big data and cognitive computing

MDPI

Systematic Review

The State of the Art of Artificial Intelligence Applications in Eosinophilic Esophagitis: A Systematic Review

Martina Votto [1,2,*], Carlo Maria Rossi [3,4], Silvia Maria Elena Caimmi [2], Maria De Filippo [1,2], Antonio Di Sabatino [3,4], Marco Vincenzo Lenti [3,4], Alessandro Raffaele [5], Gian Luigi Marseglia [1,2] and Amelia Licari [1,2]

1 Pediatric Unit, Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Piazzale Golgi 19, 27100 Pavia, Italy
2 Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, 27100 Pavia, Italy
3 Department of Internal Medicine and Medical Therapeutics, University of Pavia, 27100 Pavia, Italy
4 First Department of Internal Medicine, Fondazione IRCCS San Matteo, 27100 Pavia, Italy
5 Pediatric Surgery Unit, Fondazione IRCCS Policlinico San Matteo, 27100 Pavia, Italy
* Correspondence: martina.votto@unipv.it

Abstract: Introduction: Artificial intelligence (AI) tools are increasingly being integrated into computer-aided diagnosis systems that can be applied to improve the recognition and clinical and molecular characterization of allergic diseases, including eosinophilic esophagitis (EoE). This review aims to systematically evaluate current applications of AI, machine learning (ML), and deep learning (DL) methods in EoE characterization and management. Methods: We conducted a systematic review using a registered protocol published in the International Prospective Register of Systematic Reviews (CRD42023451048). The risk of bias and applicability of eligible studies were assessed according to the prediction model study risk of bias assessment tool (PROBAST). We searched PubMed, Embase, and Web of Science to retrieve the articles. The literature review was performed in May 2023. We included original research articles (retrospective or prospective studies) published in English in peer-reviewed journals, studies whose participants were patients with EoE, and studies assessing the application of AI, ML, or DL models. Results: A total of 120 articles were found. After removing 68 duplicates, 52 articles were reviewed based on the title and abstract, and 34 were excluded. Eleven full texts were assessed for eligibility, met the inclusion criteria, and were analyzed for the systematic review. The AI models developed in three studies for identifying EoE based on endoscopic images showed high score performance with an accuracy that ranged from 0.92 to 0.97. Five studies developed AI models that histologically identified EoE with high accuracy (87% to 99%). We also found two studies where the AI model identified subgroups of patients according to their clinical and molecular features. Conclusions: AI technologies could promote more accurate evidence-based management of EoE by integrating the results of molecular signature, clinical, histology, and endoscopic features. However, the era of AI application in medicine is just beginning; therefore, further studies with model validation in the real-world environment are required.

Keywords: artificial intelligence; big data; deep learning; eosinophilic esophagitis; machine learning

Citation: Votto, M.; Rossi, C.M.; Caimmi, S.M.E.; De Filippo, M.; Di Sabatino, A.; Lenti, M.V.; Raffaele, A.; Marseglia, G.L.; Licari, A. The State of the Art of Artificial Intelligence Applications in Eosinophilic Esophagitis: A Systematic Review. *Big Data Cogn. Comput.* **2024**, *8*, 76. https://doi.org/10.3390/bdcc8070076

Academic Editors: Arunkumar Bagavathi, Tao Hu and Atriya Sen

Received: 20 May 2024
Revised: 9 June 2024
Accepted: 3 July 2024
Published: 9 July 2024

1. Introduction

Digital information has grown exponentially, generating vast masses of electronic data or big data (BD). BD refers to a large amount of electronic data that is too huge to be conventionally visualized and stored. BD has four features: (1) a considerable amount of information, (2) a rapid rate of data spread, (3) a wide range of data variety (texts, videos, audio, and images), and (4) truthfulness (data sources are not always reliable) [1]. Medicine is a primary field in which the use of BD is significantly increasing [2]. This phenomenon is primarily due to the outstanding development and modernization of radiology and the digital revolution that replaced analogic instruments and paper supports. Also, the recent

advancement of "omics" technologies has generated vast molecular data to characterize diseases and personalize therapies [3]. Finally, the use of intelligent technologies with sensors able to collect a large variety of clinical data, including electronic clinal records, and transmit them to the network has increased [3]. Modern statistics and predictive analytic software methods have been realized and introduced in medicine to analyze data, generate new medical knowledge, and predict the natural history of diseases. Artificial intelligence (AI) is the umbrella term that includes all computer systems performing tasks that usually require human intelligence [4]. Machine learning (ML) is a sub-discipline of AI based on mathematical algorithms that simulate inductive reasoning by learning from clinical information and generating predictive models [4]. Deep learning (DL) is a sub-type of ML that autonomously processes many digitized inputs, mimicking a complex neural network [4]. ML and DL have several potential medical applications, such as precision medicine, drug development, clinical trial programming, and epidemic prediction [1]. In this context, AI has increasingly provided a new perspective on characterizing the heterogeneity of several chronic diseases, including allergic disorders, and predicting their outcomes [3].

Allergic diseases are highly recognized conditions that equally affect children and adults and account for significant healthcare utilization and economic burden. The most common allergic disorders are allergic rhinitis (AR), asthma, atopic dermatitis (AD), and IgE-mediated food allergy (FA). Eosinophilic esophagitis (EoE) is a recently characterized atopic condition with increased prevalence and incidence in the last decade [5]. EoE is a chronic disease that explicitly affects the esophagus [5]. EoE is defined by the presence of $\geq$15 eosinophils/high power field (HPF) in endoscopically obtained biopsies and suggestive symptoms of esophageal dysfunction, which are proteiform and vary with age [6]. Toddlers and young children generally experience recurrent vomiting, failure to thrive, and feeding refusal or issues. School-aged children often present epigastric pain and gastroesophageal reflux symptoms not responsive to conventional treatment. Finally, adolescents and adults most often report food impaction (FI) and dysphagia, which are suggestive symptoms of tissue remodeling and esophageal fibrosis [5].

Compelling evidence exists for a well-established clinical and pathophysiological association between EoE and various allergic conditions. This translates to a demonstrably increased risk of EoE diagnosis in individuals with a history of allergies [7]. Consequently, EoE has been proposed as a potential late-stage manifestation of the atopic march. However, it is noteworthy that a significant subset of EoE patients lack atopic predisposition, suggesting the existence of a possible non-atopic phenotype [8]. Emerging research suggests potential associations between EoE and certain non-allergic conditions, including esophageal atresia, connective tissue disorders, autoimmune pathologies (celiac disease, type 1 diabetes), and autism spectrum disorders [8].

The etiology of EoE is multifactorial but still largely undefined. EoE pathogenesis, like other allergic diseases, is influenced by variable factors such as diet, infections, exposure to allergens, gut microbiome composition, and genetic and epigenetic elements, which ultimately affect multiple molecular pathways [5]. EoE is primarily identified by the typical type 2 (Th2) inflammation, arising after exposure to food allergens and probably other less common environmental allergens in genetically predisposed individuals with a defect in esophageal epithelial barrier integrity [5]. The natural history of EoE is characterized by progressive tissue remodeling with esophageal fibrosis, which endoscopically appears with esophageal stricture or stenosis and clinically with FI episodes [9]. The confluence of all of these factors allows us to assess the relevant heterogeneity in the molecular underpinnings, clinical presentation, disease course, and treatment response. Defining the specific molecular mechanisms or endotypes is a highly active area of allergy and immunology research and is essential for developing tailored and personalized therapies. In this context, AI tools are increasingly being integrated into computer-aided diagnosis systems that can be applied to improve the recognition and clinical and molecular characterization of EoE.

Therefore, this review aims to systematically evaluate current applications of AI, ML, and DL methods in EoE characterization and management.

2. Materials and Methods

2.1. Search Strategy and Selection Criteria

The protocol of the systematic review was registered (ID registration=CRD42023451048) and published with the International Prospective Register of Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023451048, accessed on 4 July 2024) before starting the study. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to report the results [10]. We referred to the latest version of the PRISMA 2020 statement, which includes a checklist of 27 items to guide the reporting of systematic reviews with/without a meta-analysis (the complete checklist is in the Supplementary Materials).

A comprehensive search strategy was designed to retrieve all articles via the online databases PubMed, Embase, and Web of Science, combining the terms "artificial intelligence" AND "eosinophilic esophagitis", "machine learning" AND "eosinophilic esophagitis", and "deep learning" AND "eosinophilic esophagitis". The literature review, including all publication years, was performed in May 2023. Search results were compiled using the software Refworks® (version 2022). Two independent researchers (M.V. and C.M.R.) conducted a dual screening process and assessed the full texts of articles deemed potentially relevant for inclusion. Any disagreements were resolved through discussion and mutual agreement. If an article presented unclear data, the authors were directly contacted via email for clarification.

All studies that met the following criteria were included: (1) original research articles (retrospective or prospective studies) published in English in peer-reviewed journals; (2) participants were children and adult patients with a diagnosis of EoE histologically confirmed ($\geq$15 eosinophils/HPF) according to guidelines [6]; (3) studies concerning the application of AI, ML, or DL models (Table 1). Conference and congress abstracts were excluded because of limited data regarding methods (model definition and analysis) and the potential risk of bias. The risk of bias and applicability of eligible studies were assessed according to the prediction model risk of bias assessment tool (PROBAST) for studies developing, validating, or updating (for example, extending) prediction models, both diagnostic and prognostic [11]. The evaluation tool contains 20 signaling questions from four domains: participants, predictors, outcomes, and analyses [11]. The risk of bias and applicability are classified as low, unclear, or high.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
- Population: patients (children and adults) with eosinophilic esophagitis. - Study design: retrospective (cross-sectional, case–control studies) and longitudinal studies. - Outcome: application of AI, ML, or DL models to improve diagnosis and knowledge of EoE molecular signature and pathogenesis.	- Clinical guidelines, consensus documents, reviews, systematic reviews, meta-analyses, abstracts, and conference proceedings. - Studies that did not involve the application of AI, ML, or DL technologies.

AI: artificial intelligence; DL: deep learning; EoE: eosinophilic esophagitis; ML: machine learning.

2.2. Data Analysis

Two independent reviewers (M.V. and C.M.R) meticulously extracted data from each qualifying study. A standardized data extraction sheet ensured consistency throughout the process. To guarantee accuracy, both reviewers then cross-checked their findings. Any discrepancies in the extracted data were resolved through a collaborative discussion and,

if necessary, with the input of a third reviewer to reach a consensus. We extracted the following information: first author name, publication date, AI methodology, study outcome, accuracy, sensitivity, specificity of the AI models, and 95% confidence interval (CI) when available.

This study is part of the non-profit research project "National, multicenter, retrospective, prospective study to evaluate pediatric gastrointestinal eosinophilic disorders"—GOLDEN (Gastrointestinal eOsinophiLic Disorders pEdiatric patieNts) study (protocol number 0003241/22). Being a systematic review, no informed consent was needed.

3. Results

We found 120 articles. After 68 duplicates were removed, 52 articles were reviewed, the title and abstract were analyzed, and 34 articles were excluded. Eleven (11) studies were assessed for eligibility (Table 2). All of these met the inclusion criteria and were analyzed for the systematic review (Figure 1). All articles were published after 2018. Using PROBAST, 18% and 64% of the studies were classified as having a low risk of bias and applicability, respectively (Figure 2). In the domains of "participants", "predictors", and "outcomes", most studies were classified as having a low risk. However, in the domain of "analysis", most studies were classified as having unclear risks.

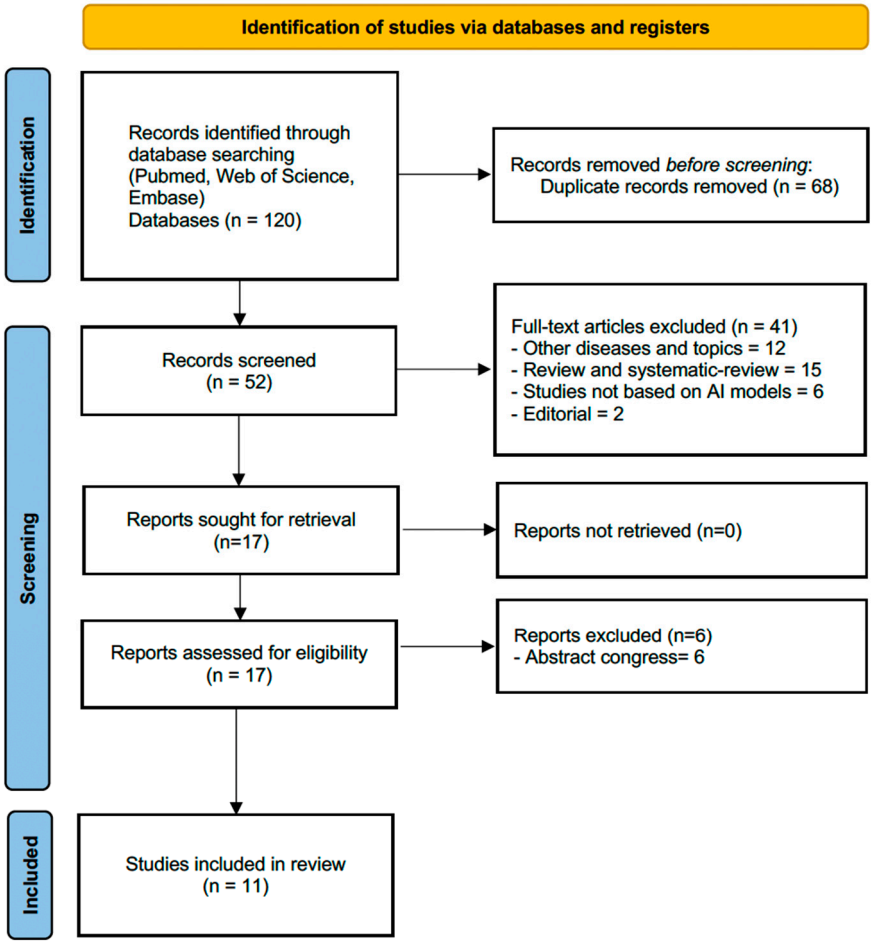

Figure 1. Study flowchart from identification to inclusion of final articles.

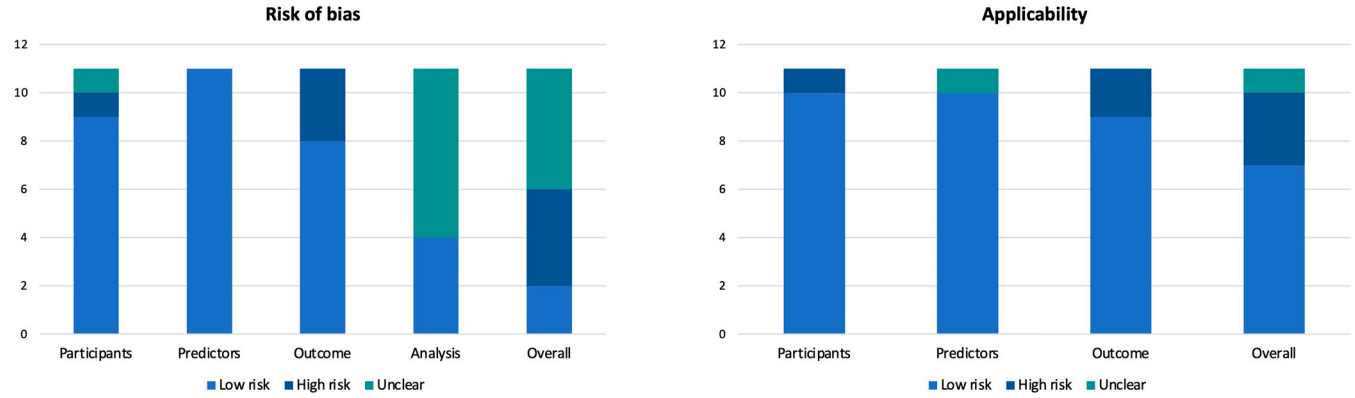

Figure 2. Risk of bias assessment according to PROBAST.

Table 2. Characteristics of included studies.

Author, Year	AI Model	Application Field	Datasets	Study Aim	Accuracy (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)
Okimoto et al., 2022 [12]	CNN	Diagnosis (endoscopy)	Endoscopic images	Analyzing multiple endoscopic images.	0.947 (0.929–0.962)	0.908 (0.865–0.941)	0.966 (0.947–0.981)
Guimarães et al., 2021 [13]	CNN	Diagnosis (endoscopy)	Endoscopic images	To distinguish the endoscopic appearance of EoE from normal findings and candida esophagitis.	0.915 (0.880–0.940)	0.871 (0.819–0.910)	0.936 (0.910–0.955)
Römmele et al., 2022 [14]	DL	Diagnosis (endoscopy)	Endoscopic images	Detecting and quantifying the endoscopic features of EoE.	0.95	0.96	0.94
Adorno et al., 2021 [15]	DL	Diagnosis (histology)	Whole-slide images (WSIs)	Quantifying tissue eosinophils using deep image segmentation.	0.99	1.0	0.982
Czyzewski et al., 2021 [16]	DCNN	Diagnosis (histology)	Whole-slide images (WSIs)	To detect histological features that are small relative to the size of the biopsy.	0.85	0.825	0.87
Daniel et al., 2022 [17]	ML	Diagnosis (histology)	Whole-slide images (WSIs)	To identify and quantitate esophageal eosinophils.	0.947	0.941	0.952
Larey et al., 2022 [18]	ML	Diagnosis (histology)	Whole-slide images (WSIs)	Extracting novel biomarkers to predict histological severity.	0.867	0.845	0.909
Archila et al., 2022 [19]	CNN	Diagnosis (histology)	Whole-slide images (WSIs)	Evaluation of histologic features in EoE spectrum.	-	-	-
Sallis et al., 2018 [20]	DL	Diagnosis (molecular profile)	Esophageal transcripts	Analysis of mRNA transcripts from esophageal biopsies.	0.985	0.909	0.932
Sallis et al., 2018 [21]	ML	Pathogenesis (molecular profile)	Esophageal transcripts	Identifying molecular pathways involved in food impaction.	0.99	0.93	1.0
Shoda et al., 2018 [22]	ML	Pathogenesis (molecular profile)	Endoscopic, histologic, and molecular (EoE diagnostic panel) features	EoE endotype prediction.	-	0.95–1.0	0.94–1.0

AI: artificial intelligence; CNN: convolutional neuronal network; DL: deep learning; ML: machine learning.

The results were analyzed and classified according to the field of AI technology application, including diagnosis (endoscopically, histologically, or molecular) and assessment of EoE heterogeneity.

3.1. AI in EoE Diagnosis

3.1.1. Endoscopic Diagnosis

Okimoto et al. designed a computer system that analyzes multiple esophageal endoscopic images to diagnose EoE. This system uses a CNN, specifically a ResNet50 architecture. To train the CNN, they used a collection of endoscopic images. This collection included images from 108 patients with confirmed EoE and images of healthy esophagi. Each group had 1192 images. After training, the system's accuracy was evaluated using a separate set of images from 35 EoE patients and 96 control subjects (756 images). The CNN achieved an accuracy rate of around 95% in correctly identifying EoE cases. Additionally, the model demonstrated high sensitivity (0.908, 95% CI 0.865–0.941), specificity (0.966, 95% CI 0.947–0.981), and accuracy (0.947, 95% CI 0.929–0.962) [12].

Similarly, Guimarães et al. built a CNN-based approach to distinguish the endoscopic appearance of EoE from normal findings and candida esophagitis. They trained and tested a CNN algorithm using 484 endoscopic images from 134 patients with a healthy esophagus, active EoE, and esophageal candidiasis. The image gallery was divided into independent datasets. Dataset 1 was used to perform 10-fold stratified cross-validation, where all folds were independent of each other. Subsequently, dataset 1 was used for training and tuning, whereas dataset 2 was used for hold-out testing. The model results were compared to those of three endoscopists. The CNN algorithm showed a global accuracy of 0.915 (95% CI 0.880–0.940), a sensitivity of 0.871 (95% CI 0.819–0.910), a specificity of 0.936 (95% CI 0.910–0.955), and an AUC of 0.966 (95% CI 0.954–0.975), which were higher than the endoscopists' experience (accuracy of 0.831; 95% CI 0.818–0.857) [13].

Römmele et al. developed a DL algorithm for detecting and quantifying the endoscopic features of EoE in white-light images as opposed to the healthy esophagus, integrating the EoE Endoscopic Reference Score (EREFS). The study included three phases. In the first phase, the CNN model was trained and validated with an internal dataset of endoscopic images from patients with EoE followed-up at the University Hospital of Augsburg, Germany. In the second phase, model performance was tested and integrated with the EREFS score on an external dataset from a separate hospital. In the third phase, the performance was compared with that of endoscopists with different experience levels. The overall sensitivity, specificity, and accuracy of the algorithm were 0.96, 0.94, and 0.95, respectively, while the AUC was 0.992. The integrated algorithm performed significantly better than endoscopists with a lower or medium experience level [14].

3.1.2. Histologic Diagnosis

Adorno et al. created and validated an automated tissue eosinophil detection model. They collected whole-slide images (WSIs), digitalizing archived biopsy slides of 44 patients with EoE. Then, they built a segmentation model with a U-Net architecture. The authors created a CNN model that predicted the location of eosinophils on histological images with an overall accuracy of 99.0%, sensitivity of 100%, and specificity of 98.2%. They linked biopsy features with treatments and clinical phenotypes (inflammatory, structuring, and PPI-responsive) [15].

Czyzewski et al. attempted to automate the manual assessment of tissue eosinophils, detecting features that are small relative to the size of the biopsy. They utilized hematoxylin- and eosin-stained slides from esophageal biopsies of 63 patients with active EoE and 63 healthy controls. The authors trained and then developed a platform based on a deep convolutional neural network (DCNN) that analyzed esophageal biopsies with an accuracy of 85%, sensitivity of 82.5%, and specificity of 87% in identifying EoE [16]. The same research group recently developed an ML pipeline to identify and quantify esophageal eosinophils at the whole-slide-image level, enrolling the highest sample of EoE patients.

They first validated the ability of the UNet++ model to detect and segment both intact and not-intact eosinophils, and then optimized the model. The final model detected intact and not-intact eosinophils with a global accuracy of 94.7%, a sensitivity of 94.1%, and a specificity of 95.2% [17].

Larey et al. developed a platform using ML that provided complete quantification of the eosinophils and basal cell fraction over the entire slide, quantifying the peak count, the basal cell fraction, the percent of HPFs that have more than 15 eosinophils, and the percent of HPFs that have more than 25% basal cells within them. They used 1,066 biopsy slides from 400 subjects with EoE to validate model performance. The algorithm predicted the histological severity better than the gold-standard method (peak of eosinophil count [PEC] $\geq$ 15 eosinophils/HPF) (accuracy of 87% vs. 79%), helping pathologists and gastroenterologists when accounting for the remission status [18].

Archila et al. developed an AI-based digital pathology model to evaluate histologic features in the spectrum of EoE [19]. Using a cloud-based DL platform, 10,726 objects and 56.2 mm^2 semantic segmentation areas were annotated on WSIs. The training set consisted of 40 selected digitized esophageal slides, which contained the full spectrum of changes typically seen in EoE, including lymphocytic inflammation, eosinophilic abscesses, basal zone hyperplasia, dilated intercellular spaces, dyskeratosis, surface epithelial change, and lamina propria fibrosis. A subset of cases was reserved as independent "test sets" to assess model validity outside the training set. Five pathologists scored each feature unquestioningly and independently of each other, as well as the AI model results. The CNN model recognized various EoE histologic features, including lamina propria remodeling. It represents an accurate and reproducible method for semi-automated quantitative analysis to evaluate esophageal biopsies. It is similar to/non-inferior to that of GI pathologists (F1-scores: 94.5–94.8 for AI vs. human) [19].

3.1.3. Molecular Profile Analysis

Sallis et al. developed an AI-based automated algorithm to generate the diagnostic probability score for EoE [p(EoE)] based on esophageal mRNA transcripts from patients with EoE, those with gastroesophageal reflux disease (GERD), and healthy controls. p(EoE) was determined by random forest classification. Accuracy was tested in an external test set, and predictive power was assessed with equivocal patients. A p(EoE) score $\geq$ 25 detected active EoE with high accuracy (sensitivity 91%, specificity 93%, and AUC 0.98) and improved the diagnosis of doubtful cases by 85%, distinguishing EoE from GERD. Moreover, the algorithm could identify patients in remission and responsive to treatments from those with active disease [20].

3.2. Application of AI Techniques in Understanding EoE Heterogeneity

The Boston Children's Hospital researchers found that EoE children with FI have a distinct esophageal mRNA pattern. The researchers used ML techniques to analyze the esophageal transcripts of EoE patients with (EoE + FI) and without FI. The ML algorithm successfully identified EoE + FI patients with accuracy values of 93% (sensitivity) and 100% (specificity). Interestingly, the analysis of the mRNA patterns in EoE + FI patients revealed lower levels of specific molecules involved in mast cell function (FCERIB, CPA3, CCL2), type 2 response (IL4, IL5), and the regulation of esophageal muscle contraction (NOS2, HIF1A). This result suggested that impaired esophageal motility may play a role in the development of FI among children with EoE [21].

Shoda et al. used ML to analyze connections between endoscopic, histologic, and molecular features of patients with EoE. Their analysis identified three distinct endotypes of EoE, called EoEe1, EoEe2, and EoEe3. Each subtype had unique characteristics. EoEe1 (35%) showed mild changes in histologic and endoscopic (normal esophagus) features and mild molecular changes (small changes in epithelial differentiation genes and pauci-inflammatory state). Notably, patients with EoEe1 were more likely to respond to steroid treatment (risk ratio [RR] 3.27, 95% CI 1.04–10.27, p = 0.0443). EoEe2 (29%) displayed a

strong type 2 inflammatory response and high levels of genes associated with inflammation. Patients with the EoEe2 endotype tended to be less responsive to steroid treatment (RR 2.77, 95% CI 1.11–6.95, $p = 0.0376$). The EoEe3 (36%) endotype was associated with adult-onset disease, a narrow-caliber esophagus, the highest degree of endoscopic and histologic severity, and the lowest expression of epithelial differentiation genes (RR 7.98, 95% CI 1.84–34.64, $p = 0.0013$). Moreover, the authors found that those endotypes were associated with distinct clinical features, including pediatric-onset vs. adult-onset EoE (EoEe1 and EoEe2 vs. EoEe3), atopic vs. non-atopic (EoEe1 and EoEe2 vs. EoEe3), normal vs. inflammatory vs. fibro-stenotic appearance (EoEe1 vs. EoEe2 vs. EoEe3), and steroid-sensitive vs. steroid-refractory (EoEe1vs. EoEe2 and EoEe3) [22].

4. Discussion

Over the past decade, the application of AI in medicine has dramatically increased and progressed mainly to BD analysis, pathology examination, and image recognition tasks. AI has been applied to many areas, especially those with medical files [2]. In radiology, AI models were created to analyze CT or X-ray images from patients with acute neurological events or breast cancer. In pathology, they were applied to improve cancer diagnosis; in ophthalmology, they were used to assess several retinal diseases [2]. In gastroenterology, AI proved helpful in supporting clinical and endoscopic diagnoses of benign and malignant gastrointestinal conditions, including esophageal diseases [23–25].

Due to its rising incidence, EoE is considered one of the most common conditions of the upper gastrointestinal tract [9]. However, an endoscopic diagnosis may be challenging considering the poor inter-observer agreement among endoscopists, especially when they are not experts in EoE or are unfamiliar with the application of the EREFS. Therefore, software or informatic models may help support the diagnostic process and differentiate patients with EoE from those with other gastrointestinal conditions. More precisely, AI models can discriminate EoE endoscopic features from a healthy esophagus and other endoscopically similar diseases, including esophageal candidiasis and GERD, with an accuracy comparable to or higher than that of endoscopists [12–14]. According to our systematic review, the AI models developed for identifying EoE based on endoscopic images showed high score performance with an accuracy that ranges from 0.92 to 0.97 [12–14]. As a result, these techniques can impact clinical practice, thus improving the diagnostic process, decreasing the diagnostic delay, and limiting misdiagnosis [26]. Diagnostic delay is still a hot issue in EoE management and is related to an increased risk of esophageal stenosis in adults and failure to thrive in children [27,28].

EoE histologic diagnosis includes the manual assessment of eosinophils in mucosal biopsies, which is a task difficult to standardize. PEC is the histological diagnostic criterion included in international guidelines [6]. Pathologists identify the area with the highest concentration of eosinophils and manually (without digital tools) count the number of eosinophils within one HPF through routine light microscopy [19]. However, esophageal eosinophilia is not the only histological feature observed in EoE patients. Other pathognomonic histological elements have been described in EoE, including basal zone hyperplasia, eosinophil abscess, dilated intercellular spaces, and thickened lamina propria fibers [29]. Collins and colleagues developed and validated the eosinophilic esophagitis histologic scoring system (EoEHSS), which, in addition to the count of eosinophils, includes a semi-quantitative scoring of other histological features of epithelial injury [30]. Although the EoEHSS provides a complete evaluation of esophageal inflammation, a semi-quantitative assessment of histologic EoE features is more time-consuming and labor-intensive than eosinophil counts. In this context, ML models could assist pathologists in diagnosing EoE, determining disease severity with a more accurate assessment of eosinophil counts and other esophageal features, thus bypassing the potential errors of the traditional evaluation of eosinophils by light microscopy [15–19]. In this systematic review, we reported studies developing AI models that histologically identified EoE with high accuracy (from 87% to 99%) [15–19]. Other authors created ML models to quantify the pathological eosinophil

count with high accuracy [31]. Javaid et al. developed an image classification model that successfully predicted the diagnosis of EoE in 99% of patches from treatment-naïve EoE patients based on structural features other than eosinophil counts. The model also predicted the resolution of symptoms at remission based on a significant reduction in EoE-classified tissue from diagnosis to follow-up [32]. Hopson et al. developed a DL digital pathology model for the assessment of whole-biopsy-slide histologic features, including novel features such as tissue subregions, dilated intracellular spaces, eosinophilic abscesses, cell types, the spatial relationship of various cells, degranulated eosinophils, collagen fibers, and inflammatory cells within the submucosa [33]. Thus, another possible application of AI may be the diagnosis of EoE in the subset of patients with borderline tissue eosinophilia taking protein pump inhibitors.

In the era of "omics" science, analyzing a large amount of genetic or molecular data requires advanced computational analysis, including artificial intelligence techniques. Lin et al. have trained different ML algorithms based on the analysis of RNA sequencing data from esophageal and buccal epithelial tissue biopsies, showing an accurate ability to classify biopsies that were not controlled for depth and were sequenced using different protocols and machines [34]. Sallis et al., applying ML models to transcriptomic data from patients with EoE, identified different transcriptional signatures corresponding to two specific EoE phenotypes (EoE patients with and without FI) [21]. The authors also designed a diagnostic probability score p(EoE) using the esophageal mRNA transcriptome. The investigators showed that a p(EoE) score of 25 detected EoE with high sensitivity and specificity [20]. Therefore, p(EoE) provided a promising tool for helping to identify EoE cases, reduce the diagnostic delay, and assess response to therapy. Recently, Oliva et al. applied an accurate ML prediction model that identified 20 uncommon features and unspecific signs predictive of an EoE diagnosis in children [35].

Despite several advances in EoE management, several clinical and pathogenetic aspects still require further investigation. EoE is a clinically heterogeneous disease. Thus, identifying subgroups of patients—distinct according to their clinical and molecular features—may help personalize care and therapies. In this context, Shoda et al. identified three distinct endotypes of EoE, integrating clinical, endoscopic, and molecular data from EoE patients. These endotypes had a therapeutic impact. EoEe1 is a mild endotype characterized by markedly low expression of ALOX15. Thus, suppressing this gene and the metabolic products of 15-lipoxygenase is therapeutic. EoEe2 is characterized by a marked expression of type 2 inflammatory cytokines (IL-4 and TSLP), suggesting that patients with this endotype may benefit from anti-IL4R/-13 or anti-TSLP therapies [22].

Subsequently, Dunn et al. applied a clustering analysis on Th2 cytokine expression to identify subgroups of patients with active EoE [36]. The authors found five groups or endotypes which did not differ significantly in esophageal eosinophil counts. Group I, with the lowest IL-5 expression, generally corresponded to EoEe1, whereas group V displayed the highest IL-5 expression and corresponded to EoEe2. Groups II-IV demonstrated the fibro-stenotic EoEe3, with groups III and IV showing elevated IL-13 expression [36]. It is still unclear whether these endotypes represent a chronologic transition from EoEe1 to EoEe2 to EoEe3, disparate pathologic mechanisms, or both. More recently, Votto et al. employed a cluster analysis approach to investigate the clinical heterogeneity within pediatric eosinophilic gastrointestinal disorders. Their multidimensional analysis revealed the existence of two distinct clinical phenotypes in pediatric EoE. Cluster 1 primarily comprised EoE patients exhibiting an atopic phenotype characterized by elevated levels of total serum IgE and peripheral blood eosinophils.

Conversely, cluster 2 consisted of a non-atopic EoE phenotype, predominantly composed of non-allergic children with a history of NICU admission, potentially linked to a high prevalence of congenital malformations (e.g., esophageal atresia) [8]. Consequently, it has become increasingly evident that beyond eosinophils, other cell types play a crucial role in EoE pathogenesis. These include Th2 cells, innate natural killer (iNK) cells, mast cells, and fibroblasts. These findings suggest the potential utility of AI in elucidating the

specific molecular pathways involved in individual patients and distinct disease phases. This approach could pave the way for a precision medicine approach, ultimately leading to improved patient care [37,38].

The strength of this systematic review is that we showed the state of AI research in EoE by applying a systematic methodology (Figure 3). We demonstrated that AI techniques provide efficient models (however not externally validated) to distinguish EoE from other GI conditions, analyze esophageal eosinophil counts and other histologic features, and identify disease phenotypes. Notably, the ML models and DL algorithms could support young endoscopists, pathologists, or gastrointestinal trainers/fellows who start caring for patients with EoE [39]. Moreover, these techniques could assist the clinical practice in peripheral or suburban hospitals where the number of patients with EoE is limited compared to university hospitals.

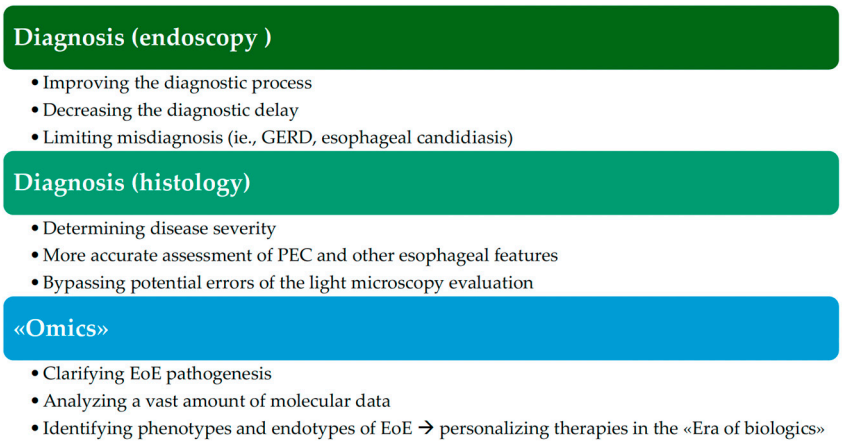

Figure 3. Graphical synthesis of main results.

This study is subject to several limitations. Firstly, the included studies exhibited marked heterogeneity, characterized by relatively small datasets, diverse clinical themes, and a variety of evaluation methods. Consequently, the systematic review was unable to yield universally applicable conclusions. Secondly, while a comprehensive search strategy was implemented encompassing three major databases, potentially relevant publications, such as preprint articles hosted on alternative online repositories, might not have been captured. Additionally, inherent biases are present. While most studies demonstrated a low risk of bias in participant selection, predictor variables, and outcome measures, the analysis domain presented an unclear risk of bias. This ambiguity stems from uncertainties surrounding the appropriate handling of missing data, the adequacy of model performance evaluation, and the ability to account for model overfitting, underfitting, and optimism. Notably, the absence of external validation emerged as a critical limitation in several studies.

5. Conclusions

Since the first description of EoE, significant progress has been made in understanding its clinical and immunopathogenic background. Nonetheless, many open issues await elucidation, and AI could help clinicians solve them. AI could promote more accurate evidence-based management of EoE by integrating the results of molecular signature, clinical, histology, and endoscopic features (Figure 4). However, the era of AI application in medicine is just beginning. This field is undoubtedly promising but needs more data and proof. AI models in EoE require further, larger, more rigorous studies and extensive validation in the real-world environment.

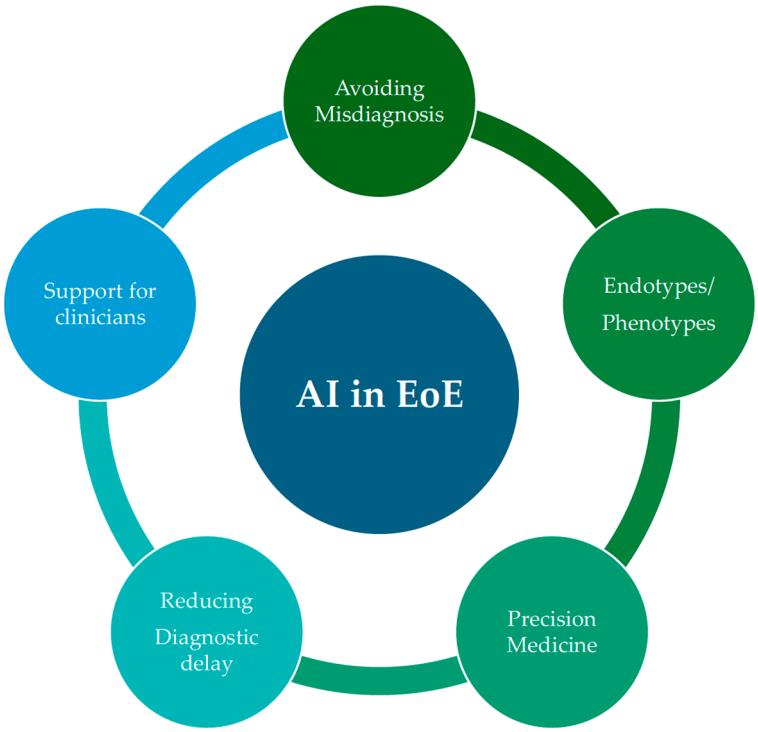

Figure 4. Advantages of application of AI tools in EoE.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/bdcc8070076/s1, PRISMA 2020 Checklist.

Author Contributions: M.V. defined the research question and the search strategies with the assistance of C.M.R. M.V. developed the data extraction form. M.V. and C.M.R. screened the articles, extracted the data, and performed the narrative synthesis. M.V. wrote the manuscript. C.M.R., S.M.E.C., M.D.F., A.D.S., M.V.L., A.R., G.L.M. and A.L. were consulted concerning the methodology and synthesis of the findings. All authors (M.V., C.M.R., S.M.E.C., M.D.F., A.D.S., M.V.L., A.R., G.L.M. and A.L.) reviewed the manuscript drafts critically. All authors have read and agreed to the published version of the manuscript.

Funding: This study received no external funding.

Institutional Review Board Statement: This study is a part of the non-profit research project "National, multicenter, retrospective, prospective study to evaluate pediatric gastrointestinal eosinophilic disorders"—GOLDEN (Gastrointestinal eOsinophiLic Disorders pEdiatric patieNts) study (protocol number 0003241/22).

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article.

Conflicts of Interest: All authors have read and approved the final manuscript and declare that there are no conflicts of interest of a financial or personal nature. The manuscript has not been published elsewhere and is not under consideration for publication elsewhere.

References

1. Musacchio, N.; Guaita, G.; Ozzello, A.; Pellegrini, M.A.; Ponzani, P.; Zilich, R.; De Micheli, A. Artificial Intelligence and Big Data in Medicine: Scenarios, opportunities, and critical issues. *JAMD* **2018**, *21*, 204–218. [CrossRef]
2. Topol, E.J. High-performance medicine: The convergence of human and artificial intelligence. *Nat. Med.* **2019**, *25*, 44–56. [CrossRef] [PubMed]
3. Ferrante, G.; Licari, A.; Fasola, S.; Marseglia, G.L.; La Grutta, S. Artificial intelligence in the diagnosis of pediatric allergic diseases. *Pediatr. Allergy Immunol.* **2021**, *32*, 405–413. [CrossRef] [PubMed]
4. Cilluffo, G.; Fasola, S.; Ferrante, G.; Licari, A.; Marseglia, G.R.; Albarelli, A.; Marseglia, G.L.; La Grutta, S. Machine learning: A modern approach to pediatric asthma. *Pediatr. Allergy Immunol.* **2022**, *33* (Suppl. S27), 34–37. [CrossRef] [PubMed]

5. Votto, M.; De Filippo, M.; Caimmi, S.; Indolfi, C.; Raffaele, A.; Tosca, M.A.; Marseglia, G.L.; Licari, A. A Practical Update on Pediatric Eosinophilic Esophagitis. *Children* **2023**, *10*, 1620. [CrossRef] [PubMed]
6. Hirano, I.; Chan, E.S.; Rank, M.A.; Sharaf, R.N.; Stollman, N.H.; Stukus, D.R.; Wang, K.; Greenhawt, M.; Falck-Ytter, Y.T.; Chachu, K.A.; et al. AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis. *Gastroenterology* **2020**, *158*, 1776–1786. [CrossRef] [PubMed]
7. Rossi, C.M.; Lenti, M.V.; Merli, S.; Licari, A.; Votto, M.; Marseglia, G.L.; Di Sabatino, A. Primary eosinophilic gastrointestinal disorders and allergy: Clinical and therapeutic implications. *Clin. Transl. Allergy* **2022**, *12*, e12146. [CrossRef]
8. Votto, M.; Fasola, S.; Cilluffo, G.; Ferrante, G.; La Grutta, S.; Marseglia, G.L.; Licari, A. Author response for "Cluster analysis of clinical data reveals three pediatric eosinophilic gastrointestinal disorder phenotypes". *Pediatr. Allergy Immunol.* **2022**, *33*, e13746. [CrossRef]
9. Dellon, E.S.; Hirano, I. Epidemiology and Natural History of Eosinophilic Esophagitis. *Gastroenterology* **2018**, *154*, 319–332. [CrossRef]
10. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; A Akl, E.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, 71. [CrossRef]
11. Wolff, R.F.; Moons, K.G.; Riley, R.; Whiting, P.F.; Westwood, M.; Collins, G.S.; Reitsma, J.B.; Kleijnen, J.; Mallett, S.; the PROBAST Group. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. *Ann. Intern. Med.* **2019**, *170*, 51–58. [CrossRef] [PubMed]
12. Okimoto, E.; Ishimura, N.; Adachi, K.; Kinoshita, Y.; Ishihara, S.; Tada, T. Application of Convolutional Neural Networks for Diagnosis of Eosinophilic Esophagitis Based on Endoscopic Imaging. *J. Clin. Med.* **2022**, *11*, 2529. [CrossRef] [PubMed]
13. Guimarães, P.; Keller, A.; Fehlmann, T.; Lammert, F.; Casper, M. Deep learning-based detection of eosinophilic esophagitis. *Endoscopy* **2022**, *54*, 299–304. [CrossRef] [PubMed]
14. Römmele, C.; Mendel, R.; Barrett, C.; Kiesl, H.; Rauber, D.; Rückert, T.; Kraus, L.; Heinkele, J.; Dhillon, C.; Grosser, B.; et al. An artificial intelligence algorithm is highly accurate for detecting endoscopic features of eosinophilic esophagitis. *Sci. Rep.* **2022**, *12*, 11115. [CrossRef] [PubMed]
15. Adorno, W., III; Catalano, A.; Ehsan, L.; von Eckstaedt, H.V.; Barnes, B.; McGowan, E.; Syed, S.; Brown, D.E. Advancing Eosinophilic Esophagitis Diagnosis and Phenotype Assessment with Deep Learning Computer Vision. In Proceedings of the In Biomedical Engineering Systems and Technologies, International Joint Conference, BIOSTEC Revised Selected Papers, Virtual Event, 11–13 February 2021; pp. 44–55. [CrossRef]
16. Czyzewski, T.; Daniel, N.; Rochman, M.; Caldwell, J.M.; Osswald, G.A.; Collins, M.H.; Rothenberg, M.E.; Savir, Y. Machine Learning Approach for Biopsy-Based Identification of Eosinophilic Esophagitis Reveals Importance of Global features. *IEEE Open J. Eng. Med. Biol.* **2021**, *2*, 218–223. [CrossRef] [PubMed]
17. Daniel, N.; Larey, A.; Aknin, E.; Osswald, G.A.; Caldwell, J.M.; Rochman, M.; Collins, M.H.; Yang, G.-Y.; Arva, N.C.; Capocelli, K.E.; et al. A Deep Multi-Label Segmentation Network for Eosinophilic Esophagitis Whole Slide Biopsy Diagnostics. In Proceedings of the Annual International Conference of the IEEE Engineering in Medicine & Biology Society, Glasgow, UK, 11–15 July 2022; pp. 3211–3217.
18. Larey, A.; Aknin, E.; Daniel, N.; Osswald, G.A.; Caldwell, J.M.; Rochman, M.; Wasserman, T.; Collins, M.H.; Arva, N.C.; Yang, G.-Y.; et al. Harnessing artificial intelligence to infer novel spatial biomarkers for the diagnosis of eosinophilic esophagitis. *Front. Med.* **2022**, *9*, 950728. [CrossRef] [PubMed]
19. Archila, L.R.; Smith, L.; Sihvo, H.-K.; Westerling-Bui, T.; Koponen, V.; O'sullivan, D.M.; Fernandez, M.C.C.; Alexander, E.E.; Wang, Y.; Sivasubramaniam, P.; et al. Development and technical validation of an artificial intelligence model for quantitative analysis of histopathologic features of eosinophilic esophagitis. *J. Pathol. Inform.* **2022**, *13*, 100144. [CrossRef] [PubMed]
20. Sallis, B.F.; Erkert, L.; Moñino-Romero, S.; Acar, U.; Wu, R.; Konnikova, L.; Lexmond, W.S.; Hamilton, M.J.; Dunn, W.A.; Szepfalusi, Z.; et al. An algorithm for the classification of mRNA patterns in eosinophilic esophagitis: Integration of machine learning. *J. Allergy Clin. Immunol.* **2018**, *141*, 1354–1364. [CrossRef] [PubMed]
21. Sallis, B.F.; Acar, U.; Hawthorne, K.; Babcock, S.J.; Kanagaratham, C.; Goldsmith, J.D.; Rosen, R.; Vanderhoof, J.A.; Nurko, S.; Fiebiger, E. A Distinct Esophageal mRNA Pattern Identifies Eosinophilic Esophagitis Patients with Food Impactions. *Front. Immunol.* **2018**, *9*, 2059. [CrossRef]
22. Shoda, T.; Wen, T.; Aceves, S.S.; Abonia, J.P.; Atkins, D.; Bonis, P.A.; Caldwell, J.M.; Capocelli, K.E.; Carpenter, C.L.; Collins, M.H.; et al. Eosinophilic oesophagitis endotype classification by molecular, clinical, and histopathological analyses: A cross-sectional study. *Lancet Gastroenterol. Hepatol.* **2018**, *3*, 477–488. [CrossRef]
23. Hassan, C.; Repici, A.; Sharma, P. Incorporating Artificial Intelligence Into Gastroenterology Practices. *Clin. Gastroenterol. Hepatol.* **2023**, *21*, 1687–1689. [CrossRef] [PubMed]
24. Visaggi, P.; Barberio, B.; Gregori, D.; Azzolina, D.; Martinato, M.; Hassan, C.; Sharma, P.; Savarino, E.; de Bortoli, N. Systematic review with meta-analysis: Artificial intelligence in the diagnosis of oesophageal diseases. *Aliment. Pharmacol. Ther.* **2022**, *55*, 528–540. [CrossRef] [PubMed]
25. Kudo, S.-E.; Misawa, M.; Mori, Y.; Hotta, K.; Ohtsuka, K.; Ikematsu, H.; Saito, Y.; Takeda, K.; Nakamura, H.; Ichimasa, K.; et al. Artificial Intelligence-assisted System Improves Endoscopic Identification of Colorectal Neoplasms. *Clin. Gastroenterol. Hepatol.* **2020**, *18*, 1874–1881. [CrossRef] [PubMed]

26. Lenti, M.V.; Savarino, E.; Mauro, A.; Penagini, R.; Racca, F.; Ghisa, M.; Laserra, G.; Merli, S.; Arsiè, E.; Longoni, V.; et al. Diagnostic delay and misdiagnosis in eosinophilic oesophagitis. *Dig. Liver Dis.* **2021**, *53*, 1632–1639. [CrossRef] [PubMed]
27. Schoepfer, A.M.; Safroneeva, E.; Bussmann, C.; Kuchen, T.; Portmann, S.; Simon, H.; Straumann, A. Delay in diagnosis of eosinophilic esophagitis increases the risk for stricture formation in a time-dependent manner. *Gastroenterology* **2013**, *145*, 1230–1236. [CrossRef] [PubMed]
28. Votto, M.; Lenti, M.V.; De Silvestri, A.; Bertaina, F.; Bertozzi, M.; Caimmi, S.; Cereda, E.; De Filippo, M.; Di Sabatino, A.; Klersy, C.; et al. Evaluation of diagnostic time in pediatric patients with eosinophilic gastrointestinal disorders according to their clinical features. *Ital. J. Pediatr.* **2023**, *49*, 9. [CrossRef] [PubMed]
29. Hiremath, G.; Sun, L.; Collins, M.H.; Bonis, P.A.; Arva, N.C.; Capocelli, K.E.; Chehade, M.; Davis, C.M.; Falk, G.W.; Gonsalves, N.; et al. Esophageal Epithelium and Lamina Propria Are Unevenly Involved in Eosinophilic Esophagitis. *Clin. Gastroenterol. Hepatol.* **2023**, *21*, S1542–S3565. [CrossRef] [PubMed]
30. Collins, M.H.; Martin, L.J.; Alexander, E.S.; Boyd, J.T.; Sheridan, R.; He, H.; Pentiuk, S.; Putnam, P.E.; Abonia, J.P.; Mukkada, V.A.; et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. *Dis. Esophagus* **2017**, *30*, 1–8. [CrossRef] [PubMed]
31. Catalano, A.; Adorno, W.; Ehsan, L.; Shrivastava, A.; Barnes, B.H.; McGowan, E.C.; Moore, S.; Brown, D.; Syed, S. Use of machine learning and computer vision to link eosinophilic esophagitis cellular patterns with clinical phenotypes and disease location. *Gastroenterology* **2020**, *158*, 814. [CrossRef]
32. Javaid, A.; Fernandes, P.; Adorno, W., III; Catalano, A.; Ehsan, L.; von Eckstaedt, H.V.; Barnes, B.; Khan, M.; Raghavan, S.S.; McGowan, E.; et al. Deep learning tissue analysis diagnoses and predicts treatment response in eosinophilic esophagitis. *medRxiv* **2021**. [CrossRef]
33. Hopson, P.; O'Sullivan, D.; Cardenas, M.F.; Westerling-Bui, T.; Koponen, V.; O'Sullivan, D.M.; Fernandez, M.C.C.; Alexander, E.E.; Wang, Y.; Sivasubramaniam, P.; et al. Evaluation of eosinophilic esophagitis with a novel artificial intelligence histopathologic feature recognition model. *J. Pediatr. Gastroenterol. Nutr.* **2022**, *75*, S490–S491.
34. Lin, E.; Flygare, S.; Peterson, K.; Clayton, F.; Yandell, M. Using machine learning and RNA-seq to increase the accuracy and decrease the invasiveness of diagnosing eosinophilic esophagitis. *J. Immunol.* **2018**, *200*, 174.14. [CrossRef]
35. Oliva, S.; Russo, G.; Rossetti, D.; Ruggiero, C.; Volpe, D.; Veraldi, S.; Rubino, C.; Costanzo, M.L.; Ciliberto, C. Machine learning as a new method for early detection of eosinophilic esophagitis. *J. Pediatr. Gastroenterol. Nutr.* **2022**, *74*, 310–311.
36. Dunn, J.L.; Shoda, T.; Caldwell, J.M.; Wen, T.; Aceves, S.S.; Collins, M.H.; Dellon, E.S.; Falk, G.W.; Leung, J.; Martin, L.J.; et al. Esophageal type 2 cytokine expression heterogeneity in eosinophilic esophagitis in a multisite cohort. *J. Allergy Clin. Immunol.* **2020**, *145*, 1629–1640. [CrossRef]
37. Arias, Á.; Lucendo, A.J. Molecular basis and cellular mechanisms of eosinophilic esophagitis for the clinical practice. *Expert. Rev. Gastroenterol. Hepatol.* **2019**, *13*, 99–117. [CrossRef] [PubMed]
38. Rossi, C.M.; Lenti, M.V.; Di Sabatino, A. Toning down the role of eosinophils in eosinophilic oesophagitis. *Gut* **2024**, *73*, 874–875. [CrossRef]
39. Rodrigues, T.; Keswani, R. Endoscopy Training in the Age of Artificial Intelligence: Deep Learning or Artificial Competence? *Clin. Gastroenterol. Hepatol.* **2023**, *21*, 8–10. [CrossRef]