can induce histological remission in significant patient subsets, potentially masking EoE diagnosis [95], optimal withdrawal timing remains empirically determined and limited evidence suggests 3–4 weeks of PPI cessation enables accurate diagnosis [96]. Biopsy sampling protocols demonstrate significant optimization potential despite current recommendations for six-biopsy approaches [97–99]. Current protocols typically follow either a comprehensive three-segment approach or a simplified two-segment approach. However, emerging evidence suggests that systematic inclusion of mid-esophageal sampling enhances diagnostic sensitivity in 17.7 % of cases compared to protocols that omit the middle esophagus [100,101], indicating that comprehensive three-segment biopsy protocols may improve diagnostic accuracy over simplified approaches.

Artificial intelligence applications show promise for standardizing EoE diagnosis, with algorithms achieving >90 % diagnostic accuracy [102] and superior eosinophil counting performance compared to manual methods [103]. Comprehensive AI systems incorporating EoE Histologic Scoring System (EoE-HSS) features demonstrate excellent performance (AUC >0.95), yet validation across diverse populations, staining protocols, and clinical settings remains incomplete [104–108],

Emerging endoscopic technologies including confocal laser endomicroscopy, narrow-band imaging, and molecular endoscopy present potential opportunities for real-time disease assessment, yet their clinical utility in EoE management lacks substantive evidence. The development of standardized implementation protocols for these advanced technologies and their integration into existing diagnostic algorithms represents another significant research priority requiring systematic evaluation and validation.

4.2. Functional assessment

The assessment of esophageal mechanical properties in EoE represents an emerging field of investigation with significant potential to enhance clinical management.

The relationship between eosinophilic esophagitis and achalasia-like motility disorders represents a critical area requiring further investigation, as this association challenges traditional

understanding of achalasia pathogenesis and may represent a distinct, potentially reversible phenotype. While systematic reviews have demonstrated that esophageal motor abnormalities occur in 25–83 % of EoE patients, with achalasia and obstructive motor disorders present in approximately 15 % of cases, fundamental questions remain unanswered regarding the mechanistic basis, optimal diagnostic approaches, and therapeutic implications of this association [109,110]. Epidemiological studies have revealed striking associations, with EoE demonstrating a 33–70 fold increased prevalence in achalasia patients compared to controls, yet the exact prevalence of muscle-predominant EoE as a cause of achalasia remains poorly defined [111]. Current limitations include the absence of standardized protocols for esophageal biopsy evaluation in achalasia patients, incomplete understanding of whether EoE-associated achalasia represents a distinct manometric or clinical phenotype, and insufficient data on long-term outcomes following different therapeutic approaches. Particularly concerning is the scarcity of prospective studies examining the reversibility of achalasia-like patterns following anti-inflammatory therapy, despite compelling case reports demonstrating complete manometric normalization after steroid treatment [112]. The pathophysiological mechanisms underlying this association require further elucidation, particularly regarding the relative contributions of eosinophil-derived neurotoxins, mast cell degranulation in esophageal muscle layers, and tissue remodeling to motility dysfunction [113,114]. Additionally, critical uncertainties exist in determining optimal treatment sequencing for patients with concurrent EoE and achalasia, establishing criteria for identifying candidates for medical versus invasive therapy, and developing biomarkers to predict treatment responsiveness.

Impedance planimetry utilizing the EndoFLIP system offers enhanced precision in measuring luminal diameter and quantifying distension pressures compared to conventional endoscopic evaluation [115]. This technology demonstrates superior sensitivity for detecting fibrostenotic alterations through direct measurement of esophageal wall compliance, identifying regions of diminished flexibility that may not be apparent during standard endoscopic examination. Comparative studies involving 33 EoE patients with endoscopically visible rings and furrows revealed equivalent distensibility measurements regardless of stricture presence, suggesting either methodological discordance or enhanced diagnostic sensitivity of functional impedance planimetry for detecting subclinical stenosis [116]. Subsequent investigations have substantiated correlations between distensibility parameters and endoscopic ring severity using the EoE Endoscopic Reference Score (EREFS) scoring [117], while pediatric cohorts demonstrate associations between distensibility indices and grade 2 endoscopic rings [118].

Recent advances in physiomechanical classification have established seven distinct EoE categories based on distensibility metrics and esophageal motility patterns, ranging from preserved function to severe fibrostenosis with absent muscular reactivity [119]. Analysis of 215 patients revealed strong correlations between these classifications and disease severity indicators including symptom duration, endoscopic manifestations, and inflammatory scores. Treatment response prediction demonstrated significant variability, with normal esophageal distensibility associated with 57–88 % PPI response rates, contrasting markedly with 11–20 % response rates in severe fibrostenotic disease. Complementing this classification approach, the development of composite scoring systems such as the C2D2 score has introduced continuous quantification of physiomechanical dysfunction through integration of four key FLIP parameters: esophageal body compliance, contractile response patterns, distensibility plateau measurements, and maximum esophagogastric junction diameter [120].

The first longitudinal prospective study examining the relationship between histologic response and esophageal distensibility in pediatric patients demonstrated that histologic remission is associated with improved esophageal distensibility over time, with participants showing histologic response exhibiting the most significant improvement in distensibility [121]. This landmark study of 112 pediatric EoE patients followed over a median of 11 months provides crucial evidence that histologic disease control during childhood can positively impact esophageal mechanical function. Additionally, the ongoing REMODEL study (NCT06101095) is investigating dupilumab's ability to prevent fibrosis as assessed by EndoFLIP, representing a pivotal Phase 4 randomized controlled trial evaluating esophageal function and remodeling over 128 weeks in adult EoE patients.

Despite these promising developments, EndoFLIP has not yet been incorporated in routine clinical practice. Future research will need to focus on establishing standardized protocols and validating clinical implementation across diverse healthcare settings [122,123]. The current diagnostic threshold of distensibility index less than 4.5 mm^2/mmHg for fibrostenotic severity requires comprehensive validation across different age demographics and clinical environments, particularly in the pediatric setting where the relationships between EndoFLIP measurements and feeding difficulties, treatment response prediction capabilities, and long-term prognostic value necessitate prospective validation through well-designed longitudinal studies [118,124,125]. The phenomenon of persistent esophageal distensibility reduction despite achieving histological remission represents a significant knowledge gap requiring mechanistic elucidation [126,127].

5. Treatment

5.1. Treatment efficacy

Eosinophilic esophagitis is treated through several therapeutic approaches including PPIs, swallowed topical corticosteroids (STCs), elimination diets, and newer biologic therapies, though the optimal first-line treatment selection remains challenging since mostly indirect evidence on treatment comparisons is available to inform hierarchies [128]. PPI evaluation remains limited to two small randomized controlled trials (RCTs) comparing PPI therapy to STCs, with no placebo-controlled PPI studies available. These trials showed mixed results: one demonstrated comparable eosinophil reduction between treatments [129], while the other showed symptomatic benefits without significant histologic improvement [130].

STCs research is limited to one comparative study of oral viscous budesonide versus fluticasone inhaler, conducted before current esophageal-specific formulations were available. This RCT ($n = 111$) showed comparable histologic response rates (71 % versus 64 % achieving <15 eos/hpf) and similar dysphagia and endoscopic outcomes [131]. However, these results cannot be extrapolated to currently approved budesonide formulations (budesonide orodispersible tablets or budesonide oral suspension) since these were unavailable during trial conduct. The ongoing DeTECTS trial (NCT06705387) represents the first head-to-head comparison of dupilumab versus topical fluticasone in patients with stenotic EoE, designed to evaluate both esophageal distensibility and histologic response as co-primary endpoints over 16 weeks in 72 patients aged 12–25 years.

Elimination diet research reveals limited comparative evidence with only two trials examining different restrictive approaches. This first RCT in adults with EoE demonstrated that one-food elimination diet (1FED) achieved similar histologic remission rates (34 % vs 40 %, $p = 0.58$) and comparable improvements in endoscopic and symptom measures as the more restrictive six-food elimination (6FED) diet, suggesting milk elimination alone is an acceptable initial dietary therapy [132]. Pediatric investigation comparing

1FED versus 4FED in patients under 18 years showed comparable histologic response rates (44 % vs 41 %; $P = 1.0$), with 4FED demonstrating superior symptom reduction [133].

Currently, there are no head-to-head trials comparing different biologic therapies in EoE, limiting evidence-based selection between dupilumab, cendakimab, and other emerging biological agents. A recent systematic review and meta-analysis of maintenance therapies demonstrated that corticosteroids achieved 86 % histologic success rates (<15 eos/hpf) in randomized controlled trials, with biologics showing 79 % success rates [134]. Notably, biologics demonstrated higher rates of deeper histologic remission (<6 eos/hpf) at 70 % compared to corticosteroids at 59 %

Esophageal dilation research demonstrates substantial evidence limitations despite widespread clinical utilization. While systematic reviews and meta-analyses document 95 % clinical improvement rates with minimal complications (<1 % post-procedural hospitalization, <0.5 % perforation risk) [135,136], only one RCT has evaluated dilation versus no dilation in 31 adults with EoE and stricture [137]. This unblinded, single-center investigation suffered from imprecision, indirectness, and bias limitations, with all other dilation studies in fibrostenotic EoE being uncontrolled observational designs including cohort, case-control, and case series [138]. The evidence quality necessitates conditional rather than strong recommendations despite documented safety improvements over time.

5.2. Combination therapy

Current therapeutic paradigms predominantly rely on single-agent interventions. Limited available evidence suggests promising outcomes for dual-therapy approaches in refractory EoE. However, substantial evidence gaps exist regarding combined therapeutic strategies for both treatment-resistant cases and initial management protocols. Sequential therapeutic approaches, analogous to inflammatory bowel disease management paradigms utilizing rapid-acting agents for induction together with slower-onset biologics that are subsequently used as stand-alone therapy for maintenance, remain unexplored in EoE despite potential advantages for optimizing both efficacy and safety profiles. Evidence of reduced elimination diet responsiveness during pollen seasons among sensitized patients [139] suggests that treatment cycling may be particularly beneficial for patients on empiric elimination diets, allowing for temporary intensification of therapy during high-allergen periods [140].

Retrospective analyses have documented both symptomatic and histological improvements using combination regimens in patients unresponsive to monotherapy across pediatric and adult populations [141,142]. A retrospective study of 12 patients demonstrated that combination PPI and food elimination diet therapy achieved histologic remission (median eosinophil count 4 vs 45–47.5 eos/hpf) and symptom resolution in 92 % of patients with EoE who had failed both treatments as monotherapy [142]. Additional retrospective data from 23 adults with EoE demonstrated that combination therapy with STCs and food elimination diet achieved symptomatic improvement in 88 % of patients at 4 months, with significant endoscopic improvements, particularly in a treatment-experienced cohort where 90 % had failed prior monotherapy [141].

Pediatric randomized controlled evidence has emerged supporting initial combination approaches, with a study of 63 children showing superior histological remission rates using 4FED plus PPI compared to PPI monotherapy, achieving partial remission rates of 88 % versus 45 % ($p = 0.002$) in per-protocol analysis [143]. Conversely, supplementing elemental formula to 4FED demonstrated quality of life improvements without enhanced histological responses compared to elimination diet alone [144]. Notably absent from current literature are investigations examining concurrent STCs and PPI combinations, despite some STCs studies including patients maintaining PPI therapy [145]. Additionally, real-world evidence supports the potential benefit of combination approaches, as demonstrated in a prospective multicenter study where 30 % of patients receiving budesonide orodispersible tablets were maintained on concurrent PPI therapy, with most being clinical non-responders (76 %) or histological non-responders to PPI monotherapy [146]. This finding suggests that while topical corticosteroids demonstrate superiority over PPIs as monotherapy, the addition of PPIs may enhance effectiveness in a subset of patients, though this requires further investigation through controlled trials.

Dupilumab's FDA approval in 2022 for patients aged 12 years and above weighing at least 40 kg was based on a phase 3 trial demonstrating 60 % histologic remission rates compared to 5 % with placebo [147,148]. Notably, patients in dupilumab trials could continue concurrent PPIs and stable food elimination diets and data analysis showed that response rates were similar regardless of ongoing PPI use [149,150]. The development of cendakimab, targeting soluble IL-13, highlights additional positioning challenges as new therapeutics emerge. Patients in cendakimab Phase 3 RCT were permitted to continue stable doses of PPIs and existing food elimination diets throughout the study, while STCs and systemic corticosteroids were prohibited within 4–8 weeks before enrolment (NCT04753697). Detailed subgroup analyses comparing efficacy outcomes across patients with ongoing PPI therapy and elimination diets have not yet been reported in the available trial results.

Regarding mechanical dilation, dilation monotherapy has been reported for stricturing disease refractory to all other interventions [151], but optimal practice involves combining mechanical intervention with anti-inflammatory treatment, supported by evidence demonstrating reduced dilation requirements following histological response achievement [91,152,153].

5.3. Positioning

The establishment of an evidence-based therapeutic hierarchy in EoE remains a fundamental unmet need, as current evidence is insufficient to determine optimal first-line treatment selection [128]. This knowledge gap significantly impacts clinical decision-making, where the choice between PPIs, STCs, dietary elimination, and biologics often relies on physician preference and patient factors rather than comparative effectiveness data. The versatility of PPIs, which demonstrate efficacy regardless of prior STCs response or elimination diet success [154,155], exemplifies the complex interplay between treatments. Studies reporting partial PPI responses or sequential use following STCs therapy further underscore the need for systematic comparative research to guide treatment sequencing [151,156,].

Despite over 13 double-blind, placebo-controlled RCTs of STCs in both pediatric and adult populations [157–162], with meta-analyses indicating 60–70 % response rates for both budesonide and fluticasone, direct head-to-head comparisons as first line modalities remain limited. This evidence gap extends to dietary interventions, where salvage strategies such as transitioning from 1FED to 6FED yield 43 % response rates, yet optimal sequencing algorithms remain undefined [132].

Notably, patients in dupilumab trials showed that response rates were similar regardless of previous STCs response [149,150]. However, the trial specifically excluded patients with severe stricturing and those requiring esophageal dilation during screening, creating uncertainty about biologic positioning in the broader EoE population. Real-world studies, including a cohort of 46 severely affected patients who would have been excluded from pivotal trials, reported similar 60 % response rates [163], suggesting potential for expanded positioning. The ongoing DeTECTS trial

(NCT06705387) represents an important step in addressing positioning questions by directly comparing dupilumab to topical fluticasone in treatment-experienced patients with stenotic EoE. Nevertheless, critical gaps persist regarding biologic use in treatment-naïve patients, optimal timing within the treatment algorithm, and comparative effectiveness against established therapies.

Regarding cendakimab, phase 2 data demonstrated significant improvements in eosinophil counts and endoscopic severity, with notable symptom improvements in steroid-refractory populations [164]. The Phase 3 trial (NCT04753697) has reported results including prespecified subgroup analyses based on steroid responder status [165]. The trial was stratified by baseline steroid inadequate responders/intolerant status (approximately 70% of the trial population) versus steroid responders/naive (approximately 30%). Results showed that reductions in dysphagia days and histologic response at week 24 were similarly improved for the subgroup of patients with prior inadequate response or intolerance to glucocorticoids, with meaningful differences in this subgroup largely consistent with the overall trial population. Benefits with cendakimab were similarly observed in this historically difficult-to-treat population of steroid inadequate responders/intolerant patients.

5.4. Predictors of response

Therapeutic response prediction, food trigger identification, and long-term treatment optimization lack reliable predictors and systematic approaches.

Personalization of PPI therapy remains hampered by the absence of reliable response predictors. While meta-analytical data suggested potential associations between abnormal gastric acid exposure and enhanced PPI efficacy [166], subsequent investigations demonstrated minimal predictive utility of pH monitoring for therapeutic response [167]. Recent mechanistic insights indicate that elevated impedance gradients between mid-esophageal and distal regions, coupled with enhanced chemical clearance through improved esophago-salivary reflex function, may correlate with favorable PPI outcomes [168,169]. Additional factors potentially diminishing PPI effectiveness include allergic rhinitis presence, accelerated CYP2C19 metabolism (though dose escalation may circumvent this limitation), and specific STAT6 genetic variants [170–173]. A predictive algorithm incorporating younger patient age, reduced body mass index, and elevated peripheral eosinophil levels identified additional non-response risk factors [174]. Notably, C2D2 endoscopic scores $\leq$3 demonstrated superior predictive performance for PPI response compared to conventional endoscopic assessment or baseline eosinophil quantification, conferring a 14.5-fold increased likelihood of therapeutic success [120]. Additionally, recent data showed that patients exhibiting positive food allergy testing (82.5 % versus 42.9 %) and heightened environmental allergen burdens showed significantly reduced therapeutic response rates [175].

Steroid response prediction is also challenging. Structural esophageal abnormalities, particularly the history of esophageal dilation or having an extremely narrow esophageal caliber associate with therapeutic failure [176], although subset populations may ultimately achieve therapeutic success [177,178]. Molecular investigations have identified single nucleotide polymorphisms within the TGF-β gene correlating with non-response [179–181]. Epigenetic approaches utilizing differentially methylated gene sets have shown promise in predicting non-response, with independent validation studies confirming these findings, though clinical implementation remains unavailable [182,183].

Food trigger identification represents perhaps the most significant diagnostic gap in EoE management. Although multiple investigations have examined allergy testing to guide individualized elimination diets, meta-analytical evidence demonstrates that sensitization-guided dietary interventions achieve inferior histological remission rates compared to empiric elimination approaches [184]. Methodological heterogeneity across included studies, which employed diverse trigger food investigation techniques including skin prick testing, atopy patch testing, and serum-specific IgE measurement, confounds interpretation of these findings. Consequently, additional prospective investigations are essential to enhance evidence quality [185]. The discovery of markedly elevated esophageal tissue IgG4 levels in EoE patients compared to controls prompted investigations into its predictive utility for treatment response and food trigger identification [186,187]. Supporting evidence emerged from the 1FED versus 6FED comparative trial, demonstrating milk-specific IgG4 associations with milk elimination response [132]. Pediatric studies have validated correlations between milk-specific IgG4 levels, T-cell stimulation responses to milk proteins, and clinical milk triggers [188]. Expanded food panels encompassing five common triggers (milk, wheat, egg, soy, peanut) assessed through food-specific IgG4 measurement in esophageal biopsies combined with peripheral blood T-cell stimulation testing achieved 53 %–75 % accuracy rates [189]. Preliminary data from a prospective study of 22 EoE patients found that serum food-specific IgG4-guided elimination diets achieved 45 % histologic remission rates [190]. The ongoing iDIET study (NCT05543512), using T-cell and IgG4 immune signatures against 18 foods to guide individualized dietary restrictions in a randomized, double-blind, sham-controlled trial of 100 patients, will shed a light on this matter.

Beyond initial treatment response prediction, these challenges extend to long-term therapeutic management, as a substantial proportion of patients across all treatment modalities experience loss of therapeutic response during maintenance therapy [173,191–194]. Biomarker development for emerging targeted therapies, including dupilumab response prediction, constitutes an essential research priority for optimizing patient selection and preventing treatment failures.

5.5. Treatment targets

The fundamental challenge in defining the optimal therapeutic target in EoE lies in understanding confounding variables that compromise correlation between clinical symptom perception and objective histological disease activity measurements. The current FDA regulatory framework requiring coprimary endpoints of histologic response ($\leq$6 eos/hpf) and validated patient-reported outcomes reveals fundamental limitations exposed by recent therapeutic developments [195]. Recent eosinophil-targeting biologics including benralizumab, lirentelimab, mepolizumab, and reslizumab have yielded paradoxical results, achieving prominent histologic responses while failing to demonstrate significant symptomatic improvement compared to placebo [196–201], findings corroborated by animal model investigations suggesting eosinophil-independent disease manifestations [202,203]. Meta-analytic evidence from 23 studies encompassing 1202 patients reveals only modest correlation ($\beta 1 = 0.64$) between symptomatic and histologic therapeutic responses, with substantial heterogeneity across investigations [204]. This diagnostic discordance becomes particularly pronounced following esophageal dilation procedures [205,206]. Confounding factors including undetected strictures, superimposed infections, esophageal hypervigilance, visceral hypersensitivity, behavioral adaptations, dietary modifications, prior interventions and feeding dysfunction require systematic characterization to optimize monitoring approaches [207]. Moreover, the variable symptomatic improvement rates demonstrated by STCs investigations are attributed partly to utilization of non-validated patient-reported outcome instruments, heterogeneous outcome measurement approaches and inadequate statistical power due to substantial

placebo response phenomena in early investigations [208,209]. This scenario is complicated by the pathophysiologic complexity extending beyond conventional eosinophil-centric disease models. Contemporary investigations document extensive multi-cellular infiltration patterns involving mast cells, various T-cell subsets, basophils, natural killer cells, and fibroblasts, yet their individual contributions to disease activity and symptoms remain not completely characterized [210–223]. Advanced single-cell RNA sequencing studies in EoE patients have uncovered distinct heterogeneity within mast cell populations, revealing pro-inflammatory mast cell subsets that persist in an activated state during clinical remission and may underlie mechanisms of disease relapse [224]. These observations reveal fundamental research deficiencies in understanding non-eosinophilic inflammatory networks and their therapeutic targeting implications.

The Assessment of Clinical endpoints in EoE for Novel Therapeutics (ASCENT) initiative has proposed incorporating comprehensive disease activity measures that capture global pathophysiologic processes rather than relying solely on eosinophil quantification [225], including the EREFS and the EoE-HSS. The EREFS was developed in 2012 to standardize endoscopic assessment, evaluates five major findings: Edema, Rings, Exudates, Furrows, and Strictures, with crêpe-paper mucosa as an adjunctive feature [14]. Endoscopic response thresholds require further validation and standardization. Cotton et al. established EREFS $\leq$2 as optimal for treatment response with 80 % sensitivity and 83 % specificity for histologic response [226,227], while post hoc analysis from budesonide trials identified EREFS $\leq$4 as moderately accurate for predicting histologic outcomes [228,229]. These discrepant thresholds highlight the need for comprehensive validation studies across diverse patient populations and treatment modalities to establish universally applicable criteria. Histologic response targets demonstrate similar complexity requiring research clarification. Multiple studies support $<$15 eos/hpf as optimal for predicting clinical improvement, achieving 90 % endoscopic improvement and 88 % symptomatic relief [230,231]. More stringent targets like complete eosinophil elimination provide minimal additional clinical benefit while significantly reducing predictive accuracy. However, investigation of $<$5 eos/hpf thresholds for clinical trial endpoints requires further validation to balance scientific rigor with clinical achievability.

The documented disconnect between eosinophil depletion and clinical improvement fundamentally challenges peak eosinophil count primacy as a regulatory benchmark. In this scenario, the EoEHSS represents potential advancement in treatment target diversification through comprehensive assessment of eight histologic features extending beyond simple eosinophil enumeration as therapeutic goals [15]. While this system demonstrates superior patient discrimination compared to peak eosinophil quantification and correlates with symptom severity scores [232], we still lack clinical guidance on how to target the non-eosinophil features, such as basal zone hyperplasia and lamina propria fibrosis which may continue causing symptoms even after eosinophils are reduced [215,233–236].

The long-term clinical significance of histologic remission in patients in maintenance therapy represents a critical research gap. Retrospective data demonstrate 65 % fewer subsequent dilations in patients achieving $<$15 eos/hpf compared to non-responders, with maintenance therapy providing 88 % risk reduction for repeat procedures [152,153]. Paradoxically, initial histologic remission alone showed no protective effect, emphasizing the importance of sustained therapeutic intervention regardless of mechanism. These findings necessitate prospective studies defining optimal maintenance strategies and their impact on long-term outcomes.

Deep remission, defined as simultaneous symptomatic, endoscopic, and histologic response, represents an idealized endpoint achieved in only 9.4 % of patients in the Swiss EoE Cohort, with median relapse occurring at 22 weeks after treatment cessation [237]. However, it's significance and feasibility are to be explored.

A fundamental challenge in EoE management is distinguishing treatment-responsive inflammation from established fibrosis. While endoscopic ultrasonography reveals esophageal wall thickening across all layers, current imaging cannot reliably differentiate inflammatory from fibrotic components [238–240], limiting optimal treatment target selection. Recent evidence challenges the traditional view of irreversible "fibrotic" features. Despite achieving good interobserver agreement among gastroenterologists, the EREFS classification of endoscopic features as "inflammatory" (edema, exudates, furrows) versus "fibrotic" (rings, strictures, crêpe-paper esophagus) lacks robust scientific evidence and appears based primarily on clinical intuition rather than empirical data. The 2022 validation study offers the most compelling evidence to date, demonstrating that inflammatory features (edema, exudates, furrows) are more responsive to treatment than fibrostenotic features (rings, strictures), with effect sizes of 1.217 versus 0.558 respectively [232]. However, a comprehensive 2025 systematic review analyzing 230 studies defining fibrostenotic disease exposed a variability in definitions, with four different categorical approaches used across studies: structural findings (88.7 %), histology (37 %), functional parameters (6.5 %), and biomarkers (3 %) [241], indicating fundamental researcher disagreement regarding fibrostenosis definition. Interobserver agreement for supposedly fibrotic features remained poor, with kappa values of only 0.40 for rings and 0.52 for strictures. The EOS-1 trial demonstrated that 6 weeks of budesonide significantly improved supposedly fibrotic subscores, including fixed rings (0.8 to 0.5, $p = 0.0061$) and strictures (0.2 to 0.1, $p = 0.0313$) [160]. Similarly, the EoE CONNECT registry showed that PPI therapy achieved significant improvements in rings and strictures within 8–12 weeks [242]. The Singla longitudinal study further revealed that 25 % of patients experienced regression of fibrostenotic features while only 1 % progressed from inflammatory to fibrostenotic disease, contradicting inevitable progression models [241]. Interestingly, patients experiencing fibrostenosis regression demonstrated significantly decreased eosinophilia in both proximal and distal esophagus.

Future studies should focus on developing regulatory frameworks that incorporate comprehensive outcome measures, including time-to-event analyses and composite endpoints that capture clinically meaningful events such as stricture development, dilation requirements, food impaction episodes, and disease flares.

6. Disease trajectory and prevention

6.1. Monitoring

Understanding EoE disease trajectory and predicting long-term outcomes represent fundamental knowledge gaps in clinical management. Optimal surveillance strategies remain undefined, particularly regarding histological monitoring frequencies for treatment-responsive patients, and robust longitudinal data comparing treated versus untreated trajectories are lacking [19,21,243]. The development of progression prediction models incorporating clinical, molecular, and imaging biomarkers is essential for personalized risk stratification and monitoring approaches.

Natural history studies demonstrate concerning progression patterns in untreated populations: prolong untreated eosinophilic inflammation progresses to fibrosis with wall thickening, abnormal fragility, and stricture formation, ultimately causing structural and functional damage that predisposes to complications including food impaction, reflux disease, and retching-induced rupture [20,69,72,244]. Age and inflammation duration are established major risk factors for stricture formation, while fibrostenotic features and impaction occur less frequently in pediatric populations

[20,245]. Importantly, care gap studies reveal that 14 % of EoE patients with 2+ year gaps in medical care demonstrated significant disease progression, with 37 % probability of developing severe fibrotic features and each additional untreated year increasing stricture odds by 26 % [23]. However, maintaining treatment during care gaps proved beneficial, with patients continuing EoE therapy showing better endoscopic severity scores and less severe fibrosis compared to those discontinuing all treatment.

These findings are complicated by significant limitations in current monitoring approaches. A longitudinal study following 30 untreated adults for an average of 7.2 years found persistent dysphagia in nearly all patients, with subepithelial fibrosis present in 86 % of esophageal biopsies [246]. Since routine biopsies inadequately sample subepithelial tissue, endoscopy remains the primary method for detecting structural consequences of remodeling that are missed by standard histopathology. However, endoscopy demonstrates poor sensitivity for stricture detection, with only 14.7 % sensitivity for narrowed esophagus detection despite 79.2 % specificity [247]. Pediatric studies revealed that 55 % of strictures identified on barium esophagram were undetected endoscopically [248,249], though barium studies have limitations in controlling intraesophageal distension pressure.

The chronic inflammatory milieu and progressive tissue remodeling characteristic of EoE theoretically create conditions conducive to malignant transformation, yet current evidence presents conflicting perspectives on this relationship [250]. While esophageal eosinophilia demonstrates associations with Barrett's esophagus, a recognized precursor to esophageal adenocarcinoma, the relationship between EoE and Barrett's esophagus remains contradictory, with some investigations demonstrating inverse correlations while others document Barrett's development during EoE follow-up [251–253]. Notably, retrospective cohort studies spanning up to 13.6 years have failed to establish any association between EoE and subsequent malignancy, and comparative analyses over five-year periods indicate that EoE, unlike gastroesophageal reflux disease and Barrett's esophagus, lacks demonstrable cancer risk [254].

Long-term cancer risk quantification will occur through large-scale, population-based cohort studies with extended follow-up periods capable of detecting rare malignant events and eventually identifying high-risk patient subgroups.

6.2. Primary prevention and risk reduction

Despite the escalating global incidence of EoE, fundamental knowledge gaps persist regarding primary prevention strategies and environmental determinants of disease development.

The strong association between EoE and atopic conditions, with 60–80 % of patients presenting concurrent allergic diseases and increasing EoE likelihood correlating with multiple atopic comorbidities, highlights critical screening gaps [255–257]. Research demonstrates that over one-third of allergy clinic patients exhibit unrecognized dysphagia or typical EoE symptoms, yet evidence supporting systematic screening protocols in these populations remains absent [258]. Similarly, while family clustering of EoE with frequent unrecognized esophageal symptoms among relatives of affected individuals suggests genetic susceptibility, and various early-life and environmental risk factors have been established, no data support implementation of screening or prevention strategies in high-risk cohorts [47,51,259,260]. Although clinical prediction tools with high discriminatory capacity for EoE diagnosis have been developed, their integration into prevention-focused screening algorithms requires validation [108,261–265].

The establishment of cost-effective screening programs necessitates identification of reliable non-invasive biomarkers and generation of robust evidence demonstrating that early detection translates to improved long-term outcomes and prevention of irreversible fibrotic complications.

7. Conclusions

The identified research opportunities across precision medicine, non-invasive diagnostics, treatment optimization, and prevention strategies represent exciting possibilities for transforming EoE care from empirical management to personalized, evidence-based medicine. The convergence of molecular endotyping, advanced biomarker development, and emerging therapeutic options positions the field to make unprecedented advances in patient outcomes over the coming decade. By systematically pursuing these research priorities through coordinated multidisciplinary efforts, EoE has the potential to evolve from a chronic condition requiring lifelong management to a precisely characterized, effectively treated, and potentially preventable disease.

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Luisa Bertin, Andrea Pasta, Matteo Ghisa, Francesco Calabrese, Pierfrancesco Visaggi, Nicola de Bortoli, Vincenzo Savarino, Elisa Marabotto, and Edoardo Vincenzo Savarino contributed to the conception and design of the review. All authors participated in the literature search and review process. Luisa Bertin, Andrea Pasta, and Edoardo Vincenzo Savarino drafted the initial manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version for submission.

Declaration of competing interest

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