A Summary of the Meetings of the Development of a Core Outcome Set for Therapeutic Studies in Eosinophilic Esophagitis (COREOS) International Multidisciplinary Consensus

Christopher Ma,[1,2] Alain M. Schoepfer,[3] Ekaterina Safroneeva,[4] on behalf of the COREOS Collaborators

[1]Division of Gastroenterology and Hepatology, Departments of Medicine and Community Health Sciences, University of Calgary, Calgary, Alberta, Canada; [2]Alimentiv Inc, London, Ontario, Canada; [3]Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland; and [4]Institute of Social and Preventive Medicine, University of Bern, Switzerland

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Meeting Summary: Overview

The Core Outcome Set for Therapeutic Studies in Eosinophilic Esophagitis (COREOS) collaborators are a group of more than 70 gastroenterologists, pathologists, allergists, researchers, dietitians, psychologists, and methodologists who convened in a series of in-person and virtual meetings between 2018 and 2020 with the aim of developing a core outcome set (COS) for use in therapeutic studies of pharmacologic and dietary therapies for the treatment of eosinophilic esophagitis (EoE). Given heterogeneity in reported outcomes and uncertainties regarding the most appropriate end points for use in both randomized controlled trials (RCTs) and observational studies involving EoE patients, the EoE experts launched the COREOS exercise in 2018 to standardize outcome definitions using methods established by the Core Outcome Measures in Effectiveness Trials (COMET) initiative.[1,2] The COS was developed using a multiphase approach, which is summarized in Figure 1. In the first phase, systematic reviews of the literature and patient engagement surveys were conducted to identify candidate outcomes that have been previously measured and are important to patients with EoE. Next, this information was used to build a framework of different outcome domains, and working groups for each domain were assembled to review the literature for relevant end points.[3–6] The relative importance of these domains was categorized in a Delphi survey as core, important, and research agenda domains, and discussed in a moderated in-person meeting on May 17, 2019 at Digestive Disease Week (San Diego, CA). In phase 3, a comprehensive list of outcome measures within each of the core domains was evaluated by the COREOS collaborators in a 2-round Delphi survey and, finally, outcomes were ratified in a virtual meeting on December 8, 2020. In this meeting summary, we highlight the major points of discussion that occurred during the development of the EoE COS.

Forming the COREOS Collaboration: Introductory Sessions

The COREOS steering committee first convened in person on June 5, 2018 at Digestive Disease Week 2018 in Washington, DC. This was followed by a teleconference on July 13, 2018. These first kick-off meetings aimed to establish timelines, primary objectives, strategic partnerships, participant recruitment, and roles and responsibilities for the group. The committee agreed that the aim of the COREOS collaboration would be to identify core outcomes in EoE to improve the efficiency of drug development and the quality of comparative research and ultimately shape clinical practice by selecting end points relevant to patients and physicians. The scope of the COS was set to include RCTs and observational studies, in both adult and pediatric populations, for dietary and pharmacologic therapies for EoE. Dilation was considered, although not included, as end points for endoscopic procedures (eg, technical success) are substantively different from those for anti-inflammatory therapies.

The Committee agreed that the collaboration would have a global and multidisciplinary scope. Expert panelists were required to have established experience in EoE, as demonstrated by at least 5 peer-reviewed publications in the preceding 10 years; participation in at least 1 RCT in EoE in the preceding 5 years; or specific methodological expertise with respect to conducting COS exercises, trial design, or instrument development. Invitations to participate in the COREOS collaboration were

Abbreviations used in this paper: **CEGIR, Consortium of Eosinophilic Gastrointestinal Disease Researchers; COMET, Core Outcome Measures in Effectiveness Trials; COREOS, Core Outcome Set for Therapeutic Studies in Eosinophilic Esophagitis; COS, core outcome set; EGID, Eosinophil Gastrointestinal Disorders; EoE, eosinophilic esophagitis; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; EUREOS, European Society of Eosinophilic Esophagitis; QoL, quality of life; RCT, randomized controlled trial.**

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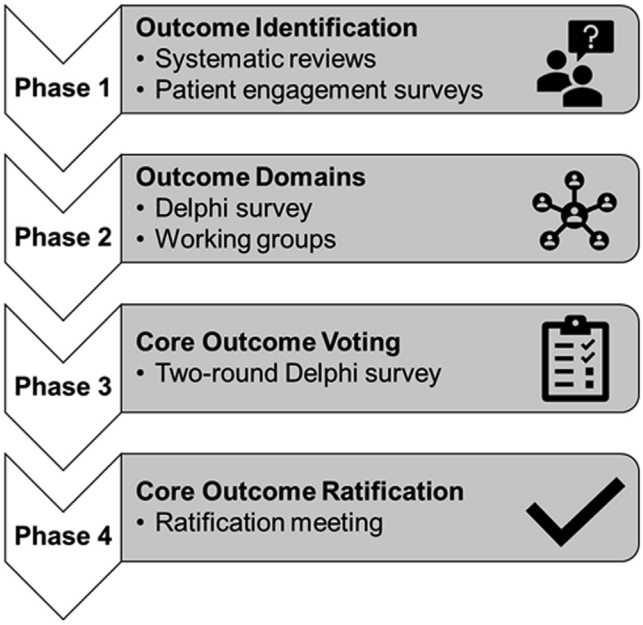

Figure 1. Core outcome set development process.

distributed to members of the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR); European Society of Eosinophilic Esophagitis (EUREOS); and Eosinophil Gastrointestinal Disorders Committee of The American Academy of Allergy, Asthma, and Immunology. The final group of collaborators included gastroenterologists, allergists, pathologists, dietitians, psychologists, and methodologists.

Defining the Core Outcome Domains

A total of 11 core outcome domains were identified; in a Delphi survey, 66 panelists voted the following 4 outcome domains as critical for inclusion: patient-reported symptoms, EoE-specific quality of life, histopathology, and endoscopy. Domains considered important but optional for inclusion included genetic profiling, biomarkers, esophageal distensibility, immunologic dissection, and patient perception of health. Secondary impact on family/caregivers and resource utilization were voted as research agenda domains. The COREOS collaborators met in person on May 17, 2019 at Digestive Disease Week in San Diego, CA to review these results and identify important areas for COS development moving into phase 3. A total of 29 COREOS members attended the meeting, with broad geographic representation. The meeting was chaired by Drs Christopher Ma and Ekaterina Safroneeva. Dr Safroneeva opened the meeting by reviewing the aims of the COREOS collaboration and reviewing the results of the outcome domain Delphi survey. Each subsequent session was focused on 1 of the core domains (ie, histology, endoscopy, and symptoms and quality of life), with a presentation by expert opinion leaders in that domain followed by an open forum discussion. Each presentation focused on key outcome measures within the domain and considerations for COS selection.

Drs Rish Pai (Mayo Clinic Arizona) and Margaret Collins (Cincinnati Children's Hospital) led the discussion regarding histopathology in EoE. Given the central role of eosinophilic inflammation in the diagnosis of EoE, there was agreement that histology should be a core outcome domain in the COS. Topics of discussion included use of the peak eosinophil count vs the EoE Histology Scoring System,[7] considerations for biopsy acquisition (including capturing subepithelial tissue and standardization of microscope field size), and advantages and disadvantages of different measures of histologic activity (including reliability, responsiveness, correlation with patient symptoms and quality of life, feasibility for measurement, and regulatory considerations for RCTs).[8,9] The experts discussed concepts important for COS development, which included defining appropriate measurement tools and measurement conventions for histologic activity, and identifying thresholds for histologic remission.

Drs Ikuo Hirano (Northwestern University), Amanda Muir (Children's Hospital of Philadelphia), and Christopher Ma (University of Calgary) presented on endoscopic assessment. The EoE Endoscopic Reference Score (EREFS)[10] was identified as the most likely tool to be used for assessing endoscopic disease activity, with demonstrated content validity, inter- and intra-rater reliability, and responsiveness.[3] For purposes of COS development, the experts discussed the most appropriate method to calculate the EREFS (ie, simple score vs weighted scoring and inflammatory vs fibrostenotic subscores[11,12]), appropriate definitions of endoscopic response and remission, and differentiation between impassable rings vs strictures. There was also a discussion around the use of distensibility measurements; this domain was voted to be important but not essential in the Delphi panel. Potential advantages of impedance planimetry as an esophageal "function test" that better measures esophageal caliber and distensibility,[13] is correlated with dysphagia symptoms, and has shown responsiveness to anti-inflammatory therapy and in a phase 2 trial of dupilumab[14] were reviewed. However, considerations of cost, availability, and incompletely characterized operating properties were identified as reasons for excluding distensibility from a core outcome that needs to be measured in every trial.

Patient-reported symptoms and quality of life (QoL) measures were reviewed by Drs Evan Dellon (University of North Carolina) and Alain Schoepfer (Lausanne University Hospital) for adult patients, and by Drs Mirna Chehade (Mount Sinai, New York) and Sandeep Gupta (Indiana University) for pediatric populations. For adult populations, the experts reviewed advantages and disadvantages of symptom-based patient-reported outcome measures, including the EoE Activity Index[15] and Dysphagia Symptoms Questionnaire.[16] There was considerable conversation regarding appropriate terminology relating to dysphagia and previous qualitative work to best elucidate this symptom. Several QoL measures were also reviewed; the EoE-QoL-A questionnaire was identified as the only validated

measure of health-related QoL for adults with EoE with internal consistency, test–retest reliability, and validity.[17] Identifying the most appropriate tool for assessing symptoms (with consideration of feasibility, scientific merit, and regulatory requirements), defining the recall period (daily vs 7 days), and defining thresholds for response/remission that are correlated with biologic activity were judged by experts to be important concepts for COS development in adults.

In pediatric populations, experts identified several potential barriers to accurate patient-reported outcome measure assessment, including the large variability in symptom presentations, the variance in presentations across different age groups from infancy to adolescence, and the accuracy of self-reporting vs parental/proxy-reporting. The broad range of symptoms was identified as potentially problematic, particularly in the RCT setting. While some panelists proposed to include only dominant symptoms for the purposes of streamlining trial recruitment, others argued that this would lead to the exclusion of a sizable proportion of pediatric patients. Although different symptoms scores were reviewed, the Pediatric EoE Symptom Score, version 2.0, was identified as the most likely candidate for inclusion into COS, as this instrument captures multiple symptom complexes (including dysphagia, reflux, nausea/vomiting, and pain) and demonstrates responsiveness to elimination diet.[18]

Discussions from this meeting, in combination with the systematic review and patient engagement surveys, were used to inform the development of the COS statements for voting in phase 3.

Establishing Consensus and Core Outcome Set Ratification

A total of 122 statements across the 4 core outcome domains were developed for the first round of the phase 3 Delphi surveys. Before the survey was distributed, an introductory videoconference was held March 19, 2020 to review the aims of the survey, instructions for survey completion, and the 9-point Likert scoring system (with outcomes scored in the 7–9 range being considered critical for inclusion in a COS, outcomes scored in the 4–6 range being considered important but not critical, and outcomes scored in the 1–3 range being considered of limited importance).[1] This videoconference was recorded and distributed to all panelists, including those who were unable to attend. After the round 1 Delphi survey, all responses were reviewed by the lead and senior investigators. A priori–defined rules were used to determine which outcomes were carried forward to round 2: outcomes scored in the 7–9 range by $\geq$50% of panelists and 1–3 range by $<$15% of panelists were carried forward. A total of 59 outcomes were included in the round 2 survey, which was distributed to panelists with a report containing their own scoring from the first round, comments, and the group scores. Outcomes that were voted by $\geq$70% of panelists in the 7–9 range and $<$15% of panelists in the 1–3 range were defined as meeting consensus for inclusion.

The final outcomes to be included in the COS were ratified in a moderated videoconference held December 8, 2020. Although this was initially planned as a face-to-face meeting with all stakeholder groups, this was amended to a virtual meeting due to COVID-19 public health restrictions. The meeting was chaired by Drs Christopher Ma and Ekaterina Safroneeva. All panelists who participated in any round of the Delphi surveys were invited to attend. The meeting date and time were chosen to accommodate the maximum number of participants: a total of 27 experts attended the ratification meeting, representing a broad range of disciplines, practice settings, and geographic regions. Dr Christopher Ma opened the meeting by summarizing the results from round 2 of the Delphi survey, outlining the objectives of the ratification meeting, and reviewing the voting procedures. All items reaching consensus in round 2 were discussed, as were all items that had a reasonable likelihood of potentially meeting the criterion for inclusion (defined as outcomes for which the upper 95% confidence interval of the proportion of panelists voting in the 7–9 category exceeded 70%). A total of 42 items were reviewed in the ratification meeting. Discussion on the merits and pitfalls of each outcome was encouraged, and panelists subsequently voted anonymously on each item to either "include in the COS," "do not include in the COS," or "unsure." Items receiving $\geq$70% of votes in the "include in the COS" category and $<$15 of votes in the "do not include in the COS" category were ratified for inclusion in the final COS.

Advantages, disadvantages, and points of consideration raised by the ratification panel for each outcome domain are summarized in Table 1. The major topics of discussion captured in the meeting included:

1. Histology end points: whether the peak eosinophil count should be reported using high-power field vs adjusted per mm^2, appropriate thresholds for histologic remission ($\leq$6 eosinophils/high-power field vs $<$15 eosinophils/high-power field), and utility of the EoE Histology Scoring System in RCTs vs observational studies

2. Endoscopy end points: most appropriate scoring conventions for the EREFS (scoring from 0 to 8 vs from 0 to 9), thresholds for endoscopic remission based on total score or inflammatory vs fibrotic subscore

3. Symptom-based and QoL end points: most appropriate instrument for measuring patient-reported symptoms in RCTs vs observational studies, instrument recall period and consistency with regulatory requirements, appropriate language that should be used to query dysphagia, use of disease-specific vs general QoL measures, and use of pediatric symptom severity scores and applicability across pediatric populations

After discussion, 33 outcomes were ratified in the COS and are presented in the accompanying consensus recommendations.

Table 1. Considerations Discussed at the COREOS Core Outcome Set Ratification Meeting

Outcome domain	Considerations	Discussion points and major conclusions
Histology	The peak eosinophil count expressed either as eosinophils/hpf or as eosinophils/mm^2	The field should move toward standardizing assessment using per mm^2 to account for differences in microscope ocular field size Expressing per hpf improves comparability against historical studies, which have almost exclusively used hpf Both measures should be presented in RCTs and observational studies, although expressing eosinophils/mm^2 may not be feasible in all observational studies
	Histologic remission defined either as $\leq$6 or $\leq$15 eosinophils/hpf	The threshold of $<$15 eosinophils/hpf was preferred due to comparability with historical studies The threshold of $<$15 eosinophils/hpf is discordant with recommendations from the US Food and Drug Administration, but the threshold of $\leq$6 eosinophils/hpf may be too stringent to achieve, especially for mechanisms of action that are not eosinophil-specific
	The use of EoEHSS to assess histologic disease activity	The EoEHSS measures other items beyond peak eosinophil density and has demonstrated reliability and responsiveness. It should be used in RCTs to capture the full spectrum of histologic manifestations The EoEHSS may not be feasible to evaluate in all observational studies
Endoscopy	The use of EREFS in RCTs and observational studies	The EREFS captures the endoscopic features of the disease and has been shown to be reliably assessed by both expert and nonexpert endoscopists. It should be used in both RCTs and observational studies
	The EREFS scoring as either 0–8 or 0–9, based on the most severe grade of features	The difference lies in scoring of furrows (as absent vs present for 0–8 scoring or as 0 (none), 1 (mild), 2 (severe) for 0-9 scoring); 0–8 scoring was preferred in the Delphi. Although the data are lacking, 0–9 scoring may hypothetically be more responsive to change and can be collapsed to 0–8 scoring in post-hoc analyses
	Endoscopic remission is defined by an EREFS score $\leq$2	Current studies suggest that this is the most appropriate threshold for endoscopic remission (either scored as the total EREFS or scoring using only the inflammatory sub-score)
Symptoms and Quality of Life	The use of DSQ and EEsAI	Both instruments have undergone an important degree of validation. The DSQ uses daily recall, which is congruent with US Food and Drug Administration recommendations, whereas the EEsAI uses a 7-d recall period. None of the current instruments captures the majority of symptoms or strategies for dealing with or avoiding dysphagia episodes The DSQ and EEsAI should be used in RCTs Both instruments are proprietary, which may limit their use, and were likely chosen from the multitude of PRO instruments, because they were the first such instrument to be validated and historically most used These instruments for measuring symptoms may not be feasible to apply in all observational studies Additional validation of PRO measures in EoE is a research priority
	The language used to define dysphagia	Both trouble swallowing and delayed/slow passage of food were considered appropriate to query dysphagia in adults with EoE While food being stuck was considered appropriate in the Delphi panel, it was excluded during ratification due to concerns that it more accurately represents long- rather than short-lasting episode of food impaction. Evidence for this based on qualitative work is limited The meaning of specific terms for capturing dysphagia symptoms likely varies by language

Table 1. Continued

Outcome domain	Considerations	Discussion points and major conclusions
	The use of the PEESS, version 2.0	The PEESS, version 2.0 is the only instrument that has undergone some degree of validation in pediatric EoE Although the diverse symptom capture reflects the broad nature of symptom presentation in children, capturing many types of symptoms poses a challenge in RCT design (resulting in potentially heterogeneous populations being enrolled in an RCT, and uncertainty of generalizability across all pediatric age groups). Appropriateness of 30-d recall period for use in RCTs remains a cause for concern Additional research in validating pediatric EoE PROs is required
	The use of validated measures to assess QoL	The EoE-QoL-A for adult patients and PedsQL (both child self-report and proxy/parent-report) should be used in RCTs These QoL instruments may not be feasible to apply in all observational studies Additional research is required to compare general QoL measures vs disease-specific QoL measures in EoE

DSQ, Dysphagia Symptoms Questionnaire; EoEHSS, EoE Histology Scoring System; EoE-QoL-A, Adult Eosinophilic Oesophagitis Quality of Life Questionnaire; EEsAI, EoE Activity Index; hpf, high-power field; PEESS, Pediatric EoE Symptom Score; PedsQL, Pediatric Quality of Life; PRO, patient-reported outcome.

Conclusions and Future Directions

In summary, the COREOS collaborators developed an internationally guided, multidisciplinary COS for use in pharmacologic and dietary therapeutic studies in pediatric and adult patients with EoE. The ratification meeting was concluded with a discussion around strategies to disseminate these recommendations. The aim was to encourage adoption of the COS to reduce heterogeneity in end-point assessment, minimize risk of reporting bias, and improve the quality of evidence synthesis by facilitating valid cross-study comparisons. The COREOS collaborators also recognized that the end points used in EoE studies have evolved rapidly over the past 2 decades. Although this is the first version of a COS in EoE, the ongoing work in developing and validating instruments for measuring disease activity will likely shape future iterations. As the COREOS collaborators agreed on only the minimum core set of outcomes that should be measured, investigators are encouraged to continue exploring additional end points of interest. Finally, the COREOS collaborators acknowledged that the field is on the cusp of many exciting advances, particularly with multiple agents targeting different mechanisms of action in development. Taken together, the group decided to reconvene to update the COS in 2024.

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Correspondence
Address correspondence to: Ekaterina Safroneeva, PhD, Institute of Social and Preventive Medicine, University of Bern, Mittelstrasse 43, Bern 3012, Switzerland. e-mail: ekaterina.safroneeva@ispm.unibe.ch.

Acknowledgments
The COREOS Collaborators: Christopher Ma (Division of Gastroenterology and Hepatology, Departments of Medicine and Community Health Sciences, University of Calgary, Calgary, Alberta, Canada and Alimentiv Inc, London, Ontario, Canada); Alain M. Schoepfer (Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland); Evan S. Dellon (Center for Esophageal Diseases and Swallowing, Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC); Albert J. Bredenoord (Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, Amsterdam, The Netherlands); Mirna Chehade (Mount Sinai Center for Eosinophilic Disorders, Icahn School of Medicine at Mount Sinai, New York, NY); Margaret H. Collins (Division of Pathology and Laboratory Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH); Brian G. Feagan (Alimentiv Inc, London, Ontario, Canada, Department of Medicine, Western University, London, Ontario, Canada; and Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada); Glenn T. Furuta (Digestive Health Institute, Children's Hospital Colorado, Gastrointestinal Eosinophilic Diseases Program, Section of Pediatric Gastroenterology, Hepatology and Nutrition, University of Colorado School of Medicine, Aurora, CO); Sandeep K. Gupta (Division of Pediatric Gastroenterology, Hepatology and Nutrition, Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, IN); Ikuo Hirano (Division of Gastroenterology and Hepatology, Northwestern University, Feinberg School of Medicine, Chicago, IL); Vipul Jairath (Alimentiv Inc, London, Ontario, Canada, Department of Medicine, Western University, London, Ontario, Canada; and Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada); David A. Katzka (Division of Gastroenterology, Mayo Clinic, Rochester, MN); Rish K. Pai (Department of Pathology and Laboratory Medicine, Mayo Clinic Arizona, Scottsdale, AZ); Marc E. Rothenberg (Division of Allergy and Immunology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH); Alex Straumann (Department of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland); Seema S. Aceves (Division of Allergy Immunology, University of California, San Diego, Rady Children's Hospital, San Diego, CA); Jeffrey A. Alexander (Division of Gastroenterology, Mayo Clinic, Rochester, MN); Nicoleta C. Arva (Department of Pathology and Laboratory Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Feinberg School of Medicine, Chicago, IL); Dan Atkins (Gastrointestinal Eosinophilic Diseases Program, Children's Hospital of Colorado, Section of Allergy and Immunology, University of Colorado School of Medicine, Aurora, CO); Luc Biedermann (Department of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland); Carine Blanchard (Nestlé Institute of Health Sciences, Nestlé Research, Société des Produits Nestlé, Vevey, Switzerland); Antonella Cianferoni (Division of Allergy and Immunology, Department of Pediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine at University of Pennsylvania, Philadelphia, PA); Constanza Ciriza de los Rios (Department of Gastroenterology, Hospital Clínico San Carlos, Universidad Complutense, Instituto de Investigación Sanitaria San Carlos (IdISSC), Madrid, Spain); Frederic Clayton (Department of Pathology, The University of Utah, Huntsman Cancer Hospital, Salt Lake City, UT); Carla M. Davis (Immunology, Allergy, and Retrovirology Section of the Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX); Nicola de Bortoli (Department of Translational Research and New Technology in Medicine and Surgery, Division of Gastroenterology, University of Pisa, Cisanello Hospital, Pisa, Italy); Jorge A. Dias (Pediatric Gastroenterology, Centro Hospitalar S. João, Porto, Portugal); Gary W. Falk (Division of Gastroenterology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA); Robert M. Genta (Inform Diagnostics, Irving, TX and Department of Pathology, Baylor College of Medicine, Houston, TX); Gisoo Ghaffari (Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Pennsylvania State College of Medicine, Hershey, PA); Nirmala Gonsalves (Division of Gastroenterology and Hepatology, Northwestern University, Feinberg School of Medicine, Chicago, IL); Thomas Greuter (Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland, and Department of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland); Russell Hopp (University of Nebraska Medical Center, Children's Hospital and Medical Center, Omaha, NE); Karen S. Hsu Blatman (Section of Allergy and Clinical Immunology, Dartmouth-Hitchcock Medical Center, Dartmouth Geisel School of Medicine, Hanover, NH); Elizabeth T. Jensen (Wake Forest University School of Medicine, Department of Epidemiology and Prevention, Winston-Salem, NC); Doug Johnston (Asthma and Allergy Specialists, Charlotte, NC); Amir F. Kagalwalla (Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL and Division of Gastroenterology, Department of Pediatrics, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL); Helen M. Larsson (Department of ENT, Head and Neck Surgery, NÄL Medical Centre, Trollhättan, Sweden); John Leung (Division of Gastroenterology, Tufts Medical Center, Boston, MA); Hubert Louis (Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium); Joanne C. Masterson (Department of Biology, Maynooth University, Kildare, Ireland); Calies Menard-Katcher (Digestive Health Institute, Children's Hospital Colorado, Gastrointestinal Eosinophilic Diseases Program, Section of Pediatric Gastroenterology, Hepatology and Nutrition, University of Colorado School of Medicine, Aurora, CO); Paul A. Menard-Katcher (Division of Gastroenterology and Hepatology, University of Colorado Anschutz Medical Campus, Aurora, CO); Fouad J. Moawad (Division of Gastroenterology and Hepatology, Scripps Clinic, La Jolla, CA); Amanda B. Muir (Center for Pediatric Eosinophilic Diseases, Division of Gastroenterology and Hepatology and Nutrition, Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA); Vincent A. Mukkada (Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH); Roberto Penagini (Department of Pathophysiology and Transplantation, University of Milano, Milano, Italy and Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy); Robert D. Pesek (Division of Allergy and Immunology, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, AR); Kathryn Peterson (Division of Gastroenterology, The University of Utah, Salt Lake

City, UT); Philip E. Putnam (Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH); Alberto Ravelli (University Department of Pediatrics, Children's Hospital - Spedali Civili, Brescia, Italy); Edoardo V. Savarino (Department of Surgery, Oncology and Gastroenterology, DiSCOG, University of Padua, Padua, Italy); Christoph Schlag (II. Medizinische Klinik, Klinikum Rechts der Isar, Technische Universität München, München, Germany); Philipp Schreiner (Department of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland); Dagmar Simon (Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland); Thomas C. Smyrk (Department of Pathology, Mayo Clinic, Rochester, MN); Jonathan M. Spergel (Division of Allergy and Immunology, Department of Pediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine at University of Pennsylvania, Philadelphia, PA); Tiffany H. Taft (Division of Gastroenterology and Hepatology, Northwestern University, Feinberg School of Medicine, Chicago, IL); Ingrid Terreehorst (Department of ENT, Amsterdam University Medical Centre, Amsterdam, The Netherlands); Tim Vanuytsel (Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium and Translational Research in Gastrointestinal Disorders, KU Leuven, Leuven, Belgium); Carina Venter (Gastrointestinal Eosinophilic Diseases Program, Children's Hospital of Colorado, Section of Allergy and Immunology, University of Colorado School of Medicine, Aurora, CO); Mario C. Vieira (Department of Pediatrics, Pontifical Catholic University of Paraná and Center for Pediatric Gastroenterology, Hospital Pequeno Príncipe, Curitiba, Brazil); Michael Vieth (Institute for Pathology, Klinikum Bayreuth, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany); Berber Vlieg-Boerstra (OLVG Hospital, Department of Pediatrics, Amsterdam, The Netherlands); Ulrike von Arnim (Department of Gastroenterology, Hepatology and Infectious Diseases, University Hospital, Magdeburg, Germany); Marjorie M. Walker (Centre of Research Excellence in Digestive Health, University of Newcastle, NSW, Australia); Joshua B. Wechsler (Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL); Philip Woodland (Wingate Institute of Neurogastroenterology, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK); John T. Woosley (Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC); Guang-Yu Yang (Division of Pathology, Northwestern University, Feinberg School of Medicine, Chicago, IL); Noam Zevit (Institute of Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, Petach Tikva, Israel and Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel); and Ekaterina Safroneeva (Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland).

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