

# Advancing patient care through the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR)



Seema Aceves, MD, PhD,<sup>a</sup> Margaret H. Collins, MD,<sup>b</sup> Marc E. Rothenberg, MD, PhD,<sup>c</sup> Glenn T. Furuta, MD,<sup>d</sup> and Nirmala Gonsalves, MD,<sup>e</sup> on behalf of the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR)\* La Jolla, Calif, Cincinnati, Ohio, Aurora, Colo, and Chicago, Ill

Recent advances in rare disease research are accelerated by the work of consortia that have been supported by the National Institutes of Health. Development of such consortia rely on multidisciplinary relationships and engagement with patient advocacy groups, as well as the National Institutes of Health and industry and academic partners. In this rostrum we present the development of such a process that focuses on eosinophilic gastrointestinal diseases. Principal investigators, patient advocacy groups, research assistants, and trainees work together to perform natural history studies that promote clinical trial readiness tools, conduct clinical trials, train a new generation of investigators, and perform innovative pilot studies. (*J Allergy Clin Immunol* 2020;145:28-37.)

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The gastrointestinal tract is a series of 4 organs separated by a series of sphincters that are defined by unique structures and specific functions. The gastrointestinal tract is normally hypoxic, regularly encounters a myriad of food particles, and houses the most concentrated microbial commensal flora compared with that of other regions of the body. Within this diverse cellular and metabolic environment quietly resides the bilobed granulated leukocyte: the eosinophil. Eosinophil levels increase along the length of the gastrointestinal tract, going from none in the

## Abbreviations used

APFED:	American Partnership for Eosinophilic Disorders
CEGIR:	Consortium of Eosinophilic Gastrointestinal Disease Researchers
COM:	Clinical outcome metric
EC:	Eosinophilic colitis
EG:	Eosinophilic gastritis
EGE:	Eosinophilic gastroenteritis
EGID:	Eosinophilic gastrointestinal disease
EoE:	Eosinophilic esophagitis
EREFS:	EoE Reference Score
GERD:	Gastroesophageal reflux disease
NIH:	National Institutes of Health
OMEGA:	Outcome Metrics for Eosinophilic Gastrointestinal Diseases Across the Ages
PAG:	Patient advocacy group
PPI:	Proton pump inhibitor
PRO:	Patient-reported outcome
RDCRN:	Rare Diseases Clinical Research Network
TIGERS:	The International Gastrointestinal Eosinophil Researchers

esophagus to the maximal number within the colon. A few studies have determined the “normal” numbers of gastrointestinal eosinophils in mucosal and full-thickness biopsy specimens taken from adults and children without identifiable gastrointestinal inflammation.<sup>1,2</sup> Because eosinophils normally reside in the

From <sup>a</sup>the Division of Allergy Immunology, University of California, San Diego, and Rady Children’s Hospital, San Diego; the Divisions of <sup>b</sup>Pathology and <sup>c</sup>Allergy and Immunology, Department of Pediatrics, Cincinnati Children’s Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine; <sup>d</sup>the Digestive Health Institute, Children’s Hospital Colorado, Gastrointestinal Eosinophilic Diseases Program, University of Colorado School of Medicine, Aurora; and <sup>e</sup>the Division of Gastroenterology, Northwestern University Feinberg School of Medicine, Chicago.

\*The list of participants is provided in the acknowledgements section.

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Corresponding author: Glenn T. Furuta, MD, Digestive Health Institute, Children’s Hospital Colorado, Gastrointestinal Eosinophilic Diseases Program, University of Colorado School of Medicine, 13123 E 16th Ave, Aurora, CO 80016. E-mail: [Glenn.Furuta@childrenscolorado.org](mailto:Glenn.Furuta@childrenscolorado.org).

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mucosa, it is likely that they play a role in innate host defense. Although this has yet to be fully determined, evidence is emerging that gastrointestinal eosinophils have the capacity to regulate local immunoglobulin production, intestinal microbial content, epithelial barrier function, and killing of intraluminal parasites.<sup>3</sup>

## DEFINING EOSINOPHILS' PATHOLOGIC ROLE IN THE GASTROINTESTINAL TRACT IS CHALLENGING

In 1937, the German surgeon Kaisjer described key features of selected, full-thickness, eosinophil-rich surgical resections of gastrointestinal tissues and thus provided a unique view of patients with gastrointestinal symptoms and a previously unrecognized type of inflammation.<sup>4</sup> Over the next 50 years and with the advent of flexible gastrointestinal endoscopy and procurement of mucosal biopsy specimens, case series provided further documentation of the clinical features reported by patients who were affected by dense gastrointestinal eosinophilia. Patients' symptoms and endoscopic findings were nonspecific, and histologic features were characterized primarily by an increased density of eosinophils, with numbers of eosinophils provided only intermittently. No other eosinophil-promoting diseases, such as parasites, cancer, or inflammatory bowel diseases, were identified, and therefore these patients were described as having an eosinophilic gastrointestinal disease (EGID).<sup>5,6</sup>

Because the gastrointestinal tract normally contains eosinophils, the major problem in the descriptions of these patients was determining what defined an abnormal number and distribution of eosinophilia; whether other features of the eosinophilia, such as degranulation, were critical to assess; and, perhaps as importantly, whether other inflammatory features were present in epithelial surfaces or submucosal spaces. Factors that contributed to difficulties in assessing these issues include the fact that EGIDs are rare, diagnoses required costly and time-consuming endoscopic procedures with sedation, biopsies captured a limited amount of the mucosal surface, densely packed eosinophils were difficult to count, states of degranulation were challenging to quantify, and the presence of extracellular granules could result from mechanical disruption of eosinophils. In fact, a trend toward overdiagnosis ensued. Attempts to characterize patients with EGID were further stymied because peripheral and stool biomarkers did not always represent local gastrointestinal mucosal activities. Thus in many ways and for numerous reasons the enigmatic eosinophil escaped deeper understanding in health and disease.

## EGIDs ARE INCREASINGLY RECOGNIZED

The increasing availability of endoscopic procedures has augmented our knowledge about EGIDs, and the diagnosis of EGID has been made more frequently.<sup>6</sup> Patients with gastrointestinal symptoms, such as heartburn, abdominal pain, or diarrhea, received the common diagnoses of gastroesophageal reflux disease (GERD), peptic disease, or irritable bowel syndrome. However, if their condition did not improve with standard therapy, they underwent diagnostic endoscopic assessment. Some of these patients were found to have mucosal biopsy specimens with increased eosinophil numbers. After exclusion of other causes of the histologic findings, a diagnosis of eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE; eosinophilia involving multiple segments of the intestine), or eosinophilic colitis (EC) was made.

Because eosinophilia in industrialized countries is associated with allergy and initial pediatric studies of EoE demonstrated food antigens as disease triggers, collaboration with allergists increased. Although the initial goal was primarily to identify triggering food antigens, the current role of the allergist in patients with EoE is to provide EoE management, define potential EoE triggers, and control concurrent atopic diseases that can exacerbate EoE.<sup>7-9</sup>

## PROGRESS WITH EoE

Although progress can never occur quickly enough for patients, the development of EoE diagnostic criteria and implementation of EoE treatment paradigms has transpired at a remarkable pace. Before 1995, EoE was a clinical rarity limited primarily to important case series.<sup>10,11</sup> Over the course of the next decade, reports published by adult and pediatric allergists, radiologists, gastroenterologists, and pathologists provided important insights into key clinical features and potential pathogenic mechanisms. Collaborative works coalesced in a working group called The International Gastrointestinal Eosinophil Researchers (TIGERS), which was supported by the Bunning family, and acted as an incubator to address clinical needs. A yearlong TIGERS project that was performed in collaboration with the American Gastroenterological Association and North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition resulted in publication of the first EoE diagnostic criteria in 2007.<sup>12</sup> In 2008, the advocacy group the American Partnership for Eosinophilic Disorders (APFED; <https://apfed.org>) succeeded in gaining approval of International Classification of Diseases codes for EGIDs. Retrospective clinical studies identified innovative approaches, including clinical assessment tools and treatment, whereas basic research determined pathogenetic pathways and novel therapeutic targets. Together, these studies encouraged development of clinical outcome metrics (COMs) and eventually prospective clinical trials.

This progress of the last 2 decades was sustained because of many factors (Table I),<sup>13</sup> not the least of which were relationships formed between collaborative researchers and patient advocates who willingly and intentionally engaged with each other to develop and execute a plan to improve the lives of patients affected by EoE. In these efforts patients of all ages, advocates from different backgrounds, pediatric and adult researchers representing different specialties, industry partners, a number of academic societies, and the National Institutes of Health (NIH) have worked together to develop diagnostic criteria, identify COMs, and perform clinical trials.<sup>14</sup>

## REMAINING CHALLENGES IN STUDYING EoE AND OTHER EGIDs

The rarity of EGIDs creates at least 2 problems related to advancing care. First, as part of their daily practice, clinicians might not recognize EGIDs in a timely fashion; in fact, some studies indicate that there can be a diagnostic delay from symptom onset to diagnosis of up to 6 years.<sup>15,16</sup> This delay limits the ability to offer proper consultation, provide appropriate treatment, and prevent complications. Second, therapeutic studies might experience slow enrollment because of the rarity of EGIDs, the burden of a number of endoscopic procedures, the distance and time needed to travel to clinical sites, and the lack of interest in enrolling in a placebo-controlled study. To combat these issues,

**TABLE I.** Factors contributing to CEGIR progress

<ul style="list-style-type: none"> <li>● Developing longstanding collegial relationships between investigators based on mutual respect and long-term vision</li> <li>● Creating a multidisciplinary approach to research that involves allergists, gastroenterologists, pathologists, dietitians, epidemiologists, clinician researchers, basic researchers, and statisticians to understand different aspects of the EGIDs</li> <li>● Involving pediatric and adult specialists to understand the natural history of EGIDs</li> <li>● Engaging with multiple PAGs to increase awareness of the patient's perspective and the importance of research and to develop patient-friendly research</li> <li>● Building close relationships with academic societies and institutional leadership to promote research and garner support</li> <li>● Partnering with NIH experts to carry out cooperative research</li> <li>● Leveraging the expertise of the RDCRN and the 20 associated consortia</li> <li>● Maintaining regular and frequent communication with NIH, NIAID, NIDDK, and NCATS program officials to conduct research in a robust fashion</li> <li>● Partnering with industry to develop and execute cutting-edge research studies</li> <li>● Fostering relationships with the US Food and Drug Administration, Department of Health and Human Services, and governmental officials to educate about EGIDs and understand regulatory and compliance aspects of therapeutics developments<sup>13</sup></li> </ul>
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NCATS, National Center for Advancing Translational Sciences; NIAID, National Institute of Allergy and Infectious Diseases; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases.

studies often require large numbers of enrolling sites, and this is associated with increased financial startup costs. In addition, the same patients can be repeatedly approached for various new studies.

Although patient-reported outcomes (PROs) and COMs have been developed for EoE, no validated metrics currently exist for EG, EGE, and EC. Correlation of PROs and COMs with histologic features and eosinophil numbers continues to be an area of investigation. Furthermore, developing better methods to detect eosinophils in gastrointestinal tissues, identifying specific peripheral biomarkers that relate to tissue eosinophilia, and defining the pathogenetic role that eosinophils have in these diseases are areas of clinical and research needs. EG, EGE, and EC diagnostic criteria have not been fully vetted, and in some situations this has hindered clinical trials in patients with non-EoE EGIDs.

Finally, the pace of basic studies that will identify pathogenic mechanisms and therapeutic targets has been slowed because of limited numbers of animal models and eosinophil cell lines, challenges in isolating and studying human eosinophils, and practical difficulties related to procuring intestinal samples from patients with EGIDs and control subjects. The development of novel model systems, including organoids and *ex vivo* functional human mucosal platforms, will hopefully lead to novel ways to study EGIDs.<sup>17</sup>

## DEVELOPMENT OF A CONSORTIUM TO IMPROVE CARE OF PATIENTS WITH EGIDs

For treatments to effectively reach patients with EGIDs, several different milestones need to be achieved. Increasing awareness of EGIDs is imperative so that affected patients can receive diagnosis and treatments and natural history can be tracked.

**TABLE II.** Clinically relevant CEGIR products

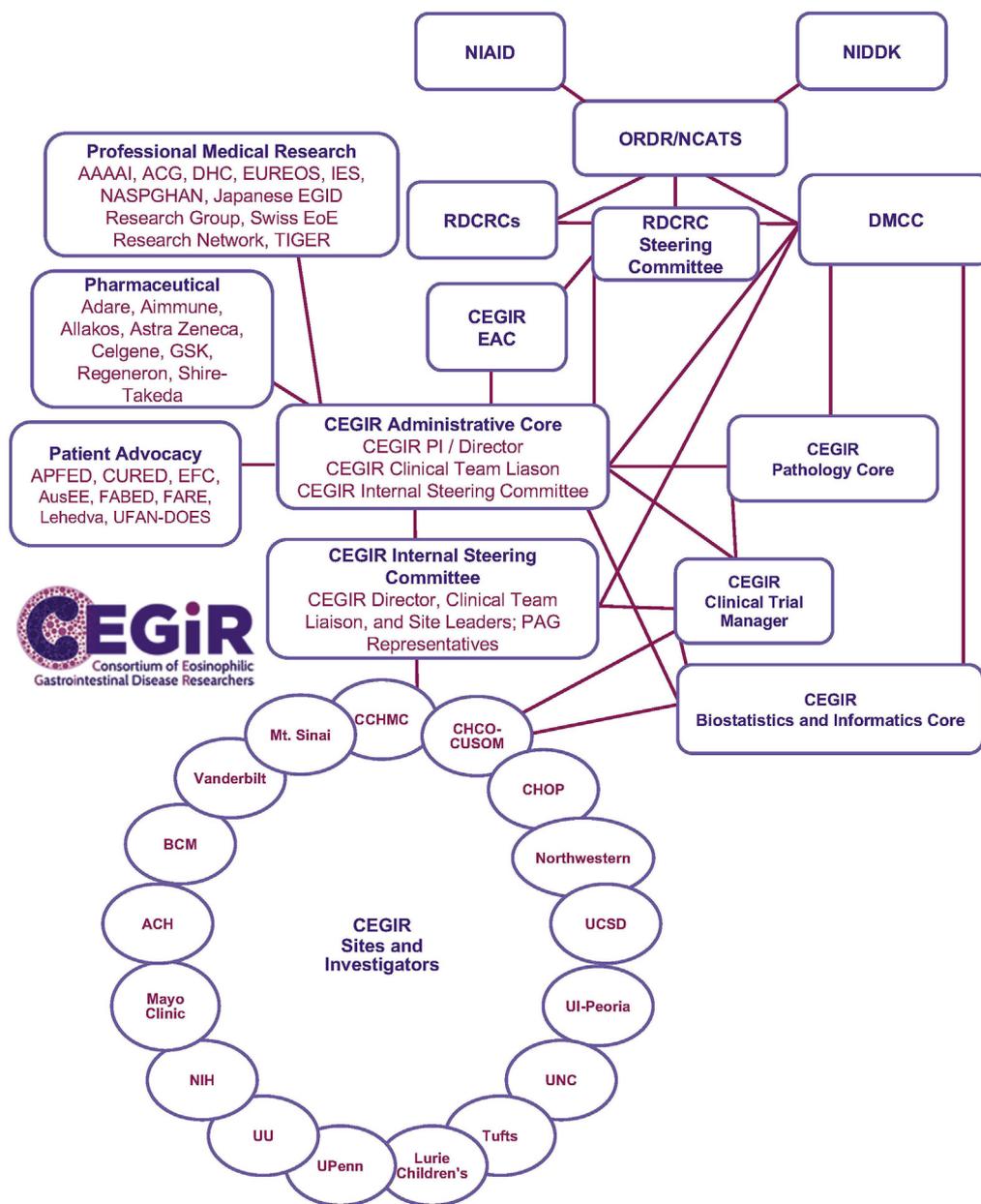
Major advances	Benefit of advance
Development and validation of EoE histologic scoring system	Extends pathologic analysis beyond eosinophil counts alone; provides tool for clinical trials
Whole slide imaging of pathology slides	Allows convenient image transfer, offsite microscopy, and central pathologic analyses
Identification of EoE endotypes	Stratifies patients into clinically significant and potentially therapeutically distinct subgroups
Validation and refinement of PROs	Allows quantitative assessment of patient well-being and parent-by-proxy monitoring
Refinement of disease characteristics	Largest analyses of EC, the rarest form of EGID, uncovering new clinical associations
Development of EG diagnostic panel and blood panel <sup>73</sup>	Assesses disease pathogenesis, defines molecular-clinical and endoscopic correlates, and provides opportunity for noninvasive biomarkers

This relies not only on educating established health care professionals but also educating new trainees and students. Developing diagnostic guidelines, creating PROs and COMs, identifying therapeutic targets, and completing clinical trials are major achievements that must be met for patients to receive better care.

To address the needs of patients affected by rare diseases, the NIH and its Office of Rare Diseases Research developed the Rare Diseases Clinical Research Network (RDCRN) by using a cooperative U54 grant mechanism to accelerate the completion of therapeutic trials. The RDCRN has been composed of a select number of consortia, each focused on a distinct set of at least 3 related rare diseases. Required elements for each consortium included a natural history study, a clinical trial study, pilot studies, a training module, and partnership with at least 1 patient advocacy group (PAG).

The RDCRN funded the Consortium for Eosinophilic Gastrointestinal Disease Researchers (CEGIR) in 2014 (CEGIR1, 2014-2019) and renewed this funding in 2019 (CEGIR2, 2019-2024; <https://www.rarediseasesnetwork.org/cms/CEGIR>). NIH funding for CEGIR is derived from the National Center for Advancing Translational Sciences, National Institute of Allergy and Infectious Diseases, and National Institute of Diabetes, Digestive, and Kidney Diseases. In addition to involving 18 academic institutions in the United States, 1 collaborative site in Switzerland, and 3 main PAGs, CEGIR collaborates with a number of professional organizations and commercial entities and has an external advisory board. In contrast to previous publications, this rostrum focuses on some of the key elements needed to develop a research consortium.<sup>18-20</sup> Other CEGIR-related reviews have focused on the overall structure of CEGIR, as laid out in Fig 1, and on the working logistics and products.

CEGIR aims to address 3 concerns (see Table II). First, because these eosinophilic diseases are rare and relatively newly recognized, few validated COMs exist, and knowledge



**FIG 1.** Organizational overview of CEGIR. The RDCRN (comprising the Rare Diseases Clinical Research Consortia [RDCRCs], RDCRC Steering Committee, and Data Management Coordinating Center [DMCC]), CEGIR Administrative Core, CEGIR Internal Steering Committee, and CEGIR External Advisory Committee (EAC) provide oversight of CEGIR. Vertical lines represent direct reporting, and horizontal and diagonal lines represent collaboration or direct reporting. The CEGIR Principal Investigator and Director is Marc Rothenberg, MD, PhD, and the CEGIR Clinical Team Liaison is Glenn T. Furuta, MD. The CEGIR Pathology Core members are as follows, with italics indicating leadership: *Margaret Collins, MD*, *Nicoletta Arva, MD*, PhD, and *Guang-Yu Yang, MD*. The CEGIR Biostatistics and Informatics Core members are as follows, with italics indicating leadership: *Lisa Martin, PhD*, *Elizabeth Jensen, MPH, PhD*, and *Zhaoxing Pan, PhD*. The Site Abbreviations are as follows: *ACH*, Arkansas Children's Hospital; *BCM*, Baylor College of Medicine; *CCHMC*, Cincinnati Children's Hospital Medical Center; *CHCO*, Children's Hospital Colorado; *CHOP*, Children's Hospital of Philadelphia; *CUSOM*, Colorado University School of Medicine; *Lurie Children's*, Lurie Children's Hospital of Chicago; *Mt. Sinai*, Icahn School of Medicine at Mount Sinai; *Northwestern*, Northwestern University; *Tufts*, Tufts Medical Center; *UCSD*, University of California, San Diego; *UI-Peoria*, University of Illinois College of Medicine at Peoria; *UNC*, University of North Carolina; *UPenn*, University of Pennsylvania; *UU*, University of Utah; and *Vanderbilt*, Vanderbilt University. The site Investigators are as follows, with italics designating CEGIR Site Leaders: *ACH*, *Robert Pesek, MD*; *BCM*, *Carla McGuire Davis, MD*, and *Anthony Olive, MD*; *CCHMC*, *Marc Rothenberg, MD, PhD*, *Vince Mukkada, MD*, *J. Pablo Abonia, MD*, *Philip Putnam, MD*, and *Ting Wen, MD, PhD*; *CHCO*, *Glenn T. Furuta, MD*, *Dan Atkins, MD*, and *Calies Menard-Katcher, MD*; *CHOP*, *Jonathan Spergel, MD*, and *Amanda Muir, MD*; *CUSOM*, *Paul Menard-Katcher, MD*; *Lurie Children's*, *Joshua Wechsler, MD*, *Barry Wershil, MD*, and *Amir Kagalwalla, MD*; *Mt. Sinai*, *Mirna Chehade, MD*; *Northwestern*, *Ikuo Hirano, MD*, and *Nirmala Gonsalves, MD*; *NIH*, *Amy Kliion, MD*, and *Panwez Khoury, MD*; *Tufts*, *John Leung, MD*, and *Peter Bonis, MD*; *UCSD*, *Seema Aceves, MD, PhD*; *UI-Peoria*, *Sandeep Gupta, MD*; *UNC*, *Evan Dellon, MD*; *UPenn*, *Gary Falk, MD*; *UU*, *Kathryn Peterson, MD*; *Vanderbilt*, *Girish Hiremath, MPH, MD*.

concerning the natural history of EGIDs is limited. Thus the Outcome Metrics for Eosinophilic Gastrointestinal Diseases Across the Ages (OMEGA) was designed to meet these concerns directly and to address the concept of clinical trial readiness. During CEGIR1, OMEGA enrolled nearly 900 patients from across the country who had EGIDs, including EoE, EG, and EC, and tracked their clinical, endoscopic, histologic, and molecular features. To date, OMEGA has allowed development of novel COMs for EG, been instrumental in the development of histologic and endoscopic COMs for EoE, and defined molecular endotypes of EoE and EG.<sup>21,22</sup> During CEGIR2, OMEGA will continue to follow patients to further understand the natural history of EGIDs and develop diagnostic criteria for EG, EGE, and EC; establish COMs for EG, EGE, and EC; and provide deeper understanding regarding the molecular underpinnings of these EGIDs.

Second, the rarity of EGIDs and the lack of adequate attention to it in most medical training has resulted in a lack of recognition of these diseases and a limited number of providers who have significant clinical experience with EGIDs. To address these concerns, the CEGIR1 Training (Career Development) Program developed a robust mentoring and research experience for junior faculty trainees, who presented 58 abstracts and posters, published 23 articles, and accrued \$4.6 million in grant funding. Selection of trainees was competitive and based not only on credentials but also location of practice to provide training in areas of geographic need. In CEGIR2 the Career Enhancement Core will further extend this training with medical school and postgraduate trainees, with an emphasis on virtual training and face-to-face mentoring.

Third, because EGIDs are early in their research history, novel and innovative pilot projects are needed to advance care and knowledge. During CEGIR1, pilot studies of the Pilot/Demonstration Clinical Research Program examined the microbiome of EGIDs, effects of a potential anti-fibrotic agent (losartan) in patients with EoE, kinetics of mucosal eosinophilia during food reintroduction with transnasal endoscopy, and effect of an elemental diet on EG. The CEGIR2 Pilot-Feasibility Core will select pilots that will use data accrued by OMEGA, provide rapid and high-impact findings, and/or promote engagement with PAGs.

## VALUE OF THE MULTIDISCIPLINARY APPROACH IN CEGIR

The EGID field has advanced relatively rapidly because of the close collaboration of physician-scientists who are closely aligned with patient advocates.<sup>14,20,23-25</sup> In this realm CEGIR is composed of a unique and extensive network of pediatric and adult allergists, gastroenterologists, pathologists, statisticians, an epidemiologist, and advocates from across the world.<sup>18,19</sup> All have taken active roles within CEGIR, and successful execution of the mission of CEGIR is done with proper synergy with all the invested disciplines. Each member of the consortium has an important role, and successful outcomes have been accomplished with this much needed balance. Below is a summary of how each has contributed to advance EGID research.

## ALLERGISTS

Pediatric and adult allergists from numerous different institutions share in contributing their expertise to CEGIR. Their

expertise and dedication have provided key guidance in developing novel treatments and addressing important questions related to atopy. In addition, leadership for CEGIR has been shared between disciplines to ensure that the needs of various specialties are addressed.

## Clinical effects

Because EoE is a disease with type 2 allergen-mediated inflammation, allergists have an integral and vital role in clinical care.<sup>8-10</sup> First, it is not unusual that an allergist might be the first to suspect EGID in a patient. As a part of the highly atopic patient's medical history and review of symptoms, subtle or overt gastrointestinal symptoms might be identified and thus prompt a referral to a gastroenterologist for evaluation and potential endoscopy.

Second, when a diagnosis of EGID is confirmed, treatments with diet elimination and topical steroids are instituted, and execution of this plan is best served often by an allergist. Because of the clinical challenges posed by EGIDs, including the interplay between multiple atopic diatheses in the same person and immunologic complexities, clinical collaboration of allergists with gastroenterologists creates benefit for patients and families. For instance, a toddler with asthma, atopic dermatitis, EoE, peripheral eosinophilia, and adrenal insufficiency who is receiving topical steroids for all their diseases will require close communication between specialties on how to successfully manage the intricacies of each disease and its complications.

Finally, identifying and treating comorbid diseases that promote healing of all affected mucosal surfaces can only benefit patient healing and potentially help with maintenance of remission. Within CEGIR, considering these types of issues allows for increasing subject enrollment into trials, a focus on understanding how allergic manifestations and treatments can be managed, and collaborative studies to unravel the meaning of atopic signals.

## Research

Clinical and basic scientists who focus on atopic diseases have long sought answers on how to measure disease activity associated with, define the underlying mechanisms of, and treat patients affected by T<sub>H</sub>2- and eosinophil-related diseases. Their efforts led to the development of EoE-related COMs, studies addressing the utility of skin testing for suspected EoE food allergens, therapeutic trials identifying dietary approaches to EoE treatment, and discovery of the novel use of a topical steroid preparation for EoE.<sup>21,26-29</sup> Basic studies identified EoE-related genes, molecular pathways, and therapeutic targets for EoE and EG and developed novel research platforms in the form of diagnostic panels.<sup>30-35</sup>

One of the most significant contributions made by allergists to the EGID field relates to studies examining the role of biologics targeting molecules related to eosinophilia. For instance, use of anti-IL-5, which is approved for severe asthma, and IL-4/IL-13 receptor blockade with dupilumab, which is approved for severe asthma and eczema, has been trialed in patients with EoE.<sup>36-38</sup>

In addition, a number of key clinical features and research topics related to atopy require greater understanding. Is there a role for skin and blood testing for food allergens that can evoke EoE? How can we test for EoE-related food allergens? What is the effect of aeroallergens on the exacerbation of EoE? Are there common pathways linking EoE with other allergic diseases?

Should COMs related to allergic diatheses be included in the therapeutic assessment of patients with EGIDs? What is the role of allergens in EG, EGE, and EC? Are there predisposing factors that can contribute to the generation of EGIDs? Some of these questions are being pursued in the context of CEGIR.

## GASTROENTEROLOGISTS

Pediatric and adult gastroenterologists from numerous different institutions participate in the collaborative research in CEGIR. Because patients with an EGID diagnosis must undergo an endoscopy, their initial evaluation is performed by a gastroenterologist. In this regard gastroenterologists are typically most familiar with their presenting symptoms related to swallowing and eating and associated endoscopic features and thus have a critical role in identifying EGIDs in patients in general and in subspecialty gastroenterology practices, developing COMs as they pertain to presenting symptoms and endoscopic features, and creating novel metrics to assess the gastrointestinal tract. In addition, sharing observations with others at international platforms permits increased understanding and recognition of EGIDs.

### Clinical effects

EGID diagnoses are made by gastroenterologists after clinical suspicion has been raised and endoscopic evaluation with mucosal biopsy has been completed. Because EGIDs are defined as clinicopathologic diseases, gastroenterologists are typically on the front line of establishing the initial diagnosis. In this regard because symptoms related to swallowing are typically addressed primarily by gastroenterologists, they have helped clarify and identify coping skills with respect to eating some foods.<sup>39-41</sup> For instance, many children and adults can compensate for their dysphagia by lubricating food during meals with water or sauces or exhibit prolonged chewing of highly textured foods.

The gastroenterologist's role with respect to endoscopic evaluation has been 2-fold. First, endoscopy must be performed to collect a mucosal pinch biopsy specimen and provide a visual assessment of the mucosa. Second, if esophageal strictures and narrowings develop as a consequence of excessive fibrosis and remodeling, therapeutic dilations are often needed to improve swallowing. Over the course of the past decade, technical aspects of this intervention have become more and more refined because they are different from the dilation of the more commonly encountered peptic strictures.

Gastroenterologists have also made strides in the clinical implementation of topical steroids and dietary restriction. With respect to the latter, the description of the 6-food elimination diet for patients with EoE was led by adult and pediatric gastroenterologists.<sup>42-46</sup> In addition, they have related strategies for implementing a dietary plan, the effect of the diet treatment on quality of life, and need for maintenance therapy.<sup>47-49</sup>

### Research

Because of the unique view offered by endoscopic assessment, gastroenterologists have provided several important research roles. Detailed inspection of the esophageal mucosa led to development of a COM for EoE. The EoE Reference Score

(EREFS) provides a validated system to assess the common endoscopic features of EoE: exudate, rings, edema, furrows, and strictures.<sup>50</sup> EREFS can be used to assess disease activity in both pediatric and adult patients with EoE to monitor disease activity, therapeutic efficacy, or both.<sup>22,51-53</sup> We are hopeful that endoscopic scoring for EG, EGE, and EC, similar to the EREFS system created for EoE, will be developed over the course of CEGIR2.

The art of dilation in patients with EoE has been increasingly described and characterized. Adult gastroenterologists are typically more experienced with esophageal dilation and, in a number of research platforms, have helped to inform pediatric practitioners and others on the subtle differences in dilating the fibrotic organ.<sup>54-59</sup> In addition, because of the visualization and clinical effect of EoE on the barrier and fibrosis, gastroenterologists have embarked on basic studies to understand their basic mechanisms.<sup>60-63</sup>

Finally, devices that have been developed to interrogate the esophagus in patients with other diseases or other parts of the gastrointestinal tract have now been brought to use in research studies focused on EoE. Examples of these include mucosal impedance probes for measuring reflux, the string test for detecting intestinal parasites, the Cytosponge (Medtronic, Minneapolis, Minn) for detecting Barrett esophagus, confocal microscopy, endoscopic functional luminal imaging probe (endoFLIP) for detecting distensibility, transnasal endoscopy, and others, which have now all been repurposed for use in tracking EoE activity and understanding the pathogenesis of EoE.<sup>64-69</sup>

## PATHOLOGISTS

Pediatric and adult pathologists from 3 different institutions contribute their shared expertise to CEGIR. Their expertise and dedication provide key guidance to both measuring and understanding the key histologic features of mucosal biopsy specimens from patients with EGIDs, as well as those of healthy control subjects.

### Clinical effects

The evaluation of mucosal biopsy specimens and, in some cases, full-thickness biopsy specimens remains a key component to making the diagnosis of EGID. The diagnostic biopsy specimen is assessed in numerous ways, including to determine whether other histologic elements are supportive of other diagnoses that might have eosinophilia as a feature, such as inflammatory bowel disease or infection.

For example, before the recognition of EoE, esophageal biopsy specimens from children that contained no or scattered eosinophils were diagnosed as GERD, and biopsy specimens that contained abundant eosinophils were diagnosed as marked GERD! Pediatric gastroenterologists consulted pediatric pathologists at conferences or across the microscope about their patients who were not responding to antireflux therapy. These consultations led to recognition of a non-GERD disease affecting the esophagus, and sharing images of esophageal endoscopies and the corresponding biopsies at a weekly conference led to the first description of endoscopic abnormalities in patients with EoE.<sup>70</sup> Observations made by pathologists in their daily practice led to publications that consistently cited 15 eosinophils/high-power field in biopsy specimens from patients with esophageal symptoms who did not have GERD or who

responded only incompletely to antireflux therapy, which remains the gold standard for the pathologic portion of the clinicopathologic diagnosis of EoE.<sup>12</sup>

More recently, pathologists reported reduced numbers of or no eosinophils in biopsy specimens after proton pump inhibitor (PPI) therapy. Most of these pathologists reviewed such biopsy specimens blinded to current therapy, which is generally not included in pathology requisitions, and this information led to the recent recommendation that PPIs are therapy for EoE rather than using PPI refractoriness as part of the diagnostic criteria.<sup>71</sup>

Understanding the day-to-day aspects of clinical practice are key to developing standardized approaches toward the assessment of mucosal biopsy specimens. For instance, in some busy clinical practices, pathologists face a difficult task when asked to rule out EGIDs in the hematoxylin and eosin–stained sample. The laborious tasks of identifying the location with peak eosinophil infiltration and counting eosinophils, especially when they are found in sheets or within a sea of eosinophilic granules, might not always be efficient or feasible. Identifying key features, such as eosinophilic abscesses, degree of degranulation, distribution along the gastrointestinal tract, and patterns of eosinophilia, is helpful in tissue characterization and for posttreatment analyses. Gastroenterology and allergy colleagues rely on these numbers to frame the clinical features in the proper fashion. For instance, large numbers of eosinophils might be present in the lamina propria, but when found in the setting of larger numbers of polymorphonuclear cells, epithelial erosions, and ulcers and crypt abscesses in the colonic mucosa, the diagnosis is likely ulcerative colitis. The experienced assessment of the entire tissue can provide supportive evidence of whether the inflammatory process appears to be chronic or acute.

## Research

Over the course of the last decade, pathologists continue to help the EGID field mature by increasing the analytic metrics for EoE. Early EoE studies were primarily limited to noting the presence of and in some cases counting eosinophils. Now, a robust scoring system, the Histologic Scoring System, has been developed that includes additional features with respect to EoE that, in addition to eosinophil density, include basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, thickened lamina propria fibers, surface epithelial alterations, and dyskeratotic epithelial cells.<sup>72</sup> Each of these features is examined for severity (grade) and extent (stage), and a total score is assigned. The system has strong interobserver reliability and revealed that basal zone hyperplasia and dilated intercellular spaces correlated strongly with treatment status. In addition, symptom scores correlated with pathology scores in children enrolled in CEGIR1.<sup>21</sup>

These key observations provide additional support for mechanistic and clinical studies showing that despite resolution of eosinophilia, some patients might continue to experience symptoms and basal zone hyperplasia. More comprehensive evaluation of biopsy pathology could potentially suggest new targets for therapy, such as epithelial hyperplasia and dilated intercellular spaces that might affect epithelial barrier function. Pathologists might contribute to the development of new therapies by participating in randomized clinical trials, including those sponsored by pharmaceutical companies because US Food and Drug Administration–approved therapies are still lacking.<sup>73</sup> In

such studies pathologists might provide a central pathology review that reduces variability and provides quality assurance of the diagnosis at baseline. CEGIR pathologists participated in a randomized trial of dietary therapy to treat EoE, and the results will be soon available.

As with the allergists, pathologists in the EGID field have many questions to be addressed: Are there biomarkers or molecular signatures in the tissue that can differentiate EGIDs from other eosinophil-associated diseases? How can eosinophilia be quantitated in a rapid fashion as a part of a busy clinical practice? Is there a value for artificial intelligence in evaluating clinical specimens after whole slide imaging? What are the histologic features associated with EG, EGE, and EC? Are there different phenotypes or endotypes of the EGIDs, as there appears to be with EoE? What are the ways that more of the gastrointestinal mucosa can be assessed histologically? Can deeper layers of the gastrointestinal tract, such as the muscularis propria, be safely biopsied endoscopically to identify inflammation in the deeper layers of patients who have persistent symptoms but not persistent mucosal eosinophilia?

One of the major contributions of pathologists that occurred during the course of CEGIR1 relates to establishing novel approaches for pathologists to economically and reliably analyze tissue slides. Initial enrollment in OMEGA1 was based on the local pathologist's assessment of mucosal biopsy specimens. The 3 CEGIR pathologists reviewed entry biopsy specimens to ensure that they met the enrollment criteria. This approach provided the consortium with a thorough assessment by experienced adult and pediatric pathologists at different geographic locations (Cincinnati, Chicago, and Denver) who could identify eosinophilia and other features in patients with these rare diseases. However, this approach posed a significant logistical concern: How would 3 pathologists at 3 different institutions analyze hundreds of slides in a reasonable time frame and accommodate regulatory and cost concerns?

This issue drove the development of an innovative research platform for the RDCRN and its associated Data Management and Coordinating Center; the patients' slides were either locally or centrally scanned at the time of study entry. The images were then stored in a safe and accessible virtual bank for pathologists to access and analyze; this process is referred to as the whole slide imaging system, which relies on digital microscopy after scanning of clinical biopsy slides. This not only provides an opportunity for convenient use of virtual microscopy using standardized procedures but also generated an EGID pathology slide database (using secure cloud services) that is available for educational and sharing purposes.<sup>18</sup> Development and execution of this plan provided CEGIR with a new resource that saved time and money and met compliance standards and provides pathologists' in other fields of study with an alternative for collaborative study platforms.

## PAGs

During CEGIR1, PAGs (APFED, the Campaign Urging Research for Eosinophilic Diseases [[curedfoundation.org](http://curedfoundation.org)], and the Eosinophil Family Coalition [[www.eoscoalition.org](http://www.eoscoalition.org)]) played a critical role in its success and refunding. Their participation in CEGIR committees and conference calls, attendance and presentations at annual meetings, and contribution of services and time to the RDCRN patient advocacy steering committee created an

increased awareness of patients' needs. In addition, they provided key advice on study designs and protocols regarding challenges in enrollment and adherence. The PAGs APFED and the Campaign Urging Research for Eosinophilic Diseases have successfully raised substantial funds, which have been distributed to EGID investigators for the purpose of advancing EGID-related research. Bestowing financial support, advertising clinical studies to a wide group of patients, and publicizing key research findings provided valuable services that would not be possible with an investigator-only consortium.

Finally, CEGIR investigators and PAGs united forces at annual patient meetings to present CEGIR-related research and meet patients and families in one-on-one settings. These relationships provide patients and families with opportunities to ask direct questions of investigators and for investigators to learn more about the leading questions needing answers from the patient's perspective and how to develop and execute patient-friendly research.

## CONSORTIUM CHALLENGES AND SOLUTIONS

Challenges related to working in a consortium are not unique to EGIDs and relate to those that would affect any diverse group of advocates, clinicians, and researchers who are dispersed across different time zones, supported by a variety of different resources, and at different professional stages in their careers. Practical challenges for patients to enroll in studies and adhere to protocols might not be recognized. The costs and environmental restraints of performing endoscopies and skin tests are not always obvious. The research infrastructure and financial support to carry out studies varies significantly between sites. Investigators' professional aspirations and requirements for independence as they relate to academic promotions and publications might be supplanted by the needs of the group. Organizing meetings and teleconferences so that people are able to complete other duties and not interfere with personal time is challenging. Communications and inclusivity of all members regarding planned changes in protocols, opportunities for participation in activities and events, and publications creates concerns. Finally, using a centralized institutional review board and understanding layers of regulatory and compliance aspects pose a different set of hurdles not always experienced in single-site or local studies.

Despite these challenges, CEGIR continues to thrive as a group and address its mission by ensuring (1) a consistent stream of communications; (2) transparency in budgets, plans, and goals; (3) diversification of leadership roles; (4) provision of opportunities for professional growth; (5) access to data and samples; (6) preservation of a spirit of collaboration, collegiality, and inclusivity; (7) provision of opportunities for subjects to promote and carry out their own innovative research ideas, often involving data and biospecimen sharing; and (8) use of CEGIR data and its derivatives (data) as a springboard for other research projects and grant applications. PAG and multidisciplinary discussions are vital to ensure that studies are designed and executed in a patient-friendly fashion and that practical and logistical concerns are addressed early. Bimonthly "all calls" are held to inform of CEGIR progress and educate members on areas of expertise. Goals and plans are discussed regularly by committees and presented at annual meetings held at the NIH. Senior investigators involve junior investigators in the various studies to help further their research career in a mutually beneficial fashion. Samples

and data are quality assured and monitored by the Data Management and Monitoring Center, and use is monitored by CEGIR committee. Annual surveys are conducted to identify areas of strength and need. Together, these help CEGIR to execute and complete research studies in a reasonable time frame.

## FUTURE FOR EGIDS

It is rare for anyone involved in medicine to be able to be involved in the early stages of the "history" of a disease, and in fact, most of the content described here has been developed in the last 25 years. The relative newness of EGIDs to the medical landscape speaks to the immense opportunities available that will shape the field for decades to come and that can improve the lives of patients in a relatively rapid manner. Research emanating from CEGIR2 will include further characterization of non-EoE EGID,<sup>74</sup> with a particular emphasis on developing consensus guidelines for these disorders, pursuing a randomized clinical trial with novel biologic therapy for EGID, and supporting innovative pilot studies. Access to CEGIR research studies can be found at the CEGIR Web site (<https://www.rarediseasesnetwork.org/cms/CEGIR>), and further information regarding biologics is summarized in recent publications.<sup>75</sup> Training of future leaders and investigators in this field is also at the forefront of CEGIR2. The NIH/RDCRN U54 Consortium opportunity provides a unique chance to participate in these advances on behalf of our patients and their families. In parallel, CEGIR will synergize with the many other research studies that will continue to advance the EGID field and will provide more data that identify key clinical features, endoscopic abnormalities, histologic findings, improved clinical trial readiness, and effects on quality of life. Developing novel devices and approaches to detect disease activity and establishing peripheral biomarkers to monitor the patient's progress will reach a greater degree of maturity. Discovery of pathogenetic pathways and novel therapeutic targets will forge new treatments and approaches for patients with EGIDs. CEGIR will promote future progress in the EGID field and clinical practice by sharing of the CEGIR database and the growing biorepository of more than 5000 samples that are linked to clinical information; CEGIR data sharing and scientific advisory committees are in place to facilitate these processes.

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Gabriela Mendoza, Melissa Mingler, Mike Minnicozzi, Amanda Muir, Vincent Mukkada, Cristin MurrayPetzold, Robert Newbury, Quan Nhu, Oghenekpaobor (Joel) Oyibo, Allisa Paliana, Zhaoxing Pan, Robbie Pesek,

Kathryn Peterson, Heidi Poppendeck, Philip Putnam, Fabian Rivera, Marc Rothenberg, Amanda Rudman-Spergel, Kathleen Sable, Alain Schoepfer, Melissa Scott, Rachel Sheridan, Selma Sinanovic, Jonathan Spergel, MaryJo Strobel, Kiki Sun, Amy Tasco, Crystal Tholen, Katherine Thompson, Tiffany Tomkinson, Daisy Tran, Alexandra Tylicki, Tiina Urv, Mei-Lun Wang, Joshua Wechsler, Barry Wershil, Lisa Wheatley, Leah Wilkey, Guang-Yu Yang, Angelika Zalewski, and Amy Zicarelli.

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