FOOD AND DRUG ADMINISTRATION

CENTER FOR EVALUATION AND RESEARCH (CDER)

Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI (GREAT VI)

Virtual Workshop on

Eosinophilic Gastrointestinal Disorders Beyond EoE

Wednesday, July 21, 2021

10:03 a.m. to 3:14p.m.

Meeting Roster

Seema Aceves, MD, PhD

University of California San Diego

Mirna Chehade, MD, MPH

Icahn School of Medicine

Margaret Collins, MD

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Calies Menard-Katcher, MD, MScs

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Marc Rothenberg, MD, PhD

Cincinnati Children's Hospital

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Patient Representative

Jonathan Spergel, MD, PhD

Children's Hospital of Philadelphia

Nicholas Talley, AC, MD, PhD

The University of Newcastle

Juli Tomaino, MD

U.S. Food and Drug Administration

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(10:03a.m.)

Opening Remarks – Erica Lyons

DR. LYONS: Hi, everyone. Good morning. My name is Dr. Erica Lyons, and I am an associate director for therapeutic review within the Division of Gastroenterology. On behalf of my division director, Dr. Jessica Lee; deputy director, Dr. Juli Tomaino; deputy director for safety, Dr. Joyce Korvick; fellow associate director for therapeutic review, Dr. Tara Altepeter; team leader, Dr. Matthew Kowalik; and the entire Division of Gastroenterology, I would like to welcome you and thank you for attending and participating in today's Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI, or GREAT VI, Workshop on EGIDs Beyond EoE.

The goal of today's workshop is to discuss the disease characteristics, natural history, and endpoints to assess treatment benefit in patients with eosinophilic gastrointestinal disorders, or

EGID, beyond EoE to provide a forum for open discussion between stakeholders to facilitate drug development. We are thrilled to have 923 registrants from across industry, patients, patient advocacy groups, our academic and clinical colleagues, as well as regulatory personnel here to participate in today's workshop.

The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices.

The Division of Gastroenterology is part of the FDA's Center for Drug Evaluation and Research, or CDER, and CDER's mission is to protect and promote public health by helping to ensure that human drugs are safe and effective for their intended use, that they meet established quality standards, and that they are available to patients.

Again, we are very pleased to welcome a wide variety of stakeholders to today's workshop. It is important to note that this workshop is intended to

provide a format for collaboration, information sharing, and discussion of how to effectively address key issues in the clinical development of treatments for EGID. It is not an advisory committee in which FDA is seeking advice or a forum during which regulatory advice will be given or agreements made, although we encourage participants to share their experience and expertise for the benefit of the group discussion and to inform future development.

We are excited for what we hope will be a vibrant dialogue during the panel discussions and Q&A that will be supported by today's presentations and focus on the strength of the available data and the areas of persistent knowledge gaps for which additional research is needed.

I'm happy to open this year's workshop with my sincere gratitude to the co-sponsors of the workshop, as well as the steering committee members who planned today's session. The co-sponsors include the American College of Gastroenterology; the American Gastroenterological Association; the

Consortium of Eosinophilic Gastrointestinal Disease Researchers; the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; and the American Academy of Allergy, Asthma and Immunology.

Here you see our partner organizations, as well as the representatives that they nominated for our steering committee. The nominees for the workshop steering committee were requested from these groups, along with Pharma and Bio.

The members of the steering committee have worked hard to make today's workshop a success. They took time from their work to get on teleconferences, create the day's agenda, and go over presentation topics and slides together. We truly appreciate the time they committed to this effort.

In addition, I would like to take this opportunity to recognize the hard work and leadership shown by our FDA staff, who dedicated efforts above and beyond their normal workload to plan the workshop.

I would particularly like to recognize Dr. Matthew Kowalik; Dr. Juli Tomaino; Dr. Jessica Lee; Dr. Jay Fajiculay; and Captain Kelly Richards for their dedication, commitment, and superior organizational skills, as well as the FDA public meeting support and information technology teams for their assistance coordinating and holding today's meeting.

This workshop will be divided into morning and afternoon sessions, each followed by panel discussions with Q&A. As we are hosting this workshop virtually, please use the Q&A box on your screen to pose a question or topic to the panel. To facilitate the discussion, please submit all questions for the panel prior to the session break, as the organizers will need to provide a list of questions to the moderators prior to the start of the panel discussion.

Our first session focuses on the diagnosis and natural history of non-EoE EGID. This session will be moderated by Drs. Matthew Kowalik and Marc Rothenberg.

Dr. Kowalik is a clinical team leader in the Division of Gastroenterology in the Office of Immunology and Inflammation, within the Office of New Drugs in the Center for Drug Evaluation and Research at the FDA. Dr. Kowalik is a pediatric gastroenterologist and has worked in a variety of therapeutic areas within gastroenterology, including inflammatory bowel disease, eosinophilic gastrointestinal disorders, erosive esophagitis, and gastroesophageal reflux disease.

Dr. Rothenberg is a professor of pediatrics and the director of the Division of Allergy and Immunology at Cincinnati Children's Hospital. As the director and founder of the Cincinnati Center for Eosinophilic Diseases and the NIH's Consortium of Eosinophilic Gastrointestinal Disease Researchers, he is a pioneer in the scientific elucidation of eosinophilic gastrointestinal diseases.

I will now turn the presentation over to our moderators for Session 1. Thank you all.

DR. KOWALIK: Thank you, Erica, and thank

you for that introduction.

It's my pleasure to open our first session with my co-moderator, Dr. Rothenberg. As Erica mentioned during the session, we will hear from several presenters on topics related to the diagnosis and natural history of EGIDs.

So with that, without further ado, I invite Dr. Rothenberg to introduce our first presenter.

DR. ROTHENBERG: Good morning, everyone. I'd like to introduce Dr. Evan Dellon. Dr. Dellon is a professor of medicine and an adjunct professor of epidemiology at the University of North Carolina School of Medicine.

Dr. Dellon is currently the director of the UNC Center for Esophageal Diseases and Swallowing and serves as associate editor for the Clinical Gastroenterology and Hepatology Journal.
Dr. Dellon's main research interest is in the epidemiology, pathogenesis, diagnosis, treatment, and outcomes of eosinophilic esophagitis and eosinophilic GI diseases.

Dr. Dellon, please start.

Presentation – Evan Dellon

DR. DELLON: Thank you so much, Dr. Rothenberg, Dr. Kowalik, and Dr. Lyons. I really appreciate the opportunity to talk and the ongoing collaboration between the FDA, researchers, clinicians, patients, advocacy groups, and industry in this field.

To get things started off, I'm going to talk about EGID pathogenesis and nomenclature. On the next slide you'll see some of my disclosures here, then for the overview on the next slide, I'm going to define EGIDs and review the general framework for diagnosis. I'll discuss nomenclature and ongoing efforts for standardization of this and review some EGID pathogenesis, and I hope through this overview, I'll be able to provide context for the remainder of the discussion today.

To start with, I'd like to answer the question of what is eosinophilic GI disorder, and I wanted to make an analogy with a conceptual definition of EoE. It's been well recognized that eosinophilic esophagitis represents a chronic

immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation; so it's a clinicopathologic condition.

Similarly, an eosinophilic gastrointestinal disorder is a chronic immune-mediated disease characterized clinically by GI symptoms and histologically by pathologically increased eosinophil-predominant inflammation.

So there are a lot of parallels there in the definition, and I think this definition impacts thinking about treatment outcomes and endpoints that we're going to discuss today. And particularly for the non-EoE EGIDs, what does it mean for tissues when eosinophils are normally present in the tissue, and is there a way when we think about outcomes to move away from a focus on a specific number or threshold?

We'll hear today, and I hope I'll set the stage, that the symptoms for EGIDs are well characterized, though as you'll hear they're

non-specific; the natural history has been described; histologic features have been described; the genetic features are beginning to be described; the epidemiology is being understood; and overall, there's a rapidly increasing knowledge base in this field.

This is, I think, very exciting, and hopefully we'll be able to review a lot of important new data. I think what also may come up through the discussion is that the knowledge base for drug development may be different than for clinical practice.

So I wanted to start with the diagnostic approach in practice. Even though there are not consensus guidelines published for the diagnosis, these are under development, and the approach to diagnosis in individual patients is known.

First, there are symptoms of organ dysfunction in the GI tract, so you'll hear about this in detail from Dr. Gonsalves, as well as potential supporting features, the clinical phenotypes and endoscopic features, and some

biomarker information. Then when you do endoscopy and biopsy, there will be abnormally high levels of mucosal eosinophilia, and you'll hear from Dr. Collins about what these are.

The thresholds for this have not been necessarily published in consensus guidelines but we certainly know how to make the diagnosis and a number of thresholds are in use. Then finally, the last step of the diagnostic algorithm is the evaluation of potential competing causes of eosinophilia, and Dr. Talley will go through the approach to this and how we can, in most cases, readily distinguish eosinophilic GI disorders from other conditions, and then you can, of course, make the EGID diagnosis.

Now, turning to the epidemiology of the non-EoE EGIDs, these are currently classified as rare diseases. In large administrative data-based studies, the prevalence estimates are about 2 to 6 per 100,000, depending on which particular location in the GI tract you're looking at, and the estimate of the number of non-EoE EGID cases in the U.S. has

been put at about 49[000]-50,000.

It's quite possible that these conditions are on the rise, and there are several reasons for this. In this multicenter retrospective study of several of the CEGIR sites, there were 376 EGID patients that were evaluated, and you can see the different GI locations there. But as you can see on the X-axis, over time the diagnosis and the number of diagnoses has been increasing.

Additionally, it's quite possible that these conditions are underdiagnosed. There's a diagnostic delay, and because people understand that they're rare, they may not be on the top of the differential diagnosis when they're looking for causes of GI symptoms. To this end, there's been very recent data presented by Dr. Talley at DDW a month and a half ago, showing a high prevalence in a subpopulation.

This was a prospective multicenter study at a number of sites throughout the U.S., where 118 out of 405 subjects, who had moderate to severe symptoms and underwent an EGD with extensive

gastric and duodenal biopsies, actually met histologic criteria for eosinophilic gastritis and/or duodenitis; so 45 percent in this subpopulation, certainly a higher prevalence than we would typically consider.

When we think about how we traditionally classify the EGIDs, the naming has been based on the location. So of course eosinophilic esophagitis is isolated to the esophagus. The non-EoE EGIDs are named by their location, so you have gastritis, stomach involvement; colitis, colon involvement; and gastroenteritis often meant to include both stomach and small bowel, but sometimes it's used as an umbrella term.

Because of some of this heterogeneity in terminology, there's an effort undergoing to update the EGID nomenclature. Particularly with eosinophilic gastroenteritis, there's been variability in clinical use and use in the literature, and in some cases it may refer to gastric only, gastric and duodenum, duodenum only, or other locations.

But when you look at this in the literature, the majority of the references to eosinophilic gastroenteritis report duodenal involvement primarily, and this is just simply because on upper endoscopy, you get duodenal biopsies, so the enteritis typically refers to duodenitis.

Because of this heterogeneity, there is some imprecision in both clinical practice and research, so there's a recognition that we need standardization and a common language for disease names before we can put forth formal diagnostic and management guidelines.

There's an ongoing international consensus process, including stakeholders. So far we've completed an initial Delphi round with 85 participants from around the world on five continents, representing GI, allergy, pathologists, adult and pediatric providers, and a wide range of researchers. The overall approach is going to be to attempt to retain the existing nomenclature when possible, consider removing or redefining eosinophilic gastroenteritis, and also having a

framework where there can be one tier for useful nomenclature in clinical practice and a second tier that's much more detailed for research use, and an expectation that this nomenclature can and will change as data emerge.

This figure shows an initial draft diagram of one proposal for the nomenclature. This is a draft and certainly not the final one. But you can see that the eosinophilic gastrointestinal disease term proposes an umbrella with subsequent naming by location, and then subsequent terms to indicate individual locations or combination of locations.

This revision is ongoing. We know for sure that EoE is not going to change, but we'll likely be under the EGID umbrella and we'll distinguish EoE from non-EoE EGIDs.

Eosinophilic gastritis and colitis will stay the same because those terms are quite clear, and the ongoing discussion will clarify for eosinophilic gastroenteritis should we use terms separately like eosinophilic gastritis and eosinophilic enteritis or eosinophilic duodenitis,

if both are present; should we redefine eosinophilic gastroenteritis so there's clarity on what we're talking about, and then how to best capture the different areas of the small bowel, with the understanding that most enteritis in the literature now often refers to the duodenum.

Let's change the discussion a little bit now from the epidemiology and terminology over to pathogenesis. Just as a reminder, we know that the EoE pathogenesis is the Th2 mediated process, and this diagram shows the general conception right now where you have food allergens or environmental allergens interacting with the microbiome and the esophageal barrier, which often has a defect.

Starting this cascade of the Th2 process is this T-cell mediated disorder leading to typical Th2 cytokines and ultimately the recruitment of effector cells like eosinophils and mast cells, and then the clinical manifestations that we know about.

For the non-EoE EGID pathogenesis, this is certainly less investigated, but the initial data

do suggest that gastric and small bowel EGIDs likely share similar pathogenic features to EoE and appear to be similar, whether it's gastric alone, gastric and small bowel, or small bowel alone.

What do I mean by this? Well, I'm going to show you some data that there's an association with atopic conditions, there's a response to elemental formula implicating food antigens, and there is a Th2 type signature and cytokines present. For eosinophilic colitis, it's still very early and pathogenesis is still under investigation.

This is some administrative data from a paper by Mansoor and colleagues showing the association of atopy and the non-EoE EGIDs. A control population is in the purple bars and the proportion is on the Y-axis. And no matter which type of atopic condition you're looking at, the eosinophilic gastrointestinal diseases in the yellow and light blue bars are far higher than the purple bars, so this is similar to what we see for EoE.

This association is also seen in that

multicenter retrospective study by Pesek and colleagues that I had mentioned, where you can see here that the majority of patients have at least one atopic condition. It's of course not universal and it's not universal in EoE, but a majority of people have associated atopy.

You'll hear Dr. Gonsalves talk about this in more detail, but the recently completed ELEMENT study was a prospective study of elemental formula treatment in adults with the eosinophilic gastritis and/or gastroenteritis. The key point with this is a hundred percent of the patients in this study met the primary outcome of histologic response, which was under the diagnostic threshold as illustrated by these graphs here showing both duodenal eosinophils and gastric eosinophils going down to essentially normal levels.

Why are these critical data? Well in 1995, Kelly and colleagues published a seminal article in EoE demonstrating that eosinophilic esophagitis improved with amino acid-based formula, essentially universally, and this was confirmation that EoE, in

fact, food allergy-mediated. Well now in 2020, Dr. Gonsalves and colleagues have provided evidence that confirms eosinophilic gastritis and/or enteritis are food allergy-mediated and likely are allergic and immune-mediated diseases.

So what about additional data from the physiologic standpoint or molecular standpoint of the eosinophilic gastritis as a Th2-mediated disease? Well, these are data from Dr. Rothenberg's group, and for the first time they were looking at eosinophilic gastritis and gene expression differences in that condition and identified a unique gastric transcriptome. This was quite characteristic for eosinophilic gastritis, and some of the genes and heatmaps are shown there on the left side of the slide.

CCL26, also known as eotaxin-3, is the most highly upregulated transcript; interestingly, it's very similar to EoE. They also found that the typical Th2 cytokines like IL-4, IL-5, and IL-13were also highly upregulated and expressed. And that graph at the bottom right interestingly

shows that the peripheral eosinophils in the blood correlated very strongly with the eosinophil count in biopsies.

More recently, Dr. Rothenberg's group and the CEGIR group, in a study by Shoda and colleagues, looked at molecular endoscopic and histologic features, as well as circulating biomarkers in eosinophilic gastritis, and they were able to identify a reduced set of genes, a so-called eosinophilic gastritis diagnostic panel, that was highly discriminatory between active eosinophilic gastritis and other non-EG conditions. That's what this heat map shows. You can see up- and down-regulated genes on the right with active EG are highly different than for non-EG conditions.

In the top two graphs, you can see the diagnostic utility of this transcription analysis almost perfectly distinguishing and diagnosing eosinophilic gastritis in both the discovery cohort and the validation cohort, which is a very strong study design for this kind of diagnostic marker work.

In the bottom panel, you can show the gene score from the eosinophilic diagnostic panel, which is high when you have non-EG conditions; and in active EG, then you can see at the very right how it's much lower when you have active EG. So again, it can distinguish between active and inactive EG and other conditions.

Then finally, if you look at this last panel, it correlates some of the gene expression differences with plasma or serum biomarkers, a number of which are in the Th2 pathway. So again, I think strong evidence of EG as a Th2-mediated condition.

What about responsive treatment by different areas of involvement? This helps to understand whether the same pathway is maybe at play in the stomach and in other locations. Well, in that ELEMENT study that I just showed you for a prospective study, all patients in that study responded similarly regardless of whether there was gastric, duodenal, or both gastric and duodenal involvement.

Similarly, a randomized trial of a biologic for treatment of EG and/or eosinophilic duodenitis, all patients similarly responded regardless of gastric, duodenal, or both locations involvement. And this to me suggests that EG with or without duodenal involvement and duodenal involvement alone may respond in the same way to treatment, and therefore could share underlying pathogenesis. Now of course, these are initial data that should be confirmed in future studies, and there is ongoing work with transcriptome data from the small bowel alone.

The pathogenesis can suggest potential future treatment targets, so some are in the same pathways that have already been looked at for EoE and there are potential targets like the Th2 cytokines. TSLP is sort of a master allergy regulator and eotaxin-3. There's also the potential for these as biomarkers, and as I just mentioned, emerging data should be forthcoming for more detail on transcriptome changes in duodenitis and enteritis, and colitis.

When we think about how the pathogenesis may relate to outcomes to some of the topics we want to talk about later in this seminar, the symptoms in pathologically elevated eosinophils are important parts of the disease activity -- and I'm sure we'll discuss it -- and it's natural to consider these as endpoints. But because the eosinophils are normally in the tissue, it will be interesting to hear everybody's thoughts on how to approach histologic endpoints in this setting and whether we should consider other endpoints such as histologic severity, not just a count; molecular activity, such as in the transcription analysis I just showed you; clinical complications that we'll hear about; and other endpoints that may allow and encourage novel drug mechanisms to be studied.

In summary, the non-EoE EGIDs are characterized clinically by GI symptoms and histologically by pathologically increased eosinophilic inflammation. These are rare diseases, but they're likely underrecognized, and the prevalence seems to be increasing.

We'll have updated nomenclature soon that will help us share a common language to discuss these and to advance the field in terms of research and the understanding of the pathogenesis is rapidly increasing. There's demonstration that EG is a Th2-mediated disease, and this has implications for diagnosis monitoring biomarkers and treatment targets, as well as thinking about outcomes, and data are coming on eosinophilic duodenitis and enteritis.

Thank you so much for the opportunity to talk today, and I look forward to the discussion.

DR. KOWALIK: Thank you so much, Dr. Dellon, for sharing your expertise, and that was really an excellent talk. You've identified many of the knowledge gaps and ongoing areas of research critical to advancing the field and highlighted how rapidly the field's advancing and the importance of standardizing nomenclature so we're all speaking the same language.

Next up, we have Dr. Margaret Collins. She will be presenting on the histopathologic

characteristics of the EGID, a pathologist's perspective. Dr. Collins is board certified in anatomic pathology and pediatric pathology. She's a professor of pathology at University of Cincinnati and a staff pathologist at Cincinnati Children's Hospital Medical Center, where she specializes in pediatric gastrointestinal disease, particularly eosinophilic gastrointestinal disorders.

Dr. Collins, please go ahead.

Presentation – Margaret Collins

DR. COLLINS: Thank you very much, Dr. Kowalik, and thank you to all of the organizers for the opportunity to be with you all this morning. This shows my disclosures.

On the next slide, by way of introduction, we've heard from Dr. Dellon that EGID are indeed clinicopathologic disorders in which symptoms are consistent with the affected part of the GI tract, and the pathologic portion of the diagnosis includes excess eosinophils in GI mucosal biopsies.

Threshold values, or cutoff points, are used to identify excess eosinophils in parts of the GI

tract where they normally occur, which is all of the GI tract except for the esophagus. These can be helpful in making diagnosis, but they can also lead to over simplification in the sense that in addition to excess eosinophils in biopsies in the GI tract, there are abnormalities in other components of the mucosa in addition to excess eosinophils.

The next two slides will demonstrate a not by any means final or set-in-stone group of numbers that represent what are currently reported in the literature as peak eosinophil counts. This was done for simplification. There are mean counts, there are median counts, and so on, but the peak count is a count in which there is a number in a population that is being studied, a number of eosinophils per high-power field that may be found in a number of high-power fields, but there aren't any high-power fields -- there aren't any areas under the microscope -- that have more eosinophils than the peak eosinophil count.

These were standardized to 0.27 millimeter

squared high-power field, as represented in the second column there, to try to cut down on the variability that occurs with different sizes of high-power fields. For example in a reference there in the third column and cited more fully below the table, a study reported using a high-power field of 0.24 to count eosinophils that was multiplied by a factor to bring it up to what would have been found in a high-power field measuring 0.27 millimeters squared.

In a paper reported using a high-power field of 0.3 millimeter squared, and that number was multiplied by a factor to reduce it to what would have been found in a high-power field measuring 0.27 millimeter squared.

In the upper GI tract, the highest number, the highest peak count reported in the stomach is 33, and that is reported in a paper that did not identify the particular part of the stomach from which that count was obtained.

None have been reported for the duodenal bulb. The highest peak count reported for the

duodenum, the second or third part, is 70. The next slide shows the counts that have been reported for the lower GI tract up to 92 in the ileum. There you can see in the colon a phenomenon that is replicated in many studies, that the greatest density of eosinophils in the colon occur in the right side of the colon and there is a lesser amount of eosinophils in the left part of the colon; so the ascending colon in the cecum compared to sigmoid in the rectum normally have more eosinophils.

It's important, therefore, for pathologists to know where colon biopsies are obtained in order for us to be adequately able to evaluate if there are too many eosinophils in those biopsies or not. And you can see the wide variability in the peak counts that are reported, from less than 1 up to 92, so there's some work to do here.

The next slide shows that there are values, threshold values, that have been used in studies; for example, eosinophils gastritis. Thirty or more eosinophils and 5 or more high-power fields have

been used in studies of both children and adults as the threshold level eosinophilic inflammation for the diagnosis of eosinophilic gastritis, and 70 or more eosinophils[indiscernible – audio distorted] from high-power fields have been used in a study of children.

The next slide shows that there are not many situations in which 10 pathologists gathered together will agree on anything, but I think this is one of those situations. There are way too many eosinophils in this biopsy, and I think any 10 pathologists would agree with that evaluation, in addition to which they're concentrated near the surface as if they're reacting to something in the lumen as opposed to if there is a gradient of inflammation in the stomach, it tends to be towards the bottom, towards the muscularis mucosa, rather than towards the surface.

The arrow is pointing to eosinophils that are in the epithelium gland, and if you look around, there are plenty of other glands that had a lot of eosinophils in the epithelium, which is a

distinct abnormality.

The next slide shows another example of eosinophilic gastritis in which there's more damage to the mucosa than in the last slide. The arrows are again pointing to eosinophils in the lamina propria. The arrowheads are pointing to eosinophils that are in and around the epithelium in the glands.

The glands don't have much in the way of mucin. Some of them are back to back, which may be because they are tortuous. The surface has some sort of ileus transformation. There are significant changes in this biopsy, in addition to having boatloads of eosinophils in the lamina propria, as well as in the glandular epithelium.

The next slide, in eosinophilic duodenitis, a threshold value could be 2 times reported normal peak value of eosinophils, so it could be 52 or more eosinophils in one high-power field. A recent study used a threshold value of 30 eosinophils in 3 high-power fields for diagnosis of eosinophilic duodenitis.

The next slide shows an example of -- again, I think those 10 pathologists, or another group of 10 pathologists, would agree; there are too many eosinophils in this biopsy. And when beginning to study diseases that are not yet well characterized, a comfort zone is to work with the patients who we know have the disease.

We know it when we see it. It may not be well defined yet, the parameters may not be set yet, the threshold value may not be determined yet, but we know it when we see it. This we know when we see it. This is eosinophilic duodenitis. The number of eosinophils in these high-power fields would exceed 30 or 70, or whatever, at least 50 for sure. And again, there are other changes. There are no villi here to speak of; certainly not a normal length of villi, and there are some epithelial reactive changes.

The next slide is another example of eosinophilic duodenitis. It's a little bit further away, so a little more difficult to see the eosinophils, but there are a lot of eosinophils in

this biopsy. If you had a closer view of it, the arrows are pointing to eosinophils. The asterisk is showing what's left of the villi.

You'd really need to know where this biopsy came from to be sure that you were dealing with a duodenal biopsy. Arrows with a little white edging are pointing to eosinophils in muscularis mucosa where we normally don't see them, and the arrowheads are pointing to them in the submucosa, where, again, we normally don't see them, which are abnormalities.

The eosinophilic colitis story is more complicated for the reason I've already alluded to in that the normal number of eosinophils in the colon vary according to the site. So we definitely need to know the site, and we very likely will need to have different threshold values for diagnosis in those sites.

The second bullet there, it shows some of the values that were used in a recent study of eosinophilic colitis in children in which they used values that were higher in the right side of the

colon compared to those in the left side of the colon.

The next slide shows an example of eosinophilic colitis. There is a crypt towards 9 o'clock there that is partly disrupted. It could be because of mechanical forces because of obtaining the biopsy, but it could be because of the number of intraepithelial eosinophils that there are in that crypt. The reactive features of the crypt epithelium in that crypt, it's just too friable to withstand normal handling.

In the next slide there are a lot of eosinophils both in the laminate propria and the tissue between the crypts, and the arrows are pointing to crypts that have significant numbers of intraepithelial eosinophils in the crypts.

The next slide by way of conclusion summary, threshold values are not currently defined or widely accepted for non-EoE EGID as the value is for EoE of 15 eosinophils in a high-power field, which is an imperfect value, but one that is useful.

There are significant changes in biopsies that have a lot of eosinophil inflammation, and it's hard not to relate the presence of those changes to the presence of the significantly increased numbers of eosinophils in those biopsies. So I, too, look forward to the continuing discussions, and I thank you very much for your attention.

DR. ROTHENBERG: Thank you very much, Dr. Collins. That's very informative and great visual presentations of what EGID looks like.

I'd like to now move on to the next talk, which will be by Dr. Nimi Gonsalves. Dr. Gonsalves is a professor of medicine in the Division of Gastroenterology and Hepatology at Northwestern University, Feinberg School of Medicine, and is the co-director of the Northwestern eosinophilic gastrointestinal disease disorders program. Her extensive clinical experience with EGID have shaped the overarching research goals that she has, which include identifying novel treatments and determining the best methods to measure disease

activity.

Dr. Gonsalves, please start.

Presentation – Nirmala Gonsalves

DR. GONSALVES: Thank you for that introduction, Dr. Rothenberg, and thank you to Drs. Kowalik and Lyons for the opportunity to join you today. My talk is Clinical Symptoms and Signs and Natural History of Non-EoE EGIDs. Here are my disclosures, none of which are relevant to the talk today, other than I will be referencing some off-label use of treatments for EGID.

What I'd like to try and do with my time is review with you the clinical presentation and endoscopic features of these disorders, touch upon the impact on quality of life, and review what we know about the natural history and disease course.

There are many phases of eosinophilic gastrointestinal disease, and as you've heard, nomenclature has been based on the organ involved. So in eosinophilic gastritis, inflammation is in the stomach; in eosinophilic gastroenteritis, in the stomach and small intestine; when it's in the

small intestine only, eosinophilic enteritis, and in the colon only, eosinophilic colitis. As we've heard from Dr. Dellon, there is some evolution in nomenclature here, but for the purpose of this talk I will be referencing these terms.

I think it's important to highlight that clinical presentation of these disorders may differ and symptoms are determined both by the organ and the layer of bowel wall involved. So when I'm commenting on bowel wall layer, I'm talking about the mucosal variant or the superficial layer of the bowel; the muscular variant or the deeper layers of the bowel; and the serosal variant, which is the outermost layer of the bowel wall.

Symptoms really do vary by organ involvement. For instance, in eosinophilic gastritis, patients may have clinical symptoms of abdominal pain, nausea, vomiting, early satiety, and diarrhea may be present. Lab testing may reveal anemia, elevated peripheral eosinophils, and you may start seeing low protein and low iron. If imaging is done, you may see some gastric

thickening and pyloric stenosis, and as we've heard from Dr. Dellon, atopy is typically present.

In eosinophilic gastroenteritis, when there is involvement of the stomach and the small bowel, you can see similar symptoms of abdominal pain, nausea, vomiting, and early satiety. Depending on how much bowel is involved, you may have more predominant diarrhea or bloating. You can see anemia, elevated peripheral eosinophils, and low protein may be more prevalent, particularly if you have protein-losing enteropathy. Imaging can also show gastric involvement, as well as small bowel thickening or strictures, and atopy is typically present.

In eosinophilic colitis, you see more of a presence of diarrhea and rectal bleeding. Lab work can be similar. On imaging, you may see colonic thickening, and atopy is not as common as the first two disorders.

Symptoms also vary by the tissue layer involvement. For instance, the mucosal variant is the most common type, and these patients can have

decreased appetite, early satiety, nausea, vomiting, and abdominal pain. When there is diffuse small bowel disease, you can see malabsorption, failure to thrive, and protein-losing enteropathy.

When we get to the muscular variant, including deeper layers of the bowel wall, you can have wall thickening, which can impair motility and create rigidity. That can lead to symptoms of intestinal obstruction like nausea, vomiting, abdominal distention, and gastric outlet obstruction.

When we have that serosal variant, and this is the least common type. It's usually associated with enteritis, and patients may have isolated ascites or ascites in combination with symptoms of mucosal and muscular EGE, and ascites is typically eosinophilic predominant.

I'll now walk you through examples of each of these subtypes. With mucosal disease, this is a 28-year-old male with nausea, vomiting, diarrhea, and 30-pound weight loss. He had lab work with an

albumin of 3.0 and an absolute eosinophil count of 2200. He had an endoscopy and colonoscopy with polypoid legions in his antrum and ileum. He was diagnosed with EGID in the mucosal form involving his stomach and ileum.

The next patient is a 24-year-old female with progressive nausea, vomiting, and diarrhea, early satiety, bloating, and weight loss. She had a refractory non-healing duodenal bulb ulcer for over a year, and her repeat endoscopy after PPI and steroids still showed a persistent ulcer, duodenal edema, and early stenosis. Her biopsies showed over a hundred eosinophils in the stomach and small intestine, and she was diagnosed with EGID, the mucosal and muscular variant, in the stomach and duodenum.

Another example of more predominant muscular disease here is a 48-year-old male with lifelong dysphasia who presents with chronic abdominal pain and non-healing duodenal ulcers with recurrent GI bleeding and vomiting. He is atopic. His eosinophils are 1200 with an albumin of 3.2. His

endoscopy was consistent with EGID with involvement in the esophagus, stomach, and the duodenum.

In the bottom panel, you see the thickened rugal folds in the stomach. In the top panel, you see a very narrow caliber esophagus, and he did have profound duodenal structuring. He represents mucosal and the muscular variant.

The last example I'll share with you is serosal disease, which is the more rare form. This was a 65-year-old male with abdominal pain and diarrhea and presents with abdominal distension. He had a history of asthma, diabetes, and hypertension. His CT scan showed significant ascites, as demonstrated by the arrow, as well as a mesenteric inflammation. He had 88 percent eosinophils in that ascitic fluid and his absolute count in the blood was 8,000. He underwent a hematology workup and was ruled out for HES and was diagnosed with EGID with a serosal variant.

I have shown you that the clinical presentation can vary quite a bit, and it's important to distinguish EGID from other disorders,

and you'll hear that in a talk from Dr. Talley shortly. I would just like to show some commonalities with EoE.

For instance, as you heard from Dr. Dellon, the diagnostic criteria for EoE, it's a chronic immune-mediated clinicopathologic disease. The diagnostic criteria for non-EoE EGIDs are coming soon and will highlight that two are chronic immune-mediated clinicopathologic diseases. We need to have clinical symptoms as well as that histologic information. And while we all believe this, the words of Dr. Collins says it best. "When you see it, you know it." When you're sitting in front of that patient with non-EoE EGID, you know what you're dealing with.

So what clues us in, as gastroenterologists in terms of endoscopy features, to think about these disorders? This is a study done through the CEGIR group and Dr. Hirano looking at endoscopic features in the stomach in eosinophilic gastritis.

This is the Eosinophilic Gastritis Endoscopic Reference System or EG-REFFS. You'll

see normal appearance of the gastric mucosa in the top two pictures and you start seeing abnormalities in the bottom two panels. These abnormalities include erosions and ulcerations, granularity, raised lesions and nodules, erythema, thickened folds, friability, and pyloric stenosis.

In these next pictures you'll see examples of each. On the left, we see erosions in the top two pictures progressing to deep ulcerations in the bottom two panels. In the middle panel you start to see these raised lesions which almost look like pseudopolyps in the antrum and they are more predominant in the antrum, and sometimes you'll even see erosions over these pseudopolyps. In the right panel, you'll see granularity or this loss of vascular pattern, which can either be fine or coarse.

We know that the severity of the disease presentation really can vary, so patients may have very mild symptoms. You may see mild clinical symptoms and subtle endoscopic abnormalities. The symptoms may be intermittent and it may not affect

them greatly in this stage.

However, you can have patients with more moderate presentation. They're having more persistent symptoms and endoscopic abnormalities, and it's starting to have more of an impact on their quality of life. On the right here, we see a patient with severe disease, with significant symptoms and complications from their disease such as GI bleeding, perforation, and this is having a marked impact on their quality of life.

What I'd like to highlight here is that clinical presentation really does determine the overall workup and the treatment plan. For instance, the treatment plan for someone with mild disease may differ from someone with severe disease, and the overall workup also may differ based on the clinical presentation and that patient in front of you. It's not a one-size-fits-all solution here, so we really take each patient as an individual.

I mentioned a bit about impact on quality of life, and what do we know about this? Data

suggests that diagnostic delay can impact disease burden. This is a study from Dr. Chehade and colleagues and this schematic in their study shows that there's an average diagnostic delay of five years prior to presentation. In our ELEMENT study, we saw an average duration of symptoms of 8.8 years prior to presentation.

So these patients are really suffering for a while prior to diagnosis. And why is that? If you can join along with the schematic, initially, patients need to present, and oftentimes they present with non-specific symptoms and signs. That may lead to a delayed referral to a gastroenterologist and a lack of thorough diagnostic workup. However, an astute clinician may pick up on their concomitant allergic disease and/or peripheral eosinophils, and then refer them on.

They then need to have endoscopy with biopsy and multiple biopsies from the stomach and the duodenum. However, another point of delay could be that there was no collection of biopsies or biopsy

samples were not sent to the pathologist.

Next, we need to have a thorough histologic evaluation with H&E and quantification of eosinophils. And as you've heard from Dr. Collins, there's no standardization of quantification of eosinophils and the number and location of biopsies may have been insufficient to make this diagnosis. But if you have an astute clinician that gets enough biopsies and an astute pathologist that makes this diagnosis, you now make the diagnosis of non-EoE EGIDs. Then we still have the hurdle of treatments, which are currently off label or in clinical trials, so patients really do have quite a journey through this process.

At our center, we looked at EGID and the impact of health-related quality of life together with our GI health psychologists, Dr. Bedell and Taft. We had patients with EG and EGE complete semi-structured interviews, assessing common domains of health-related quality of life.

Four domains really stood out: the psychosocial impact of diagnosis, patients' mood

before and after diagnosis, and while they shared with us they could be quite depressed, they actually had a relief of getting the diagnosis and having a plan in place; impact on social relationships were seen, particularly with missed work, school, and social events for fear of getting symptoms, and social isolation; financial impact with a financial cost with medications, formula, food, and repeated procedures; and the impact on the body, body imaging and strain on health activity.

A study from Dr. Jensen and the CEGIR group also showed high patient disease burden in EGID, and non-EoE EGID more frequently had non-specific symptoms of nausea, abdominal pain, diarrhea, constipation, and bloating, and a higher frequency of fatigue and isolation.

So now that we've heard a little bit about the clinical presentation, endoscopic features, and the impact on quality of life, what do we know about the natural history and disease course? There are a few studies that have looked at that,

and I will highlight a couple.

This is a study by Dr. de Chambrun looking at variations in disease course which suggests chronicity of this disease. They looked at patients with EGE, and this was defined as involvement of any segment of GI tract. It was a retrospective review where they followed patients for 13 years.

They then broke it down by subtype of disease, and this was gastric disease. In gastric disease, zero percent of patients had a single flare without relapse; 33 percent had multiple flares and periods of full remission; and 67 percent had a continuous course. Soothe majority of patients had chronicity in their disease.

Again, we see this with proximal small bowel; 20 percent had a single flare without relapse and 80 percent had either multiple flares and periods of full remission or continuous course, again suggesting chronicity.

They also looked at this based on subtype, mucosal, muscular, and serosal. What you'll see in the first two bars is that the majority of patients

with mucosal and muscular disease had either recurring or continuous disease. Fifty percent of the serosal variant did have a single flare, but that variant, as you know, is quite rare; so again, another feature of chronicity.

Another more recent study was done in Tokyo. This was the Japanese survey study surveying over a thousand hospitals. They had detailed data for 786 patients, 39 percent with EoE, 61 percent with non-EoE. In the non-EoE patience, 62 percent had small bowel involvement, 49 percent had gastric involvement. What they found was that 66 percent of their patients had continuous disease, most non-EoE EGIDs were persistent and severe, and restriction of activity, weight loss, surgery, and hypoproteinemia were more common in pediatric patients.

They also showed in this slide, based on age, that patients over the age of 5, 65 to 75 percent had the continuous type of disease; so again, really suggesting chronicity here with the non-EoE EGIDs.

The other question I was asked was to look at whether or not patients with gastric involvement fared differently than patients with gastric duodenal and isolated duodenal involvement. I'll highlight just two studies, and you've heard a bit about this from Dr. Dellon.

This was our ELEMENT study looking at 15 adults who had elevated eosinophils in the stomach and/or duodenum. You see here profound reduction in eosinophils after intervention with an elemental diet, and patients with gastric involvement, gastric duodenal, or isolated duodenal involvement fared equally.

This was also seen in the ENIGMA study which showed histologic improvement in the form of eosinophilic GI disease. So whether or not patients had eosinophilic gastritis, enteritis, or combined gastritis and enteritis, they all fared similarly after intervention, suggesting that these patients are acting similarly.

I was also asked to talk about complications and outcomes, and we can take a page from EoE here,

where we think that patients start off with an inflamed esophagus, lots of eosinophils, and as time goes on there's more fibrotic change and fibrotic deposition. And as time goes on even further, possibly a gland mucosal with more fibrotic changes.

We think this happens as a continuum over time, and we can see several associations with non-EoE EGIDs. Patients over time may have strictures, obstruction, perforation, anemia and bleeding, and malnutrition. They have chronic symptoms which can decrease quality of life and financial burden. Similarly to EoE, thankfully there's no progression to malignancy. We have not seen any predictors of disease progression or complications, and similarly to EoE, treatments are off label and in clinical trials.

In conclusion, hopefully I have shown you in non-EoE EGIDs 2021, clinical presentation is related to the organ involved and the layer of bowel wall involved. It's a clinicopathologic diagnosis with chronic symptoms. Those symptoms can

be abdominal pain, diarrhea, weight loss, nausea, vomiting, bloating, early satiety, and obstruction.

Endoscopic features include erythema, nodularity, erosions, ulcerations, thickened folds, and pyloric stenosis. Science and lab work are often suggestive of malabsorption, including anemia, peripheral eosinophilia, and low protein.

Outcomes and natural history suggest that this is a chronic disease with significant impact on quality of life. Outcomes are still an area of unmet need, but get-togethers and gatherings and conferences like this really shed light on these disorders and hopefully pave the way to learning more.

Thank you all for this opportunity, and I look forward to the discussion.

DR. KOWALIK: Thank you so much, Dr. Gonsalves, for presenting the understanding of EGIDs, signs and symptoms, and natural history. We really appreciate your experience and your highlighting some of the challenges we face as clinicians with regards to the variability of the

signs and symptoms and the natural history.

Just as a quick reminder, if you have questions during today's presentations, please enter them in the Q&A box, and we will try to address as many of them as we can during the panel discussion and Q&A, which follows each session.

Our next presentation will be from Dr. Nick Talley, who I will add is calling in all the way from Australia in the middle of the night, so thank you. Dr. Talley will be presenting on the alternative etiologies for gastrointestinal mucosal eosinophilia. Dr. Talley is a gastroenterologist with a special interest in gastrointestinal inflammatory disorders, the microbiome, and neurogastroenterology. He is currently a distinguished laureate professor at the University of Newcastle, Australia.

Dr. Talley, go ahead.

Presentation – Nicholas Talley

DR. TALLEY: Thanks very much. I appreciate being here, and it's great to be able to share information and to see this collaboration around

the world. I've been asked to talk about alternative etiologies for gastrointestinal mucosal eosinophilia, and I've also been asked to talk about the association of mucosal eosinophilia in the gut and functional GI disorders. So I'm going to cover both of those areas, as they're interrelated, and I look forward to the discussion and question time as well, as there certainly are some areas of uncertainty and controversy in this field.

But I am going to argue that mucosal eosinophilia in the gut is clinically, at least, relatively easy to recognize in terms of the pathology and the clinical presentation. At least, that's how I'm going to argue it, and I'll be interested to see what others have to say. These are my disclosures; thank you very much, and moving on to the next slide.

You've already heard from the other presenters about the traditional EGIDs, the traditional eosinophilic GI diseases. They're considered to be rare. They're linked to atopy very

strongly. There may be increasing, particularly eosinophilic gastroenteritis with recent data, and of course eosinophilic gastroenteritis, as defined by the previous presenters, can present with various phenotypes: mucosal, muscularis, and serosal.

But I'm also going to show you some data which suggest that these diagnoses of these rare conditions, actually, is frequently delayed, as already mentioned, and these patients are often initially diagnosed, actually, as having a functional GI disorder until finally the penny drops, and the pathology is recognized, and they're reclassified as having one of these disorders. But that, again, has been considered to be rare. Eosinophilic colitis is particularly rare, but eosinophilic gastritis and duodenitis we do see in practice, but not that often, according to the literature.

Again, this has been shown, but I just want to emphasize that in the United States, really, the number of cases of the non-EoE EGID is thought to

be around the 50,000 mark, and the prevalence of the various conditions -- based on one study here, and there are several others with similar numbers -- again, rare conditions.

In our series at the Mayo Clinic, which we did a number of years ago, where we looked at all the cases that have been diagnosed with eosinophilic gastroenteritis and/or eosinophilic colitis -- we looked at the symptoms these people had, and we also looked at the natural history, and the outcomes, and the initial diagnosis -- very striking in that series, and in others, is that a number of these patients, again, at initial presentation, were not diagnosed with an EGID; they were diagnosed as having a functional gut disorder, and when they had gastroduodenal disease, they had symptoms suggestive, really, of functional dyspepsia.

So this raises the tricky issue of, well, is there a relationship here and how do you separate these conditions? And I'll cover that.

What's the differential diagnosis of GI

tissue eosinophilia? Not peripherally eosinophilia, which has many, many causes and indeed needs to be thought about in this setting, with the setting of GI tissue eosinophilia. And of course there are a number of important conditions. There are various parasitic infestations that can lead to GI tissue eosinophilia.

Giardiasis, which isn't listed on here, is something we've certainly seen from time to time in clinical practice. A number of these others are really relatively rare, while there aren't good data on the exact prevalence. Some of these present with very classical syndromes. For example, dog hookworm presents with classic ileocolitis. They don't get gastroduodenal disease at all. They get an ileocolitis, and it's quite distinct and, in fact, important to recognize, although, again, relatively rare.

So while there are a large number of various potential infectious causes, in the United States if you haven't traveled to somewhere exotic, if you've lived in the U.S., really, the list of

infectious causes for tissue eosinophilia is very shorthand in most cases will not be found, even when searched for very hard.

There are infections, though, that can cause tissue eosinophilia. Here's one that we identified a few years ago in the column. This is a colonic spirochete. It is a treponeme. It actually is not picked up on 16S because the primers don't pick it up, generally, and we've shown this. But you can find this organism, and it's linked to a classic colonic eosinophilia. It's not very dramatic, but it's clearly abnormal compared to controls.

This was thought to be a very rare infection, possibly a commensal, although we show the clear link with IBS irritable bowel syndrome and diarrhea, and studies from Sweden have suggested this may be much more common than currently recognized. So for colonic eosinophilia, at least, this is very specific, but finding colonic eosinophilia otherwise -- in the setting, for example, of IBS or another functional GI disorder -- is, to be frank, very, very uncommon.

There are drugs that can induce tissue eosinophilia in the gut. We did a systematic review, actually, in preparation for today's presentation, looking at the literature, the entire literature, for the drugs that are being linked to tissue eosinophilia; and there are many, and I've listed a number of the more common ones on the slide in the box on the right-hand side.

Very few of them are GI drugs, but there are a number of drugs here. But in fact, when you look carefully and critically, very few of these have been confirmed with re-challenged testing, so a lot of this literature is anecdotal, at best, case reports and really need to be taken with a grain of salt.

There is evidence, though, the proton-pump inhibitors alter duodenal, in particular, eosinophilia. There's work on this, and I show one recent study from the Leuven group in Belgium, the Jan Tack group, and they showed, for example, that patients with functional dyspepsia, when you place them on a PPI -- this wasn't a randomized trial,

but still it was a well-done study. You place them on a PPI, you suppress the duodenal eosinophil count, and interestingly and surprisingly in the healthy volunteers, the opposite was seen.

I must say that needs to be confirmed, as that hasn't been shown by anyone else to this stage, but the suppression of duodenal eosinophilia by PPI, the suppression rather than the increase, suppression is well described. We described it a few years ago, and this is now confirmed.

Celiac disease can present with tissue duodenal eosinophilia. In fact, we know that's part of the characteristics of celiac disease, although the pathological relevance of those increased eosinophils is less clear. We've established some counts in our laboratory for what's normal versus abnormal in celiac disease, but the relevance of this, just as I said, to the disease processes isn't clear.

Celiac disease is a very straightforward, relatively straightforward, disease to diagnose and is not likely to be confused with any other

diseases and, in fact, obviously can be screened by serology and then confirmed by duodenal biopsy, at least in adults. So I think it's just important to recognize this association, but it's not something that's confusing in clinical practice or would be confusing in clinical trials.

Inflammatory bowel disease has also been linked classically to increased tissue eosinophilia. A number of studies have shown this, including work that we did many years ago. Again, the exact relevance of the increased eosinophil count in IBD is less clear, and IBD is a clinicopathological diagnosis that, again, usually in practice is straightforward and unlikely to be mixed up with another disease process, and I think not likely to be confused with an EGID of any sort, based on the clinical assessment and the histology.

There are other tissue processes that can lead to increased tissue eosinophilia, including malignancy and including, for example, eosinophilic granulomatosis with polyangiitis; extremely rare. The old name was Churg-Strauss syndrome. They get

asthma, for example, which is the clinical tip-off. But in essence, there aren't many others that are clinically very relevant for a population of patients in the United States, arguably.

H. pylori, in our hands, is associated with an increase in gastriceosinophilia. This is a study, a random population sample. We took a random sample. It's a Swedish population. We approached people in the northern parts of Sweden randomly. Eighty percent of people we approached agreed to come in for a pleasant, unsedated upper endoscopy and biopsies, and also some other sampling. We actually endoscoped 1001 subjects.

This is data from that population-based study and this is a subsegment of that. But basically, we did show that there was clearly an increase in gastric tissue eosinophilia if you were H. pylori positive, but we didn't see any increase duodenal eosinophils in the presence of H. pylori.

Hypereosinophilic syndrome is also important to recognize, and they get tissue eosinophilia, alright, in the gut. But they have very high

peripheral eosinophil counts, more than 1500 on two occasions, at least a month apart; so a chronic presence of peripheral eosinophilia, plus they have organ dysfunction.

That's a definition of the syndrome. You normally look for other causes but this doesn't get confused with EGIDs because they don't have this very high peripheral eosinophil count and they don't typically have other organ dysfunction such as cardiac dysfunction. So this isn't usually any problem sorting out from the other conditions.

Now let's turn to the functional GI disorders because, as I've intimated, some of these patients actually are found to have eosinophilic GI disorders and, in fact, in recent work, there's evidence that these are much more common than we've previously recognized.

Just to remind you, we've got functional dyspepsia on the irritable bowel syndrome that affect a very significant portion of the population. A functional dyspepsia really is a gastroduodenal syndrome very much about

postprandial symptoms of pain, irritable bowel syndrome pain with abnormal bowel habit. Of course there's essentially considered to be unexplained conditions, although there are models of gut-brain interactions that are intimated to be relevant to the disease pathogenesis.

For a number of years, we've been particularly interested because we noticed that we were missing that patients with a diagnosis of functional dyspepsia sometimes turned out to have tissue eosinophilia, and then we also performed a formal study. This was a study where we actually went into that general population in Sweden and we obtained that random sample, and we specifically looked for evidence of gastroduodenal eosinophilia. What we found in that study -- I'll show you in a moment -- was that it suggested that we were underdiagnosing eosinophilic GI disorders in this population by a significant margin.

I'm going to show you some data presented at DDW just this year which really suggest that this is true, and we are missing these cases, and they

are interlinked, I would argue, based on the evidence.

So just to remind you, functional dyspepsia is this clinical syndrome. It's thought to be unexplained. You do not see peripheral eosinophilia. Endoscopy is normal. So it's not the same as eosinophilic gastroenteritis that you've heard about in the previous presentations, at least not using the definitions that are currently applied for the syndrome.

IBS, irritable bowel syndrome, and FD, they overlap more than expected by chance. There's a very close relationship between them, so it's relevant, I guess, when we look at some of the data that's to come.

Functional dyspepsia is also increasing. This is some general population data and it's particularly the group with postprandial symptoms, early satiety and postprandial fullness. Interestingly, this is the group that seems to be linked to finding a potential eosinophilic gut tissue infiltration in the duodenum and/or the

stomach.

This is a study, and we did the original study. It was a case-control study, a nested case-control study, in that random population sample. The controls were a gold standard. It came from the same population as the cases, a randomly selected population, too, a representative population, based on all the data that we could see.

We showed that there was an increased tissue infiltration in the duodenum, in particular, in this study and there was evidence of eosinophil degranulation. They would degranulate next to the nerves also more often than expected and very significant odds ratios for increased duodenal eosinophils, between a 7- and 12-fold increased risk found for all functional dyspepsia or non-ulcer dyspepsia.

Others have shown this as well and actually extended these observations. This is work from Leuven showing not only that there's increased major basic protein release in functional dyspepsia

versus control, and increased tryptase, and evidence of increased mass selectivity, but also neuronal damage and evidence, too, of abnormal neuronal function in the duodenal neurons that were isolated and tested.

So calcium fluxes were different in functional dyspepsia, for example, versus controls; very sophisticated and really quite striking work. And what's more, the neural damage correlated with the inflammatory infiltrate, the eosinophils and mast cells that were increased.

Also interestingly, in a syndrome that overlaps with functional dyspepsia and irritable bowel syndrome, what's called non-celiac wheat sensitivity, they've also shown, at least in some cases, evidence to this duodenal eosinophilia. In fact, at least half these people with non-celiac wheat sensitivity fulfilled the Rome criteria for functional dyspepsia and/or irritable bowel syndrome.

In a meta-analysis again reported at DDW, we showed that, in fact, looking at the world's

literature, there is an association between increased eosinophils in the stomach and the duodenum with functional dyspepsia. We also showed there was that association with functional dyspepsia and irritable bowel syndrome overlap, but we could not show that association with IBS alone, at least based on the literature published up to this point.

We also have shown, interestingly, that we know that reflux disease overlaps with IBS and functional dyspepsia, but we don't know why. It's been well shown. We showed in a prospective 10-yearfollow-up of those with eosinophilic duodenitis, identified in that random population cohort, the Swedish population, they had a 6-fold increased risk of the new onset of symptomatic gastroesophageal reflux, suggesting perhaps there's a relationship between this eosinophilic infiltration in the duodenum and the onset of reflux, at least in a subset of patients, although we don't know the exact characteristics of that reflux disease work that we're currently doing now.

There's this model -- and this was inspired by Marc Rothenberg's editorial that accompanied our original work and work that we followed up in the lab as well -- showing that just like in classic eosinophilic gastroenteritis, in functional dyspepsia, there's a Th2 response going on; and, indeed, at least in our work, suggests eosinophil infiltration and degranulation of mast cell recruitment is absolutely critical for what happens in this disease process.

We've shown, for example, this increase in small intestinal homing T cells present just like in inflammatory bowel disease in functional dyspepsia. So what has been called a functional syndrome looks remarkably organic, at least in a subset.

This is the study that's already been mentioned earlier by other presenters, so I won't go through it in great detail. It's a big U.S. study, 20 centers across the United States, and 556 patients were screened. They completed a symptom questionnaire, a diary. They had to have

moderate to severe symptoms.

The symptoms were gastroduodenal as well as diarrhea when you look at them, and they had a standardized endoscopy and biopsy protocol with predefined histological cutoffs for eosinophilic GI disease in the 30 number. Greater than or equal to 30 per high-power field was used; 45 percent met that criteria.

We also included controls here from four of the centers. These people did not have GI symptoms, essentially, and went through the same protocol, and they actually, very uncommonly, had evidence of EG or EoD, 6 percent, a very small number, 33, but still they were well-defined controls. And most of these patients who actually were identified to have EGID in fact had a clinical diagnosis of irritable bowel, functional dyspepsia, or reflux.

This just shows you the data with the controls versus those patients who ended up with a diagnosis histologically of eosinophilic duodenitis or eosinophilic gastritis, just showing you there

aren't really any overlaps statistically significant; of course, differences, whether you use the mean or the peak. And you could argue, actually, the 30 cutoff is conservative. It's reasonable, but it's conservative.

Of course, we also showed it was really similar across the United States, which is really, I think, interesting. You could argue maybe slight differences, but not much, and it suggests this is much more important than we've realized.

So look; eosinophilic GI diseases, there are a number of mucosal causes, causes of mucosal disease. I've talked about parasites, various other inflammatory gut diseases, and hypereosinophilic syndrome. Frankly, these are blindingly obvious to sort out in clinical practice or for a clinical trial.

Making a diagnosis of an eosinophilic GI disease in a functional GI patient, if you take the biopsy, sufficient biopsies because it's patchy, and if you look carefully and count, it's also relatively straightforward. That's what we're

doing in our practice now, based on the results of the work that I've shown you.

I think these are underdiagnosed. I think, based on the evidence, that there's a subset with functional dyspepsia who have an EGID, and the EGID is the cause of those symptoms; at least that's the evidence that's emerged, and thank you very much for your attention.

DR. KOWALIK: Thank you, Dr. Talley, and thank you for sharing your data on many of the alternative etiologies for mucosal eosinophilia. I think we're all looking forward to more discussion on this topic during the panel discussion.

Next, we will take a 10 minute break. I've got the time as 11:24. Let's return at 11:25 [sic], so a little bit more than 10 minutes, where we will start the panel discussion and Q&A. I hope everyone can stand up, stretch their back, look at their computer, phone, or a tablet, and we'll see you back in 10 minutes at 11:35. Thank you.

(Whereupon, at 11:24 a.m., a recess was

taken.)

Panel Discussion and Q&A

DR. KOWALIK: [In progress] -- panel and Q&A discussion. Before we start, just as a reminder, this is a workshop, and it's intended to facilitate collaboration, information sharing, and scientific discussion on how to address some of the key issues in the clinical development and treatment for EGID. We are encouraging participants to share their experience and expertise for the benefit of the group, but note that today's workshop is not an advisory committee in which FDA is seeking advice or a forum during which regulatory advice will be given.

I'd like to invite all of our panelists to please turn on your video. In addition to our session speakers, we heard from four, Drs. Evan Dellon, Margaret Collins, Nimi Gonsalves, and Nick Talley, as well as moderators Dr. Marc Rothenberg and myself.

We're pleased to welcome the following panelists. Panelists, when I say your name, please

briefly introduce yourself to the group.

Dr. Seema Aceves?

DR. ACEVES: Hi. I am a pediatric allergist at the University of California San Diego and Rady Children's Hospital San Diego, with an interest in all of the EGIDs.

DR. KOWALIK: Thank you.

Dr. Glenn Furuta?

DR. FURUTA: Hi. My name is Glenn Furuta, pediatric gastroenterologist at Children's Hospital Colorado and University of Colorado School of Medicine, with a focus on eosinophilic GI diseases also. Thank you.

DR. KOWALIK: Next we have Dr. Robert Genta.

DR. GENTA: Hi. I am Robert Genta, and I am a gastrointestinal pathologist, and I work both at a private lab called Inform Diagnostics and Baylor College of Medicine as a collaborator in Houston.

DR. KOWALIK: Thank you.

Dr. Ikuo Hirano?

DR. HIRANO: Hi. Ikuo Hirano. I'm a professor of medicine and adult gastroenterologist

at Northwestern University Feinberg School of Medicine. Thank you.

DR. KOWALIK: Dr. Erica Lyons?

DR. LYONS: Hi. I'm Erica Lyons. I'm an associate director for therapeutic review in the Division of Gastroenterology at the FDA.

DR. KOWALIK: We have Dr. Veronica Mas Casullo.

DR. MAS CASULLO: I'm Dr. Veronica Mas Casullo. I'm representing Regeneron [ph] work at Regeneron.

DR. KOWALIK: And Ms. Macie Smith?

MS. SMITH: Hi. I'm Macie, and I have eosinophilic gastritis, and the patient representative.

DR. KOWALIK: Alright. Great.

With that, I will turn it over to Dr. Rothenberg to ask the first question, and we'll be incorporating the Q&A questions that we received during the presentations during this panel discussion.

DR. ROTHENBERG: Yes. This first question

is for Dr. Collins, followed by Dr. Genta, and then we will open it to the floor to the rest of the panel for our discussion.

Dr. Collins, can you please expand on histological features, including measures other than eosinophils, that might be leveraged to discriminate patients with EGID from patients with alternative diagnoses?

DR. COLLINS: A great question, Dr. Rothenberg. Thank you.

The distinction between EGID and IBD is sometimes not so straightforward in children as it is in adults. Children can present with symptoms of IBD and on their biopsies have a lot of eosinophils, and not much in the way of acute inflammation, which is the hallmark of IBD. But then on subsequent biopsies, even if the eosinophilia persists, they have more characteristic inflammation, acute cryptitís, acute crypt abscesses, and by that time, IBD grade elevations of fecal calprotectin.

So initially, the distinction between EGID

and IBD in children is sometimes difficult, but tincture of time will separate out those who have IBD.

Again, in children, mostly children, there's an immune-mediated disorder known as IPEX, immune dysregulation polyendocrinopathy, in which they usually have antibodies to their thyroid, enteropathy and X-linked inheritance. That disorder can have a number of appearances microscopically, but the one that's most common includes a lot of eosinophils. And again, that can be difficult to distinguish EGID or to identify this disorder and not EGID.

But there are several ancillary studies that can be performed, indirect immunofluorescence, looking for anti-enterocyte antibodies, for example, in the patient's serum. There are genetic alterations that are associated with IPEX that are not found in patients who have EGID.

Marc, in your lab and in the labs of other people, FOXP3 cells have been found to be increased in blood and tissue samples from patients who have

EGID, and they are characteristically either diminished or missing completely from biopsies of patients who have IPEX. So that's one way that we can distinguish between those biopsies.

I agree with Dr. Talley that for HES, we really need other studies to distinguish those biopsies, HES detecting in the GI tract. Other types of disorders associated with increased eosinophils in the GI tract, and the peripheral counts there can be very helpful.

In EGPA, eosinophilic granulomatosis polyangiitis, sometimes those GI biopsies are associated with a lot of eosinophils. And even though that is considered small vessel vasculitis, the vessels that appear in mucosal biopsies are much smaller than the vessels that are normally affected in EGPA, which used to be known as Churg-Strauss syndrome.

Really, the only way pathologists would get this sized blood vessel one would need to make a diagnosis of eosinophilic vasculitis would be in an infection, if there's been a perforation, for

example.

Infections that are associated with a lot of eosinophilia GI biopsies include anisakid. Sometimes that organism can be found in gastric biopsies, and strongyloides, the same thing. Occasionally we get to see the organism, and then you can make a specific diagnosis; otherwise, we cannot distinguish between those disorders and EGID.

Hyper IgE syndrome seems to be associated commonly now with eosinophilic esophagitis. And again, just looking through the microscope, there's not a good way to distinguish between someone who has that disorder and someone who does not. It's associated with a staph 3 deficiency, so additional lab work is necessary for that diagnosis.

Then finally, patients who have had transplants, solid-organ transplants for example, may have a lot of eosinophils in their GI tract, and we generally attribute that to the use of drugs post-transplant; that may be so.

But in patients who actually have had small

bowel transplants, I know for sure some have developed eosinophilic infiltrates in their esophagus that go away with topical steroids. And significant eosinophilic infiltrates in their small bowel transplant biopsies that diminish with dietary manipulation certainly suggest they have an allergic component to the eosinophilia that appears in their GI tract following transplant. So it may not be all drug-related eosinophilia.

So I hope that wasn't confusing. I suspect somehow.

DR. ROTHENBERG: Thank you very much.

Dr. Genta?

DR. GENTA: Well again, after this thorough synopsis, it's very difficult to add much.

(Laughter.)

DR. GENTA: I would just like to add two situations which have seen pathologists confused, eosinophilic gastritis with autoimmune gastritis. In children, it almost does not exist, so it would be very difficult. In adults, there are some cases where there are really sheets of eosinophils that

somebody inexperienced would tend to confuse with eosinophilic disease.

However, there is an extraordinary amount of intestinal metaplasia usually, but it's not a feature of most eosinophilic [indiscernible]. Then the eosinophilic distribution is limited to the corpus, not to the antrum, so that should help pathologists make the distinction.

Another situation, rarely, as Dr. Talley mentioned before, there may be a case of helicobacter gastritis where eosinophils in the stomach increased enormously. Eosinophils are usually easier to see than helicobacter, so one may be caught by the first thing that one sees, so it's important to explore the possibility of helicobacter before dismissing that as being absent and diffusing into eosinophilic gastritis.

DR. ROTHENBERG: Thank you very much. This is open for further discussion by the panelists.

DR. KOWALIK: If we could try and keep our responses brief just so that we can make sure we cover as many questions as we can. Thanks.

DR. HIRANO: If I could just ask a question for Bob and Margaret, you talked about these kind common cases, but for the common cases of EGIDs, Margaret presented convincing data about these ancillary histologic features. But I've also heard, Dr. Genta, you've mentioned that many times the only abnormality is this increase in tissue eosinophilia.

Can you comment, Bob, on your perspective on that and whether these ancillary features of mucosal injury, are they common or are they uncommon?

DR. GENTA: They are certainly very common in cases with many eosinophils. What does many eosinophils mean? But I will say when the eosinophils per high-power field exceed 60-70, then they are all the features that Margaret just showed you. However, in subtle cases, I cite the less common and certainly less obvious.

Sometimes since pathologists normally do not count or do not concentrate on eosinophils, sometimes we are told, why don't you try to teach

pathology, some features, that may alert them to wanting to find using methods, in a way similar to what we teach to detect helicobacter? What do we do? We say, extensive threats in the lamina propria . This, it cannot be missed. So at that point, you need to go high power and look for helicobacter.

These features are relatively subtle and low eosinophil numbers. So if one doesn't see the eosinophils first, it's unlikely to see all the others.

So to make the answer short, I don't believe that in eosinophil burden cases, there is much value in concentrating in the other features other than for studying the disease and seeing what they mean. But they usually react to changes quite non-specific that could be due to any number of injuries.

DR. KOWALIK: Thank you so much. I think the discussion has really highlighted some of the knowledge gaps about what are abnormal numbers of eosinophils for EGIDs outside of the esophagus; and

as Dr. Collins mentioned during her talk, even the normal values we don't have great data to support that yet either.

So it's a great discussion. I would like to move on to the next question, and this question is for Dr. Dellon. Then we'd like Dr. Rothenberg to comment before we open it up to the rest of the panel.

As the nomenclature for EGID evolves, what data are available to support EGID as a continuum versus distinct conditions based upon the region of involvement? Again, if you can keep your response succinct, we can get several panelists to weigh in.

DR. DELLON: I think this is an interesting and a common question. I think we actually know quite a bit about how the EGIDS are impacting different regions of the GI tract. In general, a portion of patients will have disease isolated to one area and others will have multiple areas impacted.

So if you look across several studies, there's one single-center study from Reed and

colleagues that had about 45 percent stomach alone; 25 percent duodenal alone; 30 percent stomach and duodenum; and 9 percent colon. The study I mentioned, the Pesek, et al. CEGIR study, had about 38 percent stomach alone; a third stomach and small bowel; and about a third other overlapping locations.

The study that Dr. Gonsalves mentioned by Yamamoto and colleagues had about a quarter stomach; a quarter stomach plus small bowel; a quarter small bowel; and about 20 percent multiple locations. Then a recent clinical trial had about 15 percent stomach alone; 38 percent duodenal alone; and 46 percent stomach and duodenum.

So overall, I think you can see about a quarter to a third of patients would have overlapping sites, and then similar proportions with individual sites in the GI tract, especially when you're looking at stomach and duodenum or the combination.

I think what's interesting about this is across these different locations, the clinical

presentations are actually quite similar when you look at these papers, and the treatment response where there's data for this is also quite similar.

I think that suggests that the patients, despite the location or responding similarly, that there could be a common pathogenesis. But what we don't know is why, really, some patients would have one location versus the other, and then patients who have may have these locations plus esophagus involved as well. So maybe I can pass off to Dr. Rothenberg to talk maybe more about the pathogenic implications of those numbers.

DR. ROTHENBERG: Thank you. I would just add to what's been stated, that the information that we currently have evolving, as well as studies of the future, including those by CEGIR, focuses on three aspects that will answer the questions of whether or not this is a continuum. One is phenotype, second is genotype, and the third is the response to treatment.

In terms of the phenotype, we've heard, but I want to emphasize, that most patients with EGID,

particularly the ones with the upper GI involving the stomach and the duodenum, have an atopic presentation, and that strongly suggests a similarity.

If we find that there is a subset of EGID that doesn't have atopic features and does not have allergic type 2 inflammation, then it would be very unlikely that it would be a continuum but perhaps a different pathogenesis and a different entity.

The other point to mention, not only is there a co-occurrence of these diseases together, but we often see that there is a transition from one form to another. So patients with EG may start off with sole involvement of only that segment of the GI tract, but later on develop involvement of the esophagus and duodenum, and the converse is also true. So that really does provide evidence in an individual that there is transformation and there's a continuum in this dynamic process.

In terms of the genotype, we really have begun to have a deep understanding of the pathogenesis genetically of EoE, and it's clear

from the genetics that there are particular variants that are specific to the esophagus that account for the tissue specificity. It is also common genetic variants that are related to type 2 immunity that are shared with other allergic diseases.

I think it's going to be important to assess the genetics, the genetic variants, that are associated with eosinophilic gastritis and other forms of non-EoE EGID, and those studies are currently underway. We predict that there will be shared elements as well as tissue-specific genetic features similar to what's in EoE.

Third, there's a response to treatments. We do see ready-emerging evidence that diet, as well as some of the biologics that have been looked at, have similar activity regardless of the segment that's involved, particularly in terms of EoE, EGID, and eosinophilic duodenitis that strongly suggests a continuum.

It will be very interesting to see the role of different specific cells, whether it be

eosinophils or mast cells, for example, and how we can use specific targeted therapy to ablate these and determine if these diseases are indeed causally related and now provide further evidence for a continuum.

DR. KOWALIK: Thank you, Dr. Rothenberg.

Dr. Mas Casullo, would you mind weighing in on weather a condition as a continuum made up of distinct disorders would impact drug development?

DR. MAS CASULLO: Yes. Clearly, for the first episode, clinical development of a new treatment, what we would like to have is involve patients with as much differentiation as possible so we can really identify if a molecule in the new treatment works for that particular group of patients.

For EGID, I would think that either in gastritis and patients with gastroenteritis may have similar clinical presentations and similar pathophysiology, we could group them potentially because we could follow similar endpoints in the clinical trials.

I would be more reluctant to include the same group patients with colitis since they have potentially different presentations that we would use different endpoints. The first step, I think the more clear presentations, the better, clearly to understand how each of these groups respond to these new treatments as a proof of concept, the better for sure, and really do not have other confounders that may really not inform as how the new treatment works in these particular populations. But for EG and eosinophilic gastroduodenitis, potentially we could combine them together since they have a lot of similarities.

DR. KOWALIK: Thank you. You did bring up your eosinophilic colitis, and we haven't heard much about that during the presentation today.

Dr. Furuta, would you mind weighing in on eosinophilic colitis, where you think it fits in the spectrum of the EGID.

DR. FURUTA: Well, it certainly is the rarest. I think that the presentation for that disease clinically can be quite striking from lower

GI symptoms. There are very few upper GI symptoms related to that, so the diarrhea, the tenesmus, the blood in the stools, and symptoms related to colonic dysfunction certainly are characteristic.

As a part of CEGIR, which has been mentioned several times, I guess I would just expand on that to say it is 18 sites contributing data related to both patient-reported outcomes, as well as samples to understand these diseases, is ongoing and contributing, I think, in many ways to much of the questions that are arising today.

Along with that, eosinophilic colitis is being examined. I think Dr. Rothenberg may want to share also, just to let us know, that these things are ongoing now and will provide, I think, more clarity with respect to the phenotype, genotype, and response to therapeutics.

So rare, easy for us to recognize, and as Dr. Collins brought up, I think the histological assessment, we're increasing in our knowledge and ability to do that.

DR. ROTHENBERG: Thank you.

I think we'll move on to another question for Dr. Gonsalves, and we'll open it up to the floor again.

Can you please expand on the variability of disease severity and rates of progression? Do they vary based upon the region of involvement?

DR. GONSALVES: Thank you, Dr. Rothenberg. I think that's a really interesting question. As I've shown in the presentation, there really is quite variability in clinical presentation of these patients. I would say the majority of us and experts on this panel see that 70 percent of our patients will be in that moderate to severe category. That certainly could be biased by the fact that we are in academic and tertiary centers.

I would say about 80 -- and probably even 90 -- percent of the patients we all see are in that mucosal and muscular combined variant. The serosal variant is really quite rare and, again, presents often with that single episode and then relapse.

We don't know enough about how these

diseases, based on organ involvement, progress over time and if they differ over time in terms of outcomes. We do suspect that over time, with longer duration of disease, similar to what we see with EoE and natural history studies coming out of the Swiss group, that untreated disease over time has increased strictures of predominance. We suspect that is what's occurring with non-EoE EGID, and patients with untreated disease and long-standing disease can have these complications with strictures, ulcer perforations, and, GI bleeding.

DR. ACEVES: Just to add, I agree with what Dr. Gonsalves said and all that you've heard during the talks. Really, the variability and severity are determined by the clinical symptoms, the endoscopic findings, and the presence of increased eos. But in terms of the number of segments that are involved and determining a clinical progression or prognosis, we really don't think that that's the case currently. We're still learning about the progression to complications and what determines

that.

Then I would just underscore that the need for biopsies in the regions that are evaluated is really based on the clinical presentation and the clinical indication in the patient in front of us.

DR. GUPTA: This is Sandeep Gupta. I would add to what Dr. Aceves mentioned that I think in addition to the disease location and progression, we also need to know about age progression, from pediatrics to adults, and how that is impacted as age progresses.

Another challenging factor, at least in pediatrics, is to reach the mid-distal small bowel is challenging. Double balloons are not that easy in kids; so just the accessibility of the organs.

DR. ACEVES: Yes. I agree with what Dr. Gupta said also. And it should be noted that eosinophilic colitis, especially in younger children, could be an entirely different entity than what is seen in an older person. There's a very different differential diagnosis that needs to be thought about with eosinophilic colitis and

often doesn't even warrant an endoscopy or a colonoscopy because the diagnosis is clinically made.

DR. GONSALVES: I would completely agree with what is said, that not every patient needs every single endoscopic workup. I think we really need to take into consideration what their clinical presentation is. And as Dr. Gupta mentioned, doing enteroscopies on all patients, pediatric or adults, can be quite complicated and should be reserved when the clinical indication warrants that.

DR. HIRANO: Can I ask a related question --

DR. KOWALIK: I think --

DR. HIRANO: -- sorry, Matt -- for Dr. Talley.

Dr. Talley, you mentioned that the EGIDs are not associated with life-threatening complications as such is with hypereosinophilic syndrome. I think you're referring to cardiac or CMS involvement.

I'm just curious. This data that you're

citing, does that include the overlap, where some EGID patients have very profound peripheral eosinophilia in excess of 1500; are those patients also included in this statement about non-life-threatening complications?

DR. TALLEY: Well, there is a group that does have a very high EO count, although it's pretty rare. As far as we know -- and I must say it's not something that's been terribly well studied -- they don't progress, or typically don't progress, to organ damage, which is the definition of hypereosinophilic syndrome.

So I think they are overlapping, actually, but I'm not sure why some progress and some don't. But I'm certainly convinced that type of EGID that occurs in those with functional GI symptoms, with a functional GI diagnosis, is very different clinically, at least, from those who have a classic traditional EGID.

They really do look very different. Whether the genetics are similar or not, we do not know. There are lots of questions, but they are different

at least clinically in their behavior.

DR. KOWALIK: Yes. I would like --

DR. LYONS: Thank you. This is Erica Lyons.

DR. KOWALIK: -- go ahead, Erica.

DR. LYONS: Thank you so much, Matt.

This is Erica Lyons. I'd like to kind of reframe this just a tad here. We have great respect and appreciation for your clinical practice, but let's steer this discussion a little bit in terms of the topics on how this would translate or apply to a clinical trial population.

We heard from Dr. Mas Casullo, representing industry, of the importance of really distinguishing and characterizing clinical trial populations, so we'd like to steer the discussion in that direction.

Now, with the evaluation that is commonly done in clinical practice, I would like the panelists to please comment on the potential differences in the evaluation for clinical practice, how that may translate to a clinical trial, and any differences therein that might be

important to highlight for this group of attendees. Thank you.

(No response.)

DR. LYONS: And to start us off --

DR. DELLON: Well, I can start.

DR. LYONS: Thank you, Evan.

DR. DELLON: Okay. Sure.

I think part of that is going to come down to what kind of treatment is being studied and what the target would be, and that would impact the selection of the clinical population. Obviously, you're going to want a moderate to severe group of patients who have chronicity in their symptoms and a clear clinical diagnosis of eosinophilic gastroenteritis or eosinophilic GI disorder, but then from that population that may be identified clinically, it really depends on what you're looking at.

So if it's a medication that's primarily focused on pain or a specific symptom, then those maybe the symptoms that you want to hone in on. If it's a systemic treatment that's anti-inflammatory,

then the symptoms have to be consistent, but you need to make sure you have that patient population with the type of inflammation that a treatment may recognize.

So I think that's the starting point. We could use the analogy, I think, for EoE where we have a little bit of a pathway. There are lots of symptoms that can be seen in EoE, but the most typical one in adolescents and adults is trouble swallowing, so that's been a symptom that's been focused on.

Even though we have a diagnostic guideline with a threshold for eosinophil counts, there can be some studies that include more severely inflamed patients; so you have a bar where you can actually see a bigger delta in the medication effect.

I think those are some of the differences where the clinical diagnosis in the population you start with can be refined in a clinical trial.

DR. KOWALIK: And I would --

MALE VOICE: Go ahead, Matt. Sorry.

DR. KOWALIK: Sorry. I would like to hear

from Ms. Smith, our patient representative. I know you'll be talking more during Session 2 about your experience with EGID, but if you could, can you share some information about the severity of your symptoms? Do the severity of your symptoms change over time? Did you have periods where you had no symptoms or were there periods when you had symptoms constantly?

If you could tell us a little bit of your experience in that context, that would be great.

MS. SMITH: Yes. In the beginning when I first got sick, I was super symptomatic, specifically with anemia, and then a year later, once I was diagnosed, my stomach pain increased. I noticed it with eating any foods, even drinking any liquids, water even.

I found that I was specifically really sensitive to gluten, but then over the course of the years that I've been sick, that's kind of faded, so now it's kind of just random foods. Honestly, for two years I was pretty symptom-free, but in the past, I would say a month and a half or

two, my symptoms have picked back up again, the greatest being my stomach pain.

That's always been the hardest symptom for me, is being in constant pain after I eat. But honestly, for six years I didn't go a day without being in pain. So it's sporadic but pretty consistent on a day-to-day basis.

DR. KOWALIK: Thank you. You heard our discussion about the workup that's performed. Could you tell us what kind of workup you had prior to your diagnosis with EGID?

MS. SMITH: Yes. I started my journey at Children's in the hematology department, and they kind of figured out that I was bleeding, but they didn't know where I was bleeding from. So they sent me to GI, and I had a colonoscopy and an endoscopy done, and they found the eosinophils in my stomach tissue. Then I just had labs and all that done, too.

DR. KOWALIK: Thank you. Thank you for sharing your experience and we look forward to hearing more from you during our next session.

I'd like to change here, if we can, to our next question, and this is for Dr. Talley followed by Dr. Hirano, then we'll open up the floor to the rest of the panel.

Although we've heard from the discussion the clinicopathologic diagnostic approach to EGID as explained by Dr. Dellon and described, Dr. Collins points out there are no clinical definitions for normal or abnormal eosinophils. So we'd like to get your take on what alternatives each of you use to distinguish patients with EGID versus alternative diagnoses for mucosal eosinophilia.

DR. TALLEY: Look, it is an important question. A number of patients will present with gut-tissue eosinophilia and peripheral eosinophilia. One potential marker, if you want to use something as well as the tissue eosinophilia, is the peripheral blood count, the eosinophil count that you can see. The problem is you'll miss a number of cases with traditional eosinophilic gastroenteritis, as it used to be called, and indeed patients who have definite increases in

duodenal or gastric eosinophilia and what are called functional GI symptoms.

So the peripheral count is helpful, but it is also limiting. You could run a clinical trial where they have to have both, but you would be limiting your population, and it wouldn't be representative of clinical practice, and you would certainly be missing cases.

Look, we heard in children it can be difficult to discriminate inflammatory bowel disease from an EGID, but in adults I would argue the clinicopathological assessment there is more straightforward, and you'd be unlikely to get confused; I mean, seriously, unlikely. Others may wish to comment, but that's my experience.

As for celiac disease, if you can't diagnose that and you're not board certified in gastroenterology, you just don't know what you're doing. It's absolutely straightforward in adults and children for most cases. There are exceptions, but they're exceptions, not far from the rule. HES is very clear certainly in terms of the dramatic

eosinophil count peripherally and other evidence.

So to be clear, you worry about parasitic infestation which you can exclude and are rare. You worry about rare vasculitides. They're extremely rare and can be picked up clinically; then the other things really are relatively straightforward.

So you can easily, for a clinical trial, select a population that have eosinophilic gastritis and/or duodenitis with chronic symptoms, which is a reasonable population and an unmet need for the U.S. and elsewhere.

DR. HIRANO: Just to follow up on that, I think Nick covered this topic extremely well in his talk and his comments. In my own clinical practice as an adult gastroenterologist, these secondary causes of mucosal eosinophilia are extremely uncommon. The majority of patients with this type of phenotype have primary eosinophilic gastrointestinal disease.

I think some of the clinical challenges that I've faced are already mentioned, the IBD overlap,

the hypereosinophilic syndrome with gastrointestinal involvement, and then less commonly are the EGIDs associated with immunodeficiency or transplant medication, and immunosuppression. But these are all, really, uncommon situations.

In those cases where I think the diagnosis is questioned or there may be a secondary cause questioned, I think this is where I find working with an allergist is extremely essential to appropriate management.

DR. TALLEY: I guess one other point to make perhaps is EoE can sometimes also have eosinophilic gastritis and/or duodenitis. They can be all present. So that might be something you do want to exclude or at least consider in a clinical trial as well as in practice. It's not that common, but it's certainly something to consider, and we do see it.

DR. HIRANO: It's interesting, because that question was also posted on the Q&A about this overlap between EoE and the subdiaphragmatic EGIDs.

It's interesting that even though we consider these to have a shared pathogenesis, the type 2 inflammatory response, the treatment effect, and the food triggers, it's very uncommon to see EGIDs in patients with EoE. It's distinctly uncommon.

So although they share a lot, this is more evidence for this kind of distinct regional specificity as opposed to a continuum of disease.

DR. TALLEY: In our population-based endoscopic study, we didn't find a single case of EoE with gastroduodenal eosinophilia, not one, so that was very striking to us as well.

DR. KOWALIK: Have other panelists had a similar experience?

DR. ACEVES: If I could just add to what Dr. Hirano and Dr. Talley said, one thing that is important with the eosinophilic gastrointestinal disorders, especially below the esophagus, is the chronicity of the disease, and that of course is this double-edged sword of maybe having a longer time to having a definitive diagnosis, assuming that you got an endoscopy.

But by the time we are convinced that somebody has an EGID, we know what it is. Sometimes it takes a couple of biopsies to be really sure in terms of the chronicity because they could have something that's a little more subtle, but I think that chronicity is important as well, like Dr. Gonsalves pointed out in her talk.

DR. FURUTA: Yes, I'd agree with those things and also comment to say that I view the GI tract as four different organs -- esophagus, stomach, small intestine, and colon -- and the symptoms associated with those may have some degree of overlap.

I think when Dr. Lyons was bringing up the evaluation of these patients, the upper endoscopy is critical for us understanding eosinophilic esophagitis. Then again, someone who has eosinophilic esophagitis would not embark on doing a colonoscopy or other kinds of testing to assess for that symptom; and likewise, if someone who's vomiting with eosinophilic gastritis or duodenitis, again, performing other types of diagnostic

procedures would not necessarily be indicated to try to understand who they are and how to provide them with entry into trials.

DR. HIRANO: One point of clarification I may make -- and maybe this is a hemispheric difference between Australia and the U.S. -- is I mentioned that EGIDs are uncommonly found in patients with primary EoE. However, the converse, at least in studies and what I've seen in my own practice, is not true.

Patients with eosinophilic gastrointestinal disease below the diaphragm commonly have esophageal involvement. In the ENIGMA trial, 40 percent had esophageal involvement, so I don't think we see the converse being the case.

DR. CHEHADE: This is Mirna Chehade. I just have a quick comment on this. I know I'm a part of Panel 2.In fact, it is possible also that we don't label the patient as having EoE if they have lower GI involvement such as stomach, gastric eosinophilia or duodenal eosinophilia. That could be a design thing and a definition thing.

So when we looked as part of a multicenter study and we used retrospective data across multicenters and patient questionnaires, we found that 10 percent of patients that identified as having EoE by symptoms and histology had also eosinophilic gastritis.

Then when we did another study where we used a population-based database, so an all-claims database, and we looked at eosinophilic gastritis and/or duodenitis, or gastroenteritis, and we found that 30 percent of these patients had concurrent eosinophilic esophagitis, and the number may be a little bit higher if this was not labeled or actually entered by the physician as part of their charts.

So I think this is relevant as part of a clinical trial. I agree with what Evan mentioned in response to Erica's question as to is there any difference in terms of organ involvement and how would this influence clinical trials. I think it's not just the type of symptom and the severity of symptoms, which Evan elegantly highlighted, but

also it could vary depending on what treatment you're trying to do.

Are you trying to use a topical therapy versus a systemic therapy? If we just draw the correlates with EoE, if you're doing a topical fluticasone or topical budesonide for EoE versus a biologic for EoE, now the degree of organ involvement and where it is might be relevant for one versus another.

So this would be the same if we're dealing with eosinophilic GI diseases below the esophagus. If we're dealing with a targeted therapy, now the delivery method of a drug to the stomach might be very different from that to the colon, for example, versus a systemic therapy that might have a more global effect.

DR. ROTHENBERG: I just wanted to summarize a couple of questions that came in, put it together, and ask the panelists to comment. This has to do with the overlap of these diseases.

Particularly the question is, should lower GI tract involvement be assessed in EoE patients?

And related is, are we missing a lot of EGID by only obtaining mucosal biopsies, particularly in the different forms of eosinophilic gastritis that we heard about earlier from Dr. Gonsalves?

When you answer this question, please consider the answer in the context of clinical trial design. This question is open to the panelists.

DR. GENTA: I think everyone who is being investigated for EoE should also be investigated for gastritis and duodenitis. I think the perceived rarity of the association is due to the fact that lots of patients with EoE, as well as part of the workup, get gastric and duodenal bulbs.

I don't know if Margaret would agree, but most pathologists find those few extra eosinophils if they see them in the duodenum and the stomach and will not comment. If they see them, they think it's part of the EoE and not worth commenting, and most of the time they're not even detected.

So I think that really helps the statistics that say it's no association between these two. I

think there is, and quite a strong one as well.

DR. COLLINS: I think you're correct, Robert, and there again a communication between the gastroenterologist and the pathologist could be very helpful. If the gastroenterologist specifically stated please note increased eosinophils in the stomach and the duodenum, that certainly would encourage pathologists to at least comment on whether they think the eosinophils are normal or increased.

DR. FURUTA: I think to dovetail off of Dr. Genta's comments, there is a large body of data that suggests that there probably is not as much involvement of the stomach or small intestine because of the original diagnostic guidelines that suggest biopsies of the stomach and small intestine be taken at the time of diagnosis; so important information for us to gather, I think, to try to understand this, especially as the potential emergence of more gastric and/or duodenal eosinophilia is occurring.

I think the second is that we really want to

target these evaluations to the symptoms. I think, as Dr. Chehade brought up also, if a type of treatment is targeted toward a specific organ, then it may be important to investigate that. But certainly I think doing a colonoscopy in the evaluation if someone has upper tract disease, when symptoms do not indicate that that may be the case, would be challenging to do, certainly from an, I think, investigational standpoint, and we don't have the evidence to date to suggest that pathogenetically those are going to be linked.

DR. TALLEY: Marc, if I could just make a quick comment; we did a population-based colonoscopy study to look at this very question, chronic unexplained GI symptoms, controls, and looked for eosinophils and other cells in the colon, and just published it a month or two ago, and basically didn't see it; just didn't see it.

So I don't think you're going to find a lot there if you search with colonoscopy in those cases; at least that's our data, or what our data suggests.

DR. HIRANO: I think there are two populations -- to get to Marc's question about who might be missed in clinical trials -- and one is these muscular serosal patients who often don't have mucosal eosinophilia and the other group is patients who have manifestations of disease.

They've got anemia like Macie mentioned or they've got protein-losing enteropathy. They have mineral deficiencies. But they have minimal symptoms. Some of them have minimal to no symptoms. Though they wouldn't meet the symptom threshold to get into a clinical trial, yet they have evidence, objective evidence, of disease. So that's another group that would not be entered into these clinical trials.

DR. COLLINS: If I may, Ikuo, for you and the other gastroenterologists, what is your threshold for getting imaging studies in someone who you think might have an EGID and his mucosal biopsies are not confirmatory of EGID, and an imaging study that might demonstrate thickening of the muscularis, and therefore increase your

suspicion that your clinical judgment is correct?

DR. ROTHENBERG: And if you could answer --

DR. GONSALVES: I would like --

DR. ROTHENBERG: -- in the context of a clinical trial, please, that would be very helpful.

DR. GONSALVES: I can take a jump at that question. If we think that someone has eosinophilic gastritis and they've had normal mucosal biopsies, and we're still highly suspicious of this diagnosis, I think that's when additional workup does come into play; for instance, imaging, like you mentioned.

Traditionally, it was going to a surgical resection to get that that full thickness biopsy, but thankfully now we have imaging to clue us in, as well as some additional biopsy techniques like endoscopic mucosal resection that can get that deeper tissue. So it is warranted in that clinical patient.

DR. HIRANO: I think when the endoscopy and biopsies aren't giving you the answer, and the patient's symptomatic, often we go to imaging,

usually cross-sectional imaging with a CAT scan, and that typically will show some thickening, and lead to a suspicion that there may be some mucosal disease.

DR. COLLINS: And then you pursue that with additional endoscopic techniques?

DR. HIRANO: Right.

DR. GONSALVES: Yes, and we would do deeper biopsies or, for instance, if we see duodenal thickening on that CT scan, that's the indication when we would put someone through a double-balloon enteroscopy to get that tissue diagnosis.

DR. KOWALIK: Alright. I just want to interject and thank all of our panelists from Session 1, and particularly thank you for spending some extra time with us. We carried it over into lunch. We had such a good discussion, I didn't want to cut us off. I think the discussion was really fantastic and highlighted some of the knowledge gaps in our understanding in the areas we need further research and also highlighted how quickly this field is evolving.

So we'll wrap this session up so everyone can get some lunch, take care of any emails and whathaveyou that's popped up during the session. We'll try to stick to our schedule and return at 1 p.m. So it will be a shorter lunch, but hopefully everyone is in agreement with that so we can stay on time for Session 2.

So please return at 1 p.m., where we will start Session 2. Thank you.

(Whereupon, at 12:15 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

DR. LYONS: Thank you very much for joining us again for Session 2 of our GREAT Workshop on Eosinophilic Gastrointestinal Disorders Beyond EoE. Again, thank you for your attendance and also thank you for abbreviating your lunch for us. We had such a great and vibrant dialogue going into the first panel discussion that we wanted to extend it a bit today.

Today, and this afternoon, rather, we have the opportunity to build on what we spoke of in the first session, where we really looked at the diagnosis and natural history of EGID. Our talks for this session are intended to communicate how we assess clinical benefit in EGID across a variety of perspectives, so we're looking forward to that.

Now, I'll just go ahead and turn it over to Ikuo to introduce our first speaker for the afternoon session.

DR. HIRANO: Thank you, Erica.

Again, my name is Ikuo Hirano, and I'm at

Northwestern University Feinberg School of Medicine, where I work as an adult gastroenterologist. It's my pleasure to introduce our next speaker, Macie Smith, who did participate in Session 1 as well.

Macie is a patient representative. She was diagnosed with eosinophilic gastritis seven years ago. Macie is going into her junior year of college. She's majoring in nursing and plans to apply to the nursing program at Aims Community College at the University of Northern Colorado in the spring of 2022.She is currently working as a certified nursing assistant, and Macie will be describing her experience living with EGID and the goals for treatment.

I'll turn it over to your Macie.

Presentation – Macie Smith

MS. SMITH: Hi. Thank you.

I'm going to talk about my experience with living with eosinophilic gastritis and then what my goals are for a treatment.

I first got sick back in 2013 with severe

anemia. A year later, after a bunch of tests and scopes, I was finally diagnosed with eosinophilic gastritis. I've had multiple GI bleeds and stomach surgeries. My first one was in November of 2014. It was my first perforation, which was an emergency surgery; then in May of 2015, I had an upper gastrointestinal bleed.

In March of 2016, I had a partial gastrectomy, and in October of 2016I had my second upper gastrointestinal bleed; then October2018 was my second perforation, which was also an emergency surgery; and then February 2019 was a contained perf, but I didn't need surgery for that one.

In January of 2016, I went on the elemental diet with an NG tube to see if my condition was food related or not. I was on this for about 11 weeks. The visual appearance, when I was done, of my stomach was better, but I still had eosinophils in my tissue.

I've tried so many different types of medications like budesonide, Prilosec, Protonix, mercaptopurine, and prednisone. I took prednisone

consistently for about six years, and it never really showed any signs of working until I tried to come off of it, and then my symptoms increased dramatically. The mercaptopurine really was only beneficial at a higher dose of 100 milligrams, but at the high of a dose, my liver started to be affected, so we had to find a different medication to use.

My biggest most debilitating symptom is the constant stomach pain, specifically after I eat. I also experience radiating pain into my left shoulder, and this really affects my breathing; and walking, the pain intensifies a lot.

I also experience intense nausea and vomiting, and then with that, I also struggle with maintaining my weight because I'm not eating as much because of the pain and the nausea. I also throw up quite frequently, which also plays a role in losing weight.

I also suffer from chronic anemia, so softball was really hard when I played back in high school because I was always super weak and tired,

which made softball and school more challenging for me.

My quality of life has definitely been affected. Over my years of being sick, I have missed over a hundred days of high school because of being too sick to be at school or due to hospitalizations.

My social relationship with food was, and still can be, very poor. I planned my eating around when I would be out and doing things with my friends or family so I would be in less pain. Eating just wasn't enjoyable to me because every time I ate, it gave me debilitating pain.

I missed out on many of the typical high school experiences because I was too sick. I also had limited playing time in softball because of how sick I was, which was the hardest part for me, in all honesty, because softball was the only thing that kept me feeling like a normal teenager.

My day-to-day life for six going on seven years, there wasn't a day I wasn't in pain at some point throughout the day. I had a select few foods

I would eat and it wouldn't cause pain, or at least I had less pain with it. During the school year, I found myself typically making it through the first half of the day, but I usually went home after lunch because the pain was too bad.

I had to strategically make my schedule, so I had lunch later in the day. I had less classes after lunch, and the classes that I did have were usually my easier ones so it was easier for me to catch up on the makeup work that I did miss. I tried really hard to keep my life as normal as possible. I didn't let my disease define me. A lot of people didn't know I was sick because I tried to hide it so well.

In my freshman year of high school, I knew I wanted to go into nursing school after being sick for that year and a half, so I followed a heavy science courseload the remaining years of school. I spent so much time in the hospital, I was always playing catch-up. There were multiple times a year I would be failing, if not all of my classes, because of missing weeks of class from being either

too sick or in the hospital.

Senior year, I started doing my makeup work in the hospital while I was still admitted. Despite missing over a hundred days of school, I did in fact finish high school with a 3.2 GPA. I'm going into my third year of college with a 3.7 GPA and my CNA license, and I have one more prerequisite until I apply to the nursing program this coming spring. I want to celebrate my accomplishments just because I did have such a challenging high school career with being as sick as I was.

My ideal treatment, I have tried a lot, and at times it feels like I've exhausted all of my options for treatment. Finding one that could combat all of my symptoms for EG so I didn't have to take four different medications for all of my different symptoms would be really great.

A medication that doesn't have too many side effects, or too many major ones, would be ideal. Feeling some sort of relief would be more noticeable because I've noticed I am on so many

different medications, but they have a lot of symptoms. Sometimes you fight the stomach pain, you fight the anemia, and you fight nausea and vomiting, or whatever it might be, but then you still have the side effects of the medication; so sometimes it doesn't necessarily feel like a win. Something that could encompass all of my symptoms and limit how the side effects affect me would be really great.

My goals for treatment, obviously, the goal for any treatment is to improve the quality of life, so that would be the main goal I would like to see come from a treatment. But on a smaller more day-to-day scope of things, I would like to be able to eat and enjoy the food I put into my body rather than dreading what will happen after I eat. I want to have energy from eating and have limited nausea throughout the day.

The last thing I hope for is a treatment to be consistent, and I know this can't be guaranteed for any condition, person, or case, but something that my body won't become tolerant to or that won't

just randomly stopped working. Granted, this can't be promised, however, so many of my medications I've tried have worked for a year or so and then stopped benefiting me. And it's really hard because you get used to being healthy and not being in pain, and then it randomly hits you again, and you're like, "Oh, we're back to square one," it almost feels like.

So trying to find something that is more consistent and just guaranteed to help for a longer amount of time would be ideal. But I am so thankful that I got this opportunity to share my story with all of you guys, so thank you.

DR. LYONS: Thank you so much.

Macie, what you've been able to accomplish, despite the obstacles in your way, is very impressive. I know I speak for everyone here when I thank you for sharing your story with us; for sharing your struggles; for sharing the path that you had for diagnosis; for what you've gone through and how you're still stepping up to be an advocate; and for those who are going under similar things

and really pursuing ways that you can care for others.

So we appreciate it. It is paramount to everything that we do, and we are here for you. So thank you so much for being a part of this conference.

With that, we'll move on to our next speaker. Our next speaker is Dr. Sarrit Kovacs. She is a clinical reviewer in the Division of Gastroenterology in the Office of New Drugs at the FDA. Prior to this role, Sarrit served within the Division of Clinical Outcome Assessment as a team leader advising the Division of Gastroenterology, among others, regarding COA or clinical outcome assessment development and analysis. She has a doctoral certificate in evaluation, measurement, and statistics, and over 20 years of applied social science research experience specifically related to qualitative and quantitative research and analysis.

Dr. Kovacs?

Presentation – Sarrit Kovacs

DR. KOVACS: Good afternoon. Thank you,

Ms. Smith, so much for sharing your story.

My name is Sarrit Kovacs, and I'm a clinical reviewer in the Division of Gastroenterology in the Office of New Drugs at FDA, and I'll be presenting an FDA perspective on defining clinical benefit in clinical trials for eosinophilic gastrointestinal disorders or EGIDs.

As Dr. Lyons mentioned, prior to joining the Division of Gastroenterology, I served as a Division of Clinical Outcome Assessment, or DCOA, team leader, advising the Division of Gastroenterology, among other FDA divisions, regarding COA endpoint development and analysis.

Before we begin, I have no conflicts of interest and nothing to disclose, and this talk reflects my own views and should not be construed to represent FDA views or policies. And additionally, when I use the term "drug," I'm referring to both drugs and biologic therapies during the presentation.

Today I'll discuss how we define clinical benefit within regulatory context and how the

approach to assessing benefit for candidate therapeutics for eosinophilic esophagitis maybe leveraged for drug development for other EGIDs, specifically regarding the clinicopathologic assessment related to both symptomatic and histologic improvement.

We acknowledge that the field of EGIDs is dynamic and rapidly evolving, and represents an area of unmet medical need for affected patients. That's why we're having this public workshop, to discuss with multiple stakeholders how to best assess clinical benefit in patients with EGIDs and identify opportunities to collaborate to facilitate drug development in EGIDs.

We are fortunate to have representatives from FDA, regulated industry, the academic community, as well as patient advocacy groups here with us today. To promote a successful dialogue, it is essential that we use a common language when discussing clinical benefit.

FDA and NIH have a joint biomarker working group that created a resource called the BEST

glossary, which is a glossary of terminology related to basic biomedical research, medical product development, and clinical care. On this slide you can see the BEST glossary definition for clinical benefit. It is a positive clinically meaningful effect of an intervention, that is, a positive effect on how an individual feels, functions, or survives.

We defined clinical benefit on the previous slide using the FDA-NIH BEST resource glossary. FDA must abide by evidentiary standards and regulatory requirements when determining clinical benefit to patients in clinical trials.

The Code of Federal Regulations, or CFR, is a codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the federal government. Title 21 of the CFR is reserved for rules of the FDA. Part 314 of Title 21 of the CFR relates to applications for FDA approval to market a new drug focusing on sponsors demonstrating substantial evidence of effectiveness. Demonstration of

clinical benefit requires adequate and well-controlled clinical studies.

Standard drug approval usually requires two adequate and well-controlled studies – one to affirm that the drug is safe and effective and that the benefit profile is favorable, and a second study to confirm this finding in a different patient sample. The effects of the drug need to be distinguished from other potential influences such as changes in the natural history of the disorder, placebo effects, biases in the observation, measurement variability, et cetera.

Part of showing substantial evidence of clinical benefit within adequate and well-controlled studies includes the methods of assessment, which must be well-defined and reliable, and this will be discussed further on a later slide.

There are regulatory challenges to defining what constitutes clinical benefit in rare diseases such as EGIDs. One challenge to defining clinical benefit in EGIDs beyond EoE is the lack of clinical

consensus diagnostic criteria for each EGID subtype. As you heard from Dr. Dellon and Dr. Gonsalves earlier, varied terminology has been used to describe non-EoE EGIDs in the clinical community and in the published literature, and this has limited the generalizability of the currently available literature to inform clinical trial design.

Although efforts are ongoing, the natural history of non-EoE EGIDs at the population level is not yet well-characterized. Additional data from natural history studies would be beneficial to inform future clinical trial designs and increase the likelihood of distinguishing between naturally occurring stabilization or waxing and waning of symptoms versus improvement or stabilization of disease due to treatment effects.

As with many rare diseases, there are no approved therapies for patients with EGIDs to provide regulatory precedent for drug developers. Additionally, small patient populations in rare diseases such as EGIDs often mean that clinical

trials need to be conducted across multiple centers and multiple countries, which may be a challenge to sponsors, for example, with recruitment of patients and translation and cultural adaptation of clinical trial assessments.

EGIDs are found in both pediatric and adult patient populations and clinical benefit can look different for adults versus children in terms of symptom presentation and how best to collect valid and reliable symptom data from patients, such as using patient report versus observer or caregiver report.

Non-EoE EGIDs are rare disorders and often difficult to diagnose. Much of the pathogenesis, risk factors, and natural history of non-EoE EGIDs are not well-characterized, and to promote successful development of drugs for the treatment of patients with EoE, FDA issued the Guidance for Eosinophilic Esophagitis: Developing Drugs for Treatment, which was finalized in September 2020.

Like EoE, non-EoE EGIDs are clinicopathologic disorders. As such, there are

elements contained in this EoE guidance that may be leveraged to support the assessment of clinical benefit for non-EoE EGIDs.

As EGIDs are clinicopathologic disorders, they are typically characterized according to symptoms, endoscopy, histology, and mucosal transcriptome. Therapeutic goals for patients with EGIDs include showing a favorable effect on underlying disease such as normalizing histology and eliminating or meaningfully decreasing symptoms of active disease. Given these two treatment goals, we recommend the assessment of co-primary endpoints to demonstrate effectiveness. These endpoints should include documentation of histologic response based on a peak eosinophil count per high-power field across all available biopsies and assessment of significant and clinically meaningful improvement from baseline in signs and symptoms, compared to placebo, using a well-defined and reliable clinical outcome assessment or COA instrument.

The clinicopathologic assessment of EGIDs

includes histologic assessment of improvement. We acknowledge that there are limitations with using eosinophil counts; however, at this time, eosinophil counts remain pivotal to the diagnosis of EGIDs and is the reportable metric for which we have the most available supportive information.

As discussed during the previous session, EGIDs are a clinicopathologic disorder defined by GI symptoms and mucosal eosinophilia in the GI tract. The nomenclature to characterize EGIDs is evolving, however, EGIDs are often described still by anatomic location as seen in this diagram.

It's estimated that up to 40 percent of patients with non-EoE EGIDs have eosinophilia in other portions of the GI tract, outside the region of primary disorder, and that this is seen more commonly in pediatric than adult patients.

Currently, there is a limitation to the characterization of eosinophilic duodenitis, which is also sometimes referred to as eosinophilic gastroenteritis. During an upper endoscopy, which is the standard of care for the initial evaluation

of upper GI symptoms that may lead to a diagnosis of an EGID, generally, the duodenum is the most distal portion of the GI tract that's assessed during routine diagnostic exams. Therefore, the determination that mucosal eosinophilia is isolated in the duodenum is often based on an evaluation limited to the portions of the GI tract that can be visualized with an upper endoscopy. In patients who undergo both upper endoscopy and colonoscopy, some are found to have increased mucosal eosinophils in both the duodenum and colon, suggesting that the underlying disease may not necessarily be isolated to specific bowel segments in all patients. Therefore, the number of patients that may have an alternate diagnosis, if assessed by colonoscopy in addition to the upper endoscopy, remains an evidence gap since the full extent of the GI tract is not routinely assessed in all patients.

As discussed earlier by Dr. Collins, unlike in the esophagus, eosinophils are found in the stomach, small intestine, and colon in the absence

of disease. Shown in this table are the normal values with references cited by Dr. Collins. Although there are normal values of eosinophils by anatomic location reported in the published literature, these values vary as reflected in the ranges presented here. Additionally, the number of eosinophils described in the GI tract by publication is absent in some regions.

Also discussed by Dr. Collins, there are not current consensus diagnostic histologic criteria for non-EoE EGIDs. Multiple thresholds have been proposed to represent how many eosinophils are considered supportive of a diagnosis of eosinophilic gastritis, enteritis, gastroenteritis, and colitis.

Clinical outcome assessments, or COAs, measure or describe how a patient feels, functions, or survives. COAs are different from other outcome assessments, such as survival, and surrogate outcomes such as biomarkers, which are intended as a substitute for how a patient feels, functions, or survives. There are four main types of COAs:

patient-reported, clinician-reported, observer-reported, and performance outcome assessments. Today we'll be focusing mainly on patient-reported outcomes or PRO assessments.

PRO assessments are a measurement based on a report that comes directly from the patient about the status of their health condition without interpretation of the patient's response by a clinician or anyone else. Only the patient can report on their own symptoms or other unobservable concepts, which are known only to the patient such as intensity of abdominal pain or severity of nausea.

Some examples of PRO assessments are rating scales where a patient rates the severity, intensity, or frequency of a symptom. Another type of PRO assessment is an event log where the patient reports the number of events or episodes they experience with a specific sign or symptom like bowel movements or vomiting, and they can answer detailed questions associated with the real-time capture of each independent episode.

Several assessments have been developed that are considered by clinicians as acceptable for clinical practice and are cited in the literature. However, many times they are not suitable for regulatory purposes, that is, for regulatory decision-making regarding drug approval. Typically, these clinical assessments do not meet the regulatory requirement of well-defined and reliable as stated in the Code of Federal Regulations. FDA has a division in the Office of New Drugs called the Division of Clinical Outcome Assessment, or DCOA, which is dedicated to determining whether COAs are well-defined and reliable for use as primary, co-primary, or secondary endpoints intended to support regulatory approval and/or labeling claims. This determination is based on both qualitative research with patients, caregivers, and/or clinicians via one-on-one interviews or focus groups to assess the COA instrument's content validity to ensure that the instrument is measuring its intended measurement concept of interest and that the items

and response options are appropriate and comprehensive for the target patient population, as well as quantitative research assessing the COA instrument's psychometric properties and performance, that is, its reliability, construct validity, and ability to detect a treatment effect.

Moving on to analysis of the COA endpoint. In order to allow for interpretable COA efficacy endpoint data, patients enrolled in a clinical trial should be sufficiently symptomatic in order to be able to demonstrate a treatment effect and to best inform a benefit-risk assessment.

Although used commonly in previous studies of patients with EoE, use of percent change from baseline or responder analysis is not recommended by FDA unless the targeted response is complete resolution of signs and symptoms. Change from baseline in sign and symptom scores should be assessed using a continuous or ordinal scale, and it's important to note that small group-level mean differences in a COA endpoint score, even if statistically significant, might not constitute a

clinically meaningful effect to patients.

To aid in determining what the COA endpoint results mean, it is helpful to propose an appropriate range of within-patient score changes that patients consider to be clinically meaningful using anchor-based methods using patient global impression of severity and change scales. This can be supplemented with empirical cumulative distribution function, or eCDF, curves using data pooled across trial arms.

Additionally, a supportive graph of within-patient change from baseline by treatment arms is beneficial to determine whether there appears to be a treatment difference within the range representing a meaningful improvement to patients. These analyses promote the detection and characterization of clinically meaningful change and facilitate interpretation of results across drug development programs.

Ideally, these analyses of clinically meaningful change in endpoint scores using a COA are conducted prospectively using data from early

stages of drug development, prior to phase 3. Patient exit interviews or surveys may also be helpful when conducted very soon after the end of the clinical trial.

Sponsors are encouraged to work with the Division during early stages of development to increase the likelihood of a successful COA program.

There are a number of factors related to patients that we must consider when collecting COA data. When there's heterogeneity in disease symptoms and signs, sponsors might consider defining the COA endpoint based on symptoms and signs that are most widely characterized and most common and meaningful to patients, and signs and symptoms which are expected to improve or stabilize with treatment during the clinical trial duration.

The COA's recall period, response options, and administration schedule should be determined based on patient input regarding how they experience their symptoms, that is, whether the symptoms are episodic or chronic, and whether the

frequency or severity of symptoms is most meaningful to patients.

It is important to take into account the patient burden; consider the frequency of site visits needed to develop a novel COA instrument, and identify the optimal number of COAs to include in a clinical trial. You can avoid duplication of the COA concepts being assessed in order to aid in minimizing the risk of missing data, and COAs should be administered to patients in order of importance to the clinical trial data intended to inform the regulatory-decision making.

Additionally, there are pediatric patient considerations when collecting COA data. Only pediatric patients who can reliably and validly self-report should complete patient-reported outcome, or PRO, instruments related to their symptoms and functioning.

For children who cannot self-report, a primary caregiver or observer should report using an observer-reported outcome, or ObsRO, instrument to document the observable signs, behaviors, and

verbalizations related to the child regarding how they're feeling and functioning.

When possible, it is important to obtain PRO data for the clinical trial, even from young children, by using simpler concepts and formats, for example, a pictorial pain scale with faces. We caution against including proxy measures, which is where caregivers or observers report as if they are the child. As I mentioned related to an earlier slide, the patient is the only one who can report unobservable symptoms, for example, abdominal pain or nausea.

There are many opportunities for advancement in non-EoE EGIDs beginning with identifying areas of potential collaboration among patients, patient advocates, researchers, clinicians, industry, regulatory agencies, and other stakeholders.

It is important to first understand the disease or condition and then conceptualize how to define clinical benefit before finally focusing on COA selection, modification, or development intended to support clinical trial endpoints.

However, many considerations related to EGIDs must be addressed to maximize the success of a drug development program.

Clinical consensus nomenclature and diagnostic criteria for EGIDs are needed, as well as further characterization of the natural history for these disorders.

Regulatory flexibility is often necessary for rare diseases. Innovation, judgment, and regulatory flexibility are all critical in facilitating EGID drug development, while at the same time adhering to regulatory requirements and good measurement principles in order to benefit patients.

Despite the wide acceptance of the importance of the evaluation of the patient voice in EGID development programs, challenges remain during COA development, implementation, and analysis. For this reason, FDA encourages frequent and early interaction and collaboration with FDA during drug development, which will help sponsors to develop appropriate measurement strategies and

optimize the success of their clinical trials.

This slide shows three of the available pathways for interaction with FDA's Center for Drug Evaluation and Research or CDER. One pathway is through medical product development within an individual development program that has the potential to result in drug approval and labeling claims. Here, advice is given and decisions are made on a case-by-case basis within the context of each individual drug development or research program.

A second pathway is through CDER's qualification program, which is outside an individual drug development program and is considered a precompetitive space available to develop either COAs or biomarkers that potentially result in a qualification statement from the FDA for use of the COA or biomarker in a particular context of use.

A third pathway is through critical path innovation meetings or other meetings. These are outside of an individual drug development program

or research program. These meetings consist of a discussion of the science, medicine, and regulatory aspects of innovation in drug development, and they're non-binding, informal meetings with the relevant FDA experts. The scope of these meetings includes early biomarkers and clinical outcome assessments; natural history studies; technologies; and clinical trial designs and methods.

This is my last slide, and it includes FDA links that you might find helpful. We thank you for your time and commitment to patients with EGIDs.

DR. HIRANO: Thank you, Dr. Kovacs. That was one of the clearest lectures on this topic that I've ever heard.

We're going to be going to our next speakers, and this is actually going to be a tag-team effort with a pediatrician and an adult gastroenterologist.

First up will be Dr. Kathy Peterson, who is a professor of medicine in the Division of Gastroenterology at the University of Utah. She has spent the majority of her career developing

multidisciplinary clinics at the university and currently runs a clinic specializing in EGIDs at the University of Utah. Dr. Peterson is highly active in both research and efficacy for patients with EGIDs and is a wonderful clinician.

Dr. Peterson will be passing the baton to Dr. Calies Menard-Katcher, who is an associate professor of pediatrics at the University of Colorado School of Medicine. She is a pediatric gastroenterologist within the Digestive Health Institute and Multidisciplinary Gastrointestinal Eosinophil Diseases program at Children's Hospital of Colorado. Dr. Menard-Katcher has conducted innovative research studies identifying important physiologic consequences of EGIDs in children.

Drs. Peterson and Menard-Katcher will be providing a clinician perspective on the assessment of meaningful benefit.

Presentation – Kathryn Peterson

DR. PETERSON: Thanks, Ikuo.

Thank you, everybody, for having me talk today. I'm very excited about talking about the

clinician perspective on the meaningful assessment of benefit, basically because this talk means that I don't have to -- everybody's already talked about all the literature that's out there, and I get to talk about what's meaningful being a clinician and taking care of EGID patients.

I don't really have any relevant disclosures, and my objective is really to talk about the dilemmas that we face every day, bringing this all together, what as a clinician we need to detail.

This is just a slide telling you these are publications that are out there talking about all the different aspects of EGID and the symptoms that we deal with. We deal with the ascites that many brought up, ulcerations, and the fact that people are using hot pads to deal with the pain, and may not even think to tell their clinicians about this. They deal with gastric obstructions, nausea, and vomiting, and sometimes long-term consequences of having possibly gastroparesis from long-term disease that may or may not be reversible once you

control the disease.

I'm only going to bring up one cohort, mostly because they talked about some symptoms that we deal with on a clinical basis. This is a retrospective cohort by Dr. Dellon and colleagues that actually looked at upper eosinophilic gastrointestinal disease, defining greater than 20 eosinophils for high-power field on either the gastric or duodenal biopsies. They looked at symptoms in these patients after they ruled out secondary causes.

What's important about this is that if you look at this list of symptoms, there's a myriad of symptoms going on. There's constipation; there's chest pain; nausea; vomiting; heartburn; there's ascites; small bowel obstructions; impactions; weight loss; that we all have to start looking at as we take care of these patients because as Nimi brought up earlier, the presentations can vary, according to the site of involvement.

But we also have to be very cognizant of what we put our patients through to really evaluate

this disease. As Dr. Dellon described in this, these cases underwent an average of five endoscopic procedures a year, then that leads to other burdens for patients that we as clinicians want to try to avoid.

Another study tried to take these variabilities of clinical manifestations into consideration, and the principal investigators looked at a PRO, which took in eight different symptoms scores for eosinophilic gastritis and/or duodenitis; and, really, they recognized that the patients can present with a myriad of problems, maybe abdominal pain, but maybe their main problem is nausea, or early satiety, or bloating to the point where they're not functional. This is taken into consideration, and all of this is what hits us at the bedside with these patients next slide.

What I'm going to talk about today -- and this is kind of fun for me -- is I get to briefly -- because this is going to have to be a short talk -- mention what we look at from the bedside point of view or the clinical point of view

with our patients.

The first thing we have to recognize is the endoscopies aren't always predictive of disease but they can also vary, and we want to know if patients have aspects to their disease that we need to follow.

In the upper left-hand corner, there's a significant ulceration in a patient that had been recently bleeding, but in the upper right-hand corner, that's almost like a watermelon appearing stomach, which is not that we have to necessarily heal up as long as the patient's feeling better.

Below on the bottom right is aphthous ulcerations in the stomach. The reason I put the bottom-left one in there is that's actually the small bowel, which is kind of like modeled and nodular. The biopsies were significant, but it looked exactly like a picture of a colon of another eosinophilic colitis patient I had, so that endoscopic picture can actually vary and it can even look normal.

So that makes things difficult for a

clinician sometimes to assess. It's great to be able to say things are better or worse if things are abnormal, but when you deal with the normal appearance, then things get a little bit more difficult for us.

Other things from a clinician point of view that we need to look at is we also know that eosinophilic gastrointestinal disease can mimic other diseases. This is actually a case that we had here recently, who presented with GI bleeding, a young man, who was really not taking a lot of nonsteroidals, ibuprofen/aspirin. He was on a PPI once daily and presented with a duodenal ulceration and kind of some gastric erosions.

The biopsies at that time were done for H. pylori. It was an outside referral kind of an emergency, a come-through-the-ER assessment, but when the gentleman woke up, he actually described more chronic symptoms. The biopsies came back actually with this histopathology variability and that was actually considered unremarkable.

The biopsies were unremarkable. There's no

H. pylori, nothing else. But when the gentleman came back, again, gastric mucosa looked ok, a little inflamed in the antrum. But the biopsies at that point, that were repeated because of this kind of nagging suspicion that something else was going on in this gentleman, came back with prominent lamina propria eosinophils.

So he went from a non-specific picture when he had H. pylori biopsies done with the Sydney protocol, and then came back, had 8 biopsies done, and they found prominent lamina propria eosinophils.

So then the question comes to the clinician, was this maybe eosinophilic duodenitis, although those biopsies came back normal or was just a peptic ulcer that triggered us into understanding maybe a little bit more about this gentleman.

We get these confounding pictures when we take care of these patients, and it gets to be confusing at times. What I think we always have to take into consideration when we do take care of patients is that there is a patchy involvement of

the disease and often the endoscopy can look normal, so we can't always trust our endoscopy to guide our decision making with our patients.

We know that even if we do the appropriate number of biopsies, the eosinophilia can be patchy, so can we really reliably count on the eosinophilia to tell us if it's normal but our patients are still having symptoms? Did we just not do enough biopsies? So this is something that becomes part of our whole assessment in our patients.

I think what it comes down to is what Macie brought up and what Dr. Gonsalves brought up, is that we care about the quality of life. And as Northwestern demonstrated, patients really have significant impacts to their quality of life, a psychological impact; impact on social relationships because of eating issues, or pain, or inability, or fear of going out; a financial impact because what we don't want to do is over-proceduralize our patients, and they're already over-proceduralized, so at what point do we get a good outcome where we can stop putting them

through testing; and then an impact on the body when they have malnutrition or they have pain.

This is what really struck home with me, and also Macie's talk struck home with me. These are these quotes that came out of this paper talking about quality of life, and this is what we hear from our patients; people secluding themselves; people not being able to afford their care because we're asking for so many procedures to help follow them to assess one back and forth about, "Here, let's try something for six weeks and see if we get any resolution." This is something that definitely affects us, and these are quotes that came out of this affecting their quality of life.

In summary, I think what we need to take in consideration as a clinical aspect to taking care of these patients is we need to always assess their quality of life and see how they feel like they're doing; how physically they're doing, and mentally. What are we doing to them financially when we're doing all of these tests on them? Can we use the endoscopy as a follow-up and the biopsies? Is this

something that we need to do? Do we need to know if the eosinophils need to be totally eradicated or partially eradicated, and do we miss eosinophilia when we do our biopsies? We always have to keep that in mind.

I think the other thing, and a take-home that I really think is important, is one of the things that leads to this quality of life is we want to control symptoms. We want to control pain. We want to control nausea. Can we get rid of pain medications on our patients? Can we give them a medication to allow them to wean off of pain medications?

Can we actually reduce their antiemetics? I have several patients, even now, that I juggle with the pharmacist at what point am I going to give them a cardiac arrhythmia to try to control this nausea that overwhelms their daily activities?

Then, can we prevent long-term complications? Can we improve their malnutrition? Can we give them back regular eating habits so that they don't have to restrict so much in order to

socialize with their friends? Can we reverse their iron deficiency? Can we ultimately give them back that quality of life that they want so badly?

I think ultimately what I'm trying to say is it's a balancing act. What we want to do is we want to balance the risk of the disease and the current medications they're on with the side effects of any therapy and the financial costs of any therapy that they may go on. And we want to reduce the procedures that we're putting patients through and the financial costs that we're putting them through, if we can.

So we have to try to balance how to treat the disease, and yet how to limit any of those side effects. And that is, ultimately from a clinician perspective, how we feel like we can be successful.

I think I will pass on to Calies at this point.

Presentation – Calies Menard-Katcher

DR. MENARD-KATCHER: Thank you for that.

So I will take the perspective of a pediatric gastroenterologist, but there will be

several common themes in this. I have no disclosures, but I will be mentioning off-label medication use.

We've heard today that common symptoms and clinical signs certainly exist in patients with EGIDs, depending oftentimes on the location of disease involvement, but that there can also be notable heterogeneity in the presentation, as well as the endoscopic appearance for these patients with EGIDs.

Therefore, as clinicians, we need to really consider that heterogeneity, as Dr. Peterson has already stated, when assessing for meaningful benefit in any particular treatment or management plan that we may put forth for our patients.

So as a clinician, I like to ask what is most important to the patient in front of me, as Dr. Peterson has said, and to also think as a clinician what is going to be most important to their health, with the goal to improve or normalize symptoms, as well as improve any abnormalities and clinical signs that can be attributed to disease;

and in doing, ideally really provide meaningful benefit by minimizing disease impact on activities of daily living such as improved school attendance, particularly in the pediatric population; eating tolerance; and avoid complications of the disease.

In example, in pediatrics it might be iron deficiency anemia, which we talked about today. Even after we have corrected the anemia, iron deficiency can be associated with fatigue and really can impact bone health, sleep, and brain development in children. So in someone with iron deficiency as their primary clinical sign, we aim to correct the deficiency to improve nutritional status of course in the short term, but really also to improve their overall health in their medium to long term.

In addition, as a clinician, normalized iron stores are an example to me -- just like albumin, for example -- as a laboratory sign that a treatment may be helping to provide mucosal healing and may be helping to reduce inflammation, and as was stated by the FDA, possibly as a sign that

we're actually improving organ function, but that may or may not be a stretch.

Here, I'm going to present three patients to hopefully illustrate how I assess clinical assessment and clinical assessment strategies, depending on the clinical features of EGIDs. It's my own opinion that I think these really do start to get at the feel and function, as what's been mentioned previously as the goals of treatment.

This is SJ. This is not her actual picture, but she presented as a 6-year-old girl with a past history of eczema and food allergy. She really presented with acute onset of vomiting, diarrhea, and abdominal cramping, which was attributed to a viral gastroenteritis of some sort, possibly, but really symptoms did not improve.

The nausea and vomiting, as well as the diarrhea and abdominal pain persisted. She was referred by her primary care pediatrician for a gastroenterology consultation. She had no NSAID use whatsoever, and she really has no infectious exposures.

As pediatricians, we often look at the growth curve, and what we can see is really over the past year prior to presentation, she's had a slowing of her weight gain. She hasn't really lost weight per se, but she is not gaining weight as we would expect.

Prior to coming, she's had abdominal x-rays done in urgent care that showed ileus without obstruction and she's had a laboratory evaluation that showed a normal albumin and normal ferritin, which is a marker of iron stores, and really an unremarkable complete blood count with a peripheral eosinophil count of 400. She's had normal celiac serologies and she's had a negative infectious workup to this point.

Based on the chronicity of her symptoms, the slowing in her weight gain, she is recommended to go through an upper endoscopy. As you can see here, this is subtle, but she has some mild erythema in her antrum, and she really has these superficial erosions scattered throughout her stomach.

Her biopsies show that she has increased eosinophils with associated eosinophils or degranulation in the stomach, and the duodenum has significantly increased eosinophils as well, also with degranulation. There's villous blunting, but without any epithelial lymphocytes that might suggest celiac disease.

The endoscopic appearance together with eosinophil activity on her biopsies, as well as negative infectious studies or other exposures that may cloud the picture, really provides convincing evidence that she has primary eosinophilic GI disease with gastric and duodenal involvement.

She's referred to our eosinophilic GI program for consultation, and she has already started a low lactose diet on recommendation from her pediatrician prior to being seen in our subspecialty clinic. She's already had some improvement in her diarrhea. Her family was particularly nervous to use budesonide and really preferred, as much as possible, a more conservative approach. So given her normal hemoglobin and

albumin, as well as improvement in her diarrhea, we did opt to try mesalamine.

In follow-up, she's somewhat improved but still really is having intermittent abdominal pain. She is still having loose stools and diarrhea despite reduction in her lactose intake and her diet. She's not able to participate in her sports. She had been an athlete up to this point and missing several days of school.

We do opt to perform an upper endoscopy as well as a colonoscopy. And again, this is really because of the poor weakening [ph]that she's been having and because of the persistence of the diarrhea, not to say that all patients necessarily need a colonoscopy. As expected possibly, she again showed small aphthous-like ulcers in her stomach and the colonoscopy is completely normal.

The histology now is largely contained to the stomach with 112 eosinophils per high-power field and continued degranulation and crypt invasion of these eosinophils. Based on this, she is started on budesonide, and at follow-up now, she

really is reported to be just tremendously better.

Parents note dramatic improvement in pain, overall well-being, and the patient herself is much more talkative and engaged in clinic. She really is not reporting any pain whatsoever, diarrhea has completely resolved, appetite is excellent, and she has great energy level. She's back playing her ice hockey. We do check her cortisol and that's normal.

So the question that comes up in this kind of assessment of treatment is whether or not to perform an endoscopy. She's feeling better. She doesn't really have any other clinical signs such as iron deficiency or low albumin, though, for me to assess.

The reason I think to perform endoscopy at this point, the argument would be that it can demonstrate treatment effect and assist in the next step in treatment decisions, so whether or not we feel comfortable deescalating treatment.

Oftentimes I do use upper endoscopy really to see whether there's been healing of those

ulcerations and whether the histology has improved, but really there is evidence to suggest that symptom improvement may be more reliable in the assessment of endoscopic and histologic improvement in these EGIDs as compared to, for example, eosinophilic esophagitis.

This is just one study that was done looking at a large cohort of patients with eosinophilic GI disease, in which 78 percent of patients with clinical improvement also had endoscopic improvement as compared to 55 percent of those without clinical improvement who had, again, endoscopic improvement. Post-treatment gastric eosinophilic counts were significantly associated with clinical and endoscopic responsiveness.

In the end, I did decide to perform the endoscopy, which was now normal. We were able to taper and then stop her budesonide, and we followed up in the clinic for symptom assessment as well as growth parameters, but she has continued to have no flares now for two years.

This next patient is a 7-year-old male who

presents to his pediatrician with severe fatigue, headaches, and mild abdominal pain and is identified to have severe iron deficiency anemia. As mentioned by Macie, he first went to hematology and was identified to have a very low hemoglobin of 4.4 and an undetectable ferritin; again, a marker of iron stores.

This hematology evaluation was unremarkable and was referred to GI. What can be seen on this growth curve is that he's really had a very low BMI, but that he has been growing and gaining weight along his growth curve, but he is small for his age.

He has an upper endoscopy that's performed that shows nodularity and erythema of the stomach with old blood and no ulcers or active bleeding seen. He does have a capsule endoscopy as part of his evaluation. Just pointing out some of the things that we can see here are these salmon-colored vacuole patches that appear in the mucosa as compared to the more pale, healthy villi that are seen. The histopathology shows the

stomach with diffusely prominent eosinophils.

This patient, and his family I should say, has very strong preferences to avoid any type of corticosteroids at all cost and to attempt dietary therapy. They also really want to minimize anesthesia effects. In pediatrics, we really need to think oftentimes about the invasive procedures and the potential effects of the anesthesia. While thought to be and known to be very, very safe in older patients, it is something that we do consider.

So we decide, with the help of hematology, his hemoglobin has been corrected and we attempt to treat him with a dietary approach, removing the top 8 allergens and to monitor his ferritin. He's getting routine regular iron infusions throughout this time but we are unable to make any impact in his ferritin levels whatsoever.

So follow-up endoscopy eventually was performed and confirmed continued inflammation and nodularity. I was able to convince the family to consider the use of budesonide, at least in the

short period, to see whether we were able to improve both his ferritin, but also his chronic symptoms of headache and inability to attend to his homework.

With this, histology was normalized. The family, though, did decrease and then stop the budesonide on their own, and because of COVID-19, we do not have follow-up endoscopic assessment on him.

For this assessment of this benefit and this case of improvement in ferritin as a marker of iron stores and improved headaches and, really, the ability to participate in school and homework, here the endoscopic results happened to parallel his ferritin, as can be seen in this graph.

In this patient, this is a 17-year-old patient who presents with abdominal pain and nausea after being lost to follow-up six years earlier. At 11 years old, he presented with abdominal pain and weight loss. He had an upper endoscopy that showed erythema of the duodenal bulb, and biopsies from that area showed eosinophilic inflammation of

the esophagus, stomach, and duodenum, about 60 eosinophils per high-power field.

He did have an upper GI at that time which was normal, and he was recommended to treat with a proton-pump inhibitor but was lost to follow-up despite recommendation to follow up within 1 to 2 months; and really reports that symptoms had completely resolved in that interim period, who now presents with symptoms of progressive daily epigastric abdominal pain with associated nausea. He is not vomiting.

He goes through an upper endoscopy, and what can be seen here is the duodenum has this appearance of dilation of the foreground and apparent narrowing and really the inability to pass the endoscope. Biopsies are obtained, which show active chronic duodenitis again with villous blunting, mucin depletion, and an increase in eosinophils per high-power field. His stomach biopsies are normal and he does have distal eosinophilia of his esophagus with reactive epithelial changes.

Because of this finding on upper endoscopy, he has an upper GI that is shown, that shows a circle that's highlighting discrete narrowing in his duodenum. There are attempts to go through endoscopic dilation and treatment with corticosteroids, but ultimately he is referred to surgery and has a laparoscopic gastrojejunostomy.

In this patient, the primary goal of management for him is really to relieve obstruction and improve the associated symptoms. Of course, while we would really like to treat the mucosal eosinophilia that might be seen, really our goal is to relieve the obstruction and to improve his symptoms, and really for the long term to prevent other strictures from forming and further bowel resection.

To summarize, we have several tools to assess for meaningful benefit, including upper endoscopy and/or histology. We can look at clinical lab tests such as ferritin or albumin, but ultimately we want to help our patients feel better and for their GI tracts to function better. We

also have -- when needed, when complications arise or we aren't reaching benefit -- imaging techniques like fluoroscopy and possible capsule endoscopy can be used.

As Dr. Peterson recommended, as she's talked about, this is really a balancing act with reality that these assessments, particularly in the invasive testing such as endoscopy, can really have a negative impact on our patients' lives, and this needs to be weighed in the balance. Ultimately, the patient's symptoms and symptom course dictate which assessments I may hang my hat on.

Just briefly, when attempting timing of assessments in terms of when I think to do these assessments is when attempting to adjust treatment; when treatment and symptom changes don't align; and symptom assessment and laboratory monitoring between endoscopy and histology.

To summarize, endoscopic assessment with histology is really most helpful at providing objective information if treatment is impacting the underlying pathology, but it's not without risks or

cost. Improvement in symptoms may correlate with reduction in tissue eosinophils and endoscopic improvement, and better in these EGIDs rather than eosinophilic esophagitis. Non-invasive assessments may be helpful in providing reassurance, or not, when attempting to minimize invasive testing, and I think that's it.

DR. LYONS: Thank you so much.

Those are all wonderful talks. We were so fortunate to be able to hear from a patient about what is really meaningful and her experience, her personal past, and her personal course with EGID; and from FDA about what is really required to ensure the safety and health of the American people as we consider new experimental therapies; as well as from clinicians with both adult and pediatric patients about how they assess their patients currently. These groups coming together are really what is essential to help us to make significant strides in this rapidly advancing field that is EGID, so thank you all for the wonderful presentations.

At this time, we're going to take a break. I would ask that everyone please come back at 2:10. Sorry. We're going to cut it just a little bit short so that we can get to the panel discussion, where I know it will be a lot of very interesting and productive dialogue. Thank you.

(Whereupon, at 2:00 p.m., a recess was taken.)

Panel Discussion and Q&A

DR. LYONS: Welcome back. I hope you had some time to stand up and stretch your legs a bit. Welcome back to our final panel discussion of the workshop. Again, we are very happy to welcome our panelists back, and we request that if you are on the panel for this session, if you could please share your video so that we can see you.

Now, in addition to our session speakers, Ms. Macie Smith, Dr. Sarrit Kovacs, Dr. Kathryn Peterson, and Dr. Calies Menard-Katcher, as well as moderators, Dr. Ikuo Hirano and myself, we are very pleased to welcome the following panelists for Session 2.

Panelist, after I say your name, would you please briefly introduce yourself to the group? Again, I am Dr. Erica Lyons. I'm an associate director for therapeutic review within the Division of Gastroenterology at the FDA.

Ikou?

DR. HIRANO: Ikuo Hirano, professor of medicine in the Division of Gastroenterology at Northwestern and co-director of the Northwestern Eosinophilic Gastrointestinal Disease Program.

DR. LYONS:

Dr. Chehade?

DR. CHEHADE: Hi. Mirna Chehade, associate professor of pediatrics and medicine at the Icahn School of Medicine at Mount Sinai, and I'm also the founding director of the Mount Sinai Center for Eosinophilic Disorders.

DR. LYONS: Excellent.

Dr. Dellon?

DR. DELLON: Hi. Evan Dellon, adult gastroenterologist and professor of medicine and epidemiology at University of North Carolina School

of Medicine.

DR. LYONS: Dr. Furuta?

DR. FURUTA: Hi. Glenn Furuta, pediatric gastroenterologist, Children's Hospital of Colorado and University of Colorado School of Medicine.

DR. LYONS: And Dr. Gupta?

DR. GUPTA: Hi. I'm Sandeep Gupta, professor and pediatric gastroenterologist at Indiana University and Community Health Network, Indianapolis.

DR. LYONS: Dr. Mas Casullo?

DR. MAS CASULLO: My name is Veronica Mas Casullo. I'm the pharmaceutical industry representative.

DR. LYONS: Dr. Rothenberg?

DR. ROTHENBERG: Hi. Marc Rothenberg, Cincinnati Children's Hospital.

DR. LYONS: Ms. Smith?

MS. SMITH: I'm Macie Smith. I was a patient representative and I have eosinophilic gastritis.

DR. LYONS: Dr. Spergel?

DR. SPERGEL: Hi. I'm Jonathan Spergel.

I'm an allergist/immunologist at Children's Hospital of Philadelphia and the University of Pennsylvania.

DR. LYONS: Dr. Tomaino?

DR. TOMAINO: I'm Juli Tomaino. I'm a pediatric gastroenterologist, and I'm the deputy director in the Division of Gastroenterology at the FDA.

DR. LYONS: Wonderful. We'll now go ahead and start the panel discussion, and I will turn it over to Ikuo to ask our first question.

DR. HIRANO: Thank you, Erica.

Our first question for this session is for Ms. Smith, and then we'll open up the question to the floor for the other panelists if they have comments.

First of all, thank you so much, Macie, for sharing your experience with EGID. What you shared is both inspirational and invaluable for all of us to frame the goals of this workshop. After all the time you spent in the hospital as a patient, it's wonderful to see how dedicated you are to pursuing

a career in health care.

You described an ideal treatment that would treat all your symptoms, and we're just wondering if you could expand on that. For you as a patient, what is the most important symptom, or perhaps symptoms, that a treatment should improve?

MS. SMITH: Yes. Thank you for having me and letting me share my story. It is such an honor. But I, for me, the biggest symptom that I would like to have treated would be my stomach pain just because it is so debilitating, and I honestly don't go a day without having some sort of pain in whatever severity it might be. Not only does it hurt, obviously, but it's very emotionally exhausting. Trying to live everyday life while in pain is tiring on your body, but also mentally.

I think if I were able to have a treatment that would target the stomach pain specifically, I think that it would lessen the rest of the symptoms. If that could be all encompassed in one specific medication, or treatment, or whatever it might be, so it can knock out the nausea, the

vomiting, the stomach pain, and all of those symptoms I guess, would be really great; so you do have that kind of sense of still not having to wake up every morning and take four or five different medications.

It's kind of exhausting and kind of makes you feel less of a person, I guess in a way, just because you're so consistently taking a medication, and it's hard when you have to pick up a new med every day.

I hope that answers your question.

DR. HIRANO: It does.

If I could actually just follow up on that a little bit? When you described your story, I was struck by also all the complications or signs of disease beyond the symptoms. You had bleeding, your preparation, and surgeries, and a lot of fatigue from the anemia.

How do you as a patient weigh the signs of disease that the doctor will talk about versus your symptoms? How do you weigh those two?

MS. SMITH: As far as like what I'm feeling?

DR. HIRANO: Right, the way you feel versus what the doctor might say your biopsy shows this, or you've got an ulcer here, or your hemoglobin is low. How do you weigh the signs of disease that the physician talks about versus how you're feeling?

MS. SMITH: Okay, gotchu.

This actually happens pretty frequently with my scopes, but specifically with the last one I had, the past month and a half has been pretty rough for me, in all honesty, and my scope really didn't show any signs of active disease or anything to be super concerned with.

So it's hard to hear from your doctor that there's not any signs of an active disease in your stomach when you, on a day-to-day basis, feel like, honestly, garbage. It's hard to see that my stomach looks fine but I don't feel fine. It's hard not to see the two things line up because then it makes people wonder, "Oh, is it really as bad as she's saying it is?" Is it as severe as everybody's making it seem when the signs of it aren't correlating with the symptoms that I'm having?

DR. HIRANO: Maybe we could briefly open that up to the panel to talk about this dissociation between what we consider to be objective measures of disease versus symptoms. We've certainly seen that with eosinophilic esophagitis, but I think it's less well described for EGIDs.

Do any of the panel have any comments about symptom information or objective evidence dissociation?

DR. SPERGEL: This is Jonathan Spergel. It's an interesting problem because when I see normal endoscopies in patients in pain, I'm worried that I'm missing something. And that's what I worry about, that symptoms don't correlate. I believe the patient's having symptoms. I believe you're really symptomatic, but that tells me I need to look for something else. What I worry about is that there's nothing else, and then we're missing disease in the biopsies. There's disease below what we can see.

So I think that's why we need both measures

because then it goes the other way, too, that patients endoscopies look terrible, but patients feel fine. Then those patients I worry about later on having a lot of severe complications because we left untreated disease because we know almost every untreated disease is bad. So you need that combination.

DR. PETERSON: I'm happy to always weigh in. You know you can't keep me quiet.

I agree with Jonathan. I think the issues we deal with is the fact that we want to have something completely objective to hang our hats on, like Jonathan says. But when we don't have that -- like that one patient I showed earlier -- it's like did I just miss it? Did we just miss it on the biopsy or is it a muscular form and we're missing some of the biopsies? So it becomes this dilemma that we have when the patients have symptoms and things look great.

But Jonathan also brings a really good point that when you have a patient who is relatively asymptomatic, and they came in with something and

got biopsies for some routine other assessment for anemia that they didn't even know they had, and you find the eosinophils, and they otherwise feel well, I think what we worry is we worry shouldn't we treat that. But then you hate to give a drug to a patient that potentially is going to have more issues than actually the disease itself.

So I think that we do worry about these long-term outcomes. But I think the thing I worry about the most is missing disease, and I think Jonathan brings up a really good point that I think we all miss it.

DR. SPERGEL: We treat disease all the time. We do this for diabetes. Someone comes in with high sugar, they feel fine, and we know it's bad. We know high cholesterol is bad, but yet we treat it. Having active disease is probably bad, and we need to think about those things. We need the combination. I feel pretty strongly about that because we know active disease in almost anything else is bad. Why would EGIDs be different than every other human disease?

DR. HIRANO: Another, though, important aspect of dissociation between symptoms and objective markers of disease is the patient's anxiety and hypervigilance. After going through Macie's story with all the horrible things that happened to her, I would always be anxious about my symptoms and when is the next flare-up going to happen. That can actually also intensify symptoms.

There's a recent paper in Gastro about this for EoE -- not for EGIDs but for EoE-- showing that a lot of the correlation between symptom intensity is not directly correlated with the eosinophil count or the endoscopy findings. It's actually patients' anxiety and hypervigilance and their own experiences with their disease. Sometimes you keep searching and searching, but it's also because there are other things that affect symptom intensity beyond our objective measures.

MS. SMITH: Thank you for bringing that up because that is something that I struggle with. I go a year and a half, two years, on a treatment and it's working totally fine. But since I have been

through so much, I'm almost waiting for the second shoe to drop, like when is the next bleed going to happen, the next perforation.

So I never thought about that being a correlation between my pain and active disease or not, so thank you.

DR. DELLON: Macie, the other thing that I was really interested in what you were talking about was you repeatedly, in addition to the pain, said you want your quality of life to improve and you want to have better quality. And we heard that in some of the other talks from the clinicians as well. In addition to that, you had other things happen to you, like perforations, and bleeding, and anemia.

I wanted to try to bring this back to the FDA in terms of outcomes and understand how do we think about outcomes of quality of life and of disease complications when we're thinking about clinical trials, because those direct exactly what's going on with you, and how can we address those in the drug development process?

DR. CHEHADE: That's an excellent point. I'd like to add also the pediatric perspective to this. You guys highlighted very well the fact that sometimes you have a lot of symptoms and not much histology or on endoscopy.

In the pediatric population, you see the reverse. And I see it way often in my clinical practice where the patient may have abdominal pain, daily abdominal pain, and get diagnosed with eosinophilic gastritis. They have, for example, low albumin and low hemoglobin from a protein-losing enteropathy, and now hemoglobin's great, the protein is great when we put them on a diet or other treatments, and the pain is gone. But you do a repeat endoscopy, and the stomach looks still horrible.

So then what do you do with that child and that family, where we don't have yet enough data to say you're guaranteed a long-term complication? We don't know when? We don't know what's the frequency of it or not? We don't know if you're going to have that complication or you will just do

ok? We don't know when it will happen and what's the chance of that?

So that becomes a problem. But that makes me also think that we should look at all of these until we really feel comfortable to know and phenotype these patients as who's the one who's going to develop complications and who's the one who's going to be safe?

So for those patients, even though they're struggling, and we're struggling convincing them and putting them through all of these, I think it's important that we keep all outcomes for now until we know more about the phenotypes.

DR. LYONS: I think that's an excellent point and one reason why we feel that additional natural history for these patients is going to be so beneficial, not only to inform trial design that has a high likelihood of detecting treatment effect, but also to inform which patients should be which candidates for which treatment, and how frequently we monitor that progression and how frequently we can expect a change so that our

patients are not just waiting for another shoe to drop.

It all comes together. And when we're dealing with such a heterogeneous presentation of a group of disorders, we do really have to consider all perspectives. And I think it's just essential and how helpful workshops like these are to open and continue that dialogue, and bring that richness of perspective to clinical trial development.

Dr. Kovacs, would you comment a bit on quality-of-life metrics and how we view that from a regulatory perspective?

DR. KOVACS: Sure. When we look at the context of regulatory drug approvals, we do focus on primary efficacy data points; so clinical outcomes that directly reflect a favorable effect on underlying disease, it's hard for us to interpret sometimes the health-related, quality-of-life assessments.

While they are extremely important as a measure in clinical trials, they don't typically support primary endpoints for drug approvals. It's

oftentimes difficult to isolate what aspects of the quality of life are affected by the patient's disease and treatment rather than external factors such as psychosocial factors in a patient's life.

But if you are measuring health-related quality of life, as stated in FDA's 2009 patient-reported outcome guidance for industry, you want to demonstrate general improvement, and there are a number of things that you need to get a claim for health-related quality of life.

Then with regard to functioning and feeling, looking at patient functioning, you can focus on impairment in daily functioning, and activities of daily living and stuff like that, that can be affected by how the patient is feeling and the signs and symptoms that they're experiencing.

DR. DELLON: Thank you very much.

Could you expand a little bit more on the quality of life, I guess, and also the disease complications? Say in a trial setting, quality of life is poor at the beginning and they get a treatment, and it's better at the end of the study

compared to placebo, how does the other stuff necessarily fit in? Because you're isolating it in the experimental design just looking at that factor, and if it's a factor that's so important to patients, how does that get balanced?

DR. KOVACS: Again, I guess I would just mention about external factors like psychosocial factors and that kind of thing. We do have a gap here with EGIDs looking at health-related, quality-of-life assessments. That is something that is helpful to put in exploratory assessments or health-related, quality-of-life assessments; exploratory endpoints that are not serving for regulatory decision making as primary and co-primary endpoints, and getting more data on that, or early-phase trials that are not necessarily pivotal trials, and looking at that.

DR. LYONS: I'll bring that back. When we look at these metrics and these assessments, we really do want to ensure that we are evaluating something that is impacting the actual disease state, and that's very tough.

With the balance that Dr. Peterson and Dr. Menard-Katcher mentioned about treatment benefit versus the risk of a treatment, we, in a regulatory perspective, balance having a clinical trial population that is so similar versus so heterogeneous to be able to mimic the intended-use population that will be seen in the community for eventual group therapy.

With these kinds of objective markers, that speaks to the need for additional characterization and natural history and whether or not there are symptoms that can correlate with what we see for the more objective markers of disease, such as eosinophilic count or endoscopic abnormalities.

But in quality-of-life metrics, in there is something that we definitely feel could be valuable for patients because we want to know how patients are doing. It's just difficult to translate that down to something that will correlate with other markers of disease so that we can have confidence that it's directly reflected on the treatment's effect on the condition of interest.

With that, I think that there's very much value in it, and I think it's something to definitely incorporate. And the more that we hear from patients about what aspects of their condition can improve with treatment or improve with dietary elimination or elemental formula, that's helpful to inform potential future endpoints for consideration.

DR. TOMAINO: I just want to add one thing to what Dr. Lyons just said. Just take a step back for a minute. It's important to differentiate what Dr. Kovacs mentioned in her talk about patient-reported outcomes from quality of life. These two are often used interchangeably in the community, but from a regulatory perspective, they're very different.

When we're talking about obtaining input from patients as far as what is most meaningful to them and what's important to them, we're talking more about patient-reported outcomes rather than broader quality-of-life assessments that can have many contributing factors that are often not a

direct reflection of the underlying disease.

So we're not saying that quality of life isn't important. Everybody here fully appreciates that it is and that's one of the reasons why we're here. But when you're talking about a clinical trial intended for drug development, usually the primary efficacy assessments that are most appropriate are either clinical signs and symptoms and/or endoscopic outcomes and histologic outcomes; and when we're talking about clinical signs and symptoms, that's when we're talking about the aspects that are most meaningful to the patient and that are the closest direct reflections of the underlying disease process.

So that's why we're making this distinction between Pros and quality of life. And it's not that quality of life can't be measured in a clinical trial; it certainly can. It's just not usually appropriate as a primary endpoint. But when we look at the data, we do look at all of these things, and sometimes quality of life assessment can be helpful to interpret the overall context of

the data that we're seeing and the impact that that's having on the patient.

DR. PETERSON: I think one of the problems that we have with PROs -- and I don't mean for it to be a problem, but you're asking patients in some of these trials, who are extremely limited in their lifestyle, and in their eating habits, and socialization, to maintain that.

They're in a randomized-controlled trial, and they're looking at it -- I would look at it this way. They're looking at it as finally I can eat more than three foods or I can finally do something.

I think even though you try to control for that and say you need to keep your diet stable, and blah, blah, blah, first of all, from a clinician's perspective, I feel cruel doing that because, really, for the patient, what the patient wants is the patient wants to say, "Okay. I want my abdominal pain controlled" -- I mean, I don't want to speak for the patient, but I would assume I would want to say this; that I want my abdominal

pain or my nausea controlled well enough so that I can actually go out with my friends and eat, and that's really what matters, really.

I guess that's what worries me a little bit by doing PROs, because are one thing but they're also going to be somewhat subjected to the fact that you're hoping those patients aren't feeling good enough that they're going to try to eat other foods because they want hope.

I would want hope, and having -- my heart just speaks to some of these patients. They go through so much. So to not be able to offer them hope, then I think that's the difference with these PROs. And that's where quality of life does come into play because a PRO cannot measure whether they can get a life back, necessarily, if that life that they get back means that they still are limited to an elemental diet. They just need to get out of that fear.

Sorry. That's just my two cents.

DR. LYONS: No, thank you, and thank you for bringing it back to our patients.

If I can switch gears a little bit here and direct something to Macie, again, if you have participated in a clinical trial, or in your envisioning of a clinical trial -- and I also will open this up to the broader group that has experience -- what are a few things -- 3 to 5 things -- that sponsors or companies can do, or even the primary investigator, to make participating in these studies easier for you or more tolerable? Because we definitely do want to consider that as paramount as we are advising folks to be able to design these trials.

Can you comment on that for us, please?

MS. SMITH: Yes. I haven't done a trial, but I think that they would be challenging but rewarding. If you do get the placebo, you are constantly having this hope that something's going to work. So if you don't actually get the drug, it's kind of a let-down, but I understand that that's just how clinical trials work.

But then again, I think a lot of us -- I think I can speak for a lot of different patients

when I say that we don't have a whole lot of hope when it comes to different kind of treatments and medications. We are looking for literally anything to help us at this point. So if it even means that we get the placebo and we don't even get the real medication, it gives us hope back that things are starting to be developed, and people are thinking and looking at this disease at a more intense level than it was before.

So it's kind of you have to weigh your cards a little bit. You might not get the med, but at least people are working to try and find a different medication. And if you do end up getting the medication in the trial, then that's great, and hopefully it worked. Hopefully something good comes from it. But that's a hard question.

DR. HIRANO: Macie, one nice thing about the trials, many of them are set up that after the placebo randomized portion, patients get the open-label drug. So many of them have that design as an incentive to participate, but also so you can try to see if the medication helps you.

DR. SPERGEL: So here's a question to the FDA and a pharma representative. Why don't we mandate that; that trials should have an open-label extension until the drug is shown to be approved or doesn't work? That would be an improvement for patient outcomes. And I think from both pharma and the FDA, that should be standard.

DR. LYONS: I'll pop up first. So that is something that we do encourage in terms of the context of the development program, to consider the balance between allowing patients to have access, and doing it in such a way that you can capture that valuable patient experience, and not let any of that information be lost. Because we do recognize that it is such an investment of patients' time, of their energy, of their emotion and their hope into being involved in a clinical trial.

So that is something that the FDA does encourage. It's not something that's within our purview to be able to mandate. With the individual pharmaceutical representatives, they may have

various different reasons why they're pursuing one development program versus another. But allowing access to be able to try experimental therapies is encouraged within consideration of a development program such that we can get informative data and not miss out on an opportunity to honor the sacrifice that patients have made by enrolling.

DR. MAS CASULLO: Most of the time, as part of the development program in these chronic diseases, we try to include an open-label extension that is in a way going to provide access to those patients that were in the placebo arm, and now they have the opportunity to receive the medication if we find that it's starting to be positive for sure. At the same time, we provide this long-term treatment information that is valuable, as well, in these chronic diseases.

Most of the time, if possible, I believe nowadays the pharmaceutical industry is trying to provide that as a long-term follow-up in open-label extension types of studies.

DR. LYONS: Thank you so much.

Now, we'd like to refocus a bit and get back to clinical symptoms so we can have more discussion on potential objectives and endpoints for consideration. Our next question is for Dr. Menard-Katcher followed by Dr. Chehade, and then we'll open to the floor for the rest of the comments.

In your clinical experience, what clinical signs and symptoms of EGID, if any, are specific to location of the involvement versus more broadly generalizable to the disorders as a whole or groups of the disorder?

DR. MENARD-KATCHER: I would say I think pain is common to all locations, and I think diarrhea can be common, really, to all of the locations I find. Even with gastritis, I think that diarrhea can sometimes be seen, so I don't know that that is necessarily specific.

I think, really, the nausea and the pain in relation to eating is more commonly seen in the patients who present with gastritis or duodenitis location compared to ileitis or colitis, which may

have more urgency as their pain symptom rather than related to eating specifically.

In terms of the signs, I think low albumin, and certainly I think more commonly seen when there is intestinal involvement rather than just colonic or just gastritis, although it can occur in just gastritis involvement. Then the iron deficiency I think really can be seen in all, but I think more commonly would say I see that with upper GI involvement rather than colonic involvement.

Mirna, I don't know if you want to add to that.

DR. CHEHADE: Yes, I agree with you, Calies. I think to just delve into it in a little bit more detail, I see both kids and adults, so I get a little bit more of that perspective. There are more common symptoms than differences, and I think maybe that's why, Erica, you asked that question.

Most patients will have abdominal pain, nausea, vomiting, early satiety, low appetite, and even failure to thrive in the pediatric population. But what I notice is that -- and I agree with

Calies -- some of the patients with eosinophilic gastritis have diarrhea and we don't know why, even though we dig and dig to see. And with the confines of what we can do without going overboard with diagnostic testing is we don't find intestinal involvement in many of these patients that would explain the diarrhea.

However, patients with duodenitis would really describe the diarrhea in a different way. They have abdominal pain that's not epigastric most of the time. They actually have abdominal cramping and loose stools, loose frequent stools, especially if they consume some of their food triggers.

So you would see that, and that really makes me think always duodenitis or enteritis I should say, and we do see -- now I'm always saying duodenitis because that's the one that's most commonly diagnosed with our standard techniques, and you see it. You see it in those duodenitis patients. They have that type of symptom with the bloating diarrhea and cramps proceeding to diarrhea as opposed to the other symptoms we describe.

But also that kind of makes sense because it is the symptoms related to the actual organ dysfunction that is involved, so the intestine is going to give you diarrhea and the stomach is going to give you pain and nausea.

The other thing to point out is that many patients -- and that's what makes this question difficult to answer -- have a combination of symptoms, and not only have a combination of symptoms but also a combination of frequency of symptoms.

I want to go back to what Macie mentioned, which is really important. She said if she had to choose one thing, she pointed to abdominal pain, but she also said, "I don't want to wake up every morning with abdominal pain." And that's what we see most of the time with most patients, is that the abdominal pain happens to be the one that's more frequent and regular in occurrence, as opposed to vomiting, for example, which can be intermittent in some of the patients.

If you ask me, I would never want to vomit.

I would prefer to be in pain. I could still talk to you, but I don't want to vomit. But if I have to vomit infrequently versus daily abdominal pain, so now the frequency is becoming important in addition to the type of symptom and severity.

So that's going to be a problem when we are thinking clinical trials because now we have to follow the symptom that's most frequent, or frequent enough to be measured, something that can be measured, and you have to worry about its responsiveness to the treatment. So you may have a drug that will fix something because it's more responsive, but another symptom that doesn't get fixed because it's less responsive; failure to thrive being one, for example. So these are all important.

Now, when we're dealing with eosinophilic colitis, I barely see eosinophilic colitis in my practice, pediatric or adult patients. So I echo those who mentioned it in the first session. But that's sometimes easier because you get diarrhea and sometimes the blood is visible.

Now, in terms of signs, the anemia and the low protein, I see it often with eosinophilic gastritis as well, without any intestinal involvement. In fact, we published a series of pediatric patients that had that. We looked even to see if they had intestinal blunting, like duodenal villous blunting, to see if that could explain it. They didn't.

We looked at mast cell numbers in those patients even though they didn't have eosinophilic infiltration of the duodenum. There was a slight uptick there in terms of mast cell number in those with eosinophilic gastritis only, but our numbers are too small for me to give you a real firm answer on that.

So in terms of signs, I don't think we can really comfortably differentiate them. Peripheral eosinophilia is the same. You see it elevated in some, in a subset of patients just like with EoE, and in my experience it does not correlate with response to therapy. So you could have sometimes complete healing of the gut, but you still have

high peripheral eosinophils and is something that I see a good number of times.

DR. HIRANO: If I could just dovetail on the discussion about PROs and symptom assessment, there were a lot of questions, or concerns rather, raised by several of the panelists about the very careful and meticulous, but also arduous, regulatory pathway that we've seen play out for eosinophilic esophagitis therapies. I think the concerns are that this may portend a very similar process for EGIDs as well.

Maybe, Glenn, I think you mentioned some comments there. If you could just tackle that one a little bit about the concerns about the whole process.

DR. FURUTA: Sure, Ikuo.

I think a little over 10 years ago, we embarked on a process like this for eosinophilic esophagitis and had meetings with the FDA to talk about how we might be able to advance the field. And together, in collaboration with the FDA and investigator and industry, have gone forward to

develop a number of different kinds of PROs, quality-of-life metrics, and innovative ways to address these concerns.

I think we don't have a medication today, and I think we want to try to work together again to help develop those for these lower track EGIDs and figure out what the best pathway forward is for that. We've certainly heard some of these gaps in knowledge that have been identified, but I think we've also heard a lot about the much more rapid progress that's been made now within these lower track eosinophilic GI diseases; so just how we can push forward in a much more rapid way with the momentum we've garnered already, hopefully in a little bit of a different pathway than before.

DR. FURUTA: I think maybe to re-emphasize the concept of having worked together, we've worked with the NIH to develop the CEGIR, the consortium that Marc is leading us through and, really, the whole concept of CEGIR, I think, is to develop clinical outcome metrics that can address these diseases in a way that we can push forward and help

industry to address these issues, and to help understand what Macie is going through in a better fashion that lead to these kinds of metrics that will allow us to gain and take advantage of the novel and innovative types of pharmacological products that are under development now and get help for our patients.

We don't want to be here 10 years from now in the same situation as we are with you, with no approved treatments.

DR. HIRANO: Sandeep?

DR. GUPTA: Yes. Thanks. I just wanted to actually fill in some of the prior comments. The good part, from a pediatric perspective, for non-esophageal EGIDs is that there is quite a bit of overlap between the adult and pediatric symptomatology, unlike EoE where the adult instruments do not really capture the pediatric symptomatology, which is very variable compared to adults. In the non-esophageal EGIDs, this hopefully will be an easier reach for pediatrics because the symptoms are not carbon-copy same but a

lot of overlap.

So I just wanted to put that out there to try and encourage pediatric studies, and the PROs may be able to be spread to the younger age from adults.

DR. LYONS: Thank you all for those comments. I think we are in a very fortunate position here, and I know it's definitely been a frustrating road. And being able to see the amount of dedication and commitment to your patients, to your science, to the process, and to just being here today, it's easily apparent how valuable this collaboration is.

We are fortunate with the lower track EGIDs that we are able to potentially build on and leverage approach and the lessons learned from EoE. So, although we are focusing this workshop on the knowledge gaps and the areas that need to be addressed to move the field forward in a more expeditious fashion, we can look back and see what we do have to build on.

We're not starting from where we were

10 years ago with EGID, we're starting from a place where we have that knowledge; the CEGIR network and all of these people who have shown up for this workshop that are committed to moving the field forward to not getting into stalls, but also to consider, as we go and as we make progress, what can be improved on for the next cycle so that we are continuously evaluating the design, and the enrollment criteria, and the endpoints for patients to expedite drug development in this area as much as possible.

So although we are focusing on knowledge gaps and areas for collaboration and areas for the future, we really do have a tremendous footing under us that has been built by many of the people here as we look back towards what has happened with EoE and what is still happening with EoE today in terms of understanding the process and how we can use that approach potentially the future going with the lower EGIDs.

DR. TOMAINO: Also to clarify, when we talk about PROs, or patient-reported outcomes, we're not

necessarily talking about a fully qualified, lengthy instrument that measures multiple things. There are ways to measure one or two signs and symptoms that are most important to patients to keep clinical trials moving forward. For example, we have a good idea of how to measure pain. That's not something that is going to need a new instrument to be developed. That's something that can be measured now in a clinical trial.

I think Dr. Kovacs mentioned these in her talk. There are various regulatory pathways to developing these instruments. That full lengthy qualification process is only one way. There are other ways within an individual development program to work directly with the patient community, the academic community, FDA, industry, and there are even some already established ways to measure certain signs and symptoms that can be used now in clinical trials.

Then moving forward, as Dr. Lyons said, we can continue to address the additional knowledge gaps and develop other instruments and better

instruments to capture signs and symptoms that maybe don't have a clear-cut pathway at this time.

DR. HIRANO: Thanks for those words. Thank you very much for those words.

DR. LYONS: Thank you.

Along those lines, we'll move on to our next question, as we are interested in exploring potential alternative approaches that may be able to facilitate the assessment of benefit in patients. This question we'll direct towards Dr. Peterson, followed by Dr. Rothenberg first, and then to the rest of the panel.

Could you please comment on data available to support the use of assessments other than symptoms to clinically monitor patients, and whether there is data to support that these measures are associated with changes in clinical symptoms?

DR. PETERSON: You mean as far as data support system symptoms right now for EGID patients.

DR. LYONS: Data to support assessments that

maybe in addition to symptoms; alternative assessment metrics, whether they be signs or other findings, and whether or not those that you use routinely in your clinical practice and your clinical experience correlate with patient symptoms.

DR. PETERSON: I think the best thing that we have is the correlation between histopathology right now in symptoms. We look at the burden of eosinophilic or inflammatory disease, the extent of it.

There's more data coming out about not even just the cell count but the activation of other cells. It's coming out slowly. That will, I think, speak a little bit more to symptoms and speaks a little bit more to potentially what we talked about a little bit, like visceral hypersensitivity, or even neurogenic stimulation that can occur with chronic inflammation that we see with a lot of GI diseases.

I don't think at this point -- and maybe somebody can correct me if I'm wrong -- we have a

lot of data, and I think part of it is because of the kind of relative variability that we see in patients. I don't think we have a lot of data saying, okay, well we can follow improvements in anemia, not to mention it takes a little while to improve your anemia, or that you can look at other things.

I think at this point, outside of symptoms, it is kind of what Jonathan mentioned. We have endoscopic. If it is abnormal, then we can look for that to improve, which is helpful, as long as we know that the abnormality is not from something else, but again we talked about20 percent look normal. Then really, we have our histopathology that we rely on, that Margaret so nicely delineated earlier, that we can follow.

What I would say, really quickly, and Marc can comment on this, is I don't think you have to necessarily eradicate eosinophils or inflammatory cells to get the outcome that you want to achieve.

DR. ROTHENBERG: I think Dr. Peterson said it well, and I agree with her comments. I would

just say that I would bring to your attention -- and maybe add a little bit more details -- that CEGIR, for example, is developing, based on our research and data, and longitudinal study of patients with non-EoE EGID, metrics that can quantitate and validate the things that she mentioned.

In particular, just as we have AGIS as the histological scoring system for EoE, we now have increasing data with an HSS and EG instrument that's going over a number of features of histology and also an ED HSS that's being studied.

We also have an EREF. Just as we heard about earlier for the esophagus, we're developing an EREF scoring system for the stomach and also for the duodenum. It turns out in contrast to the PROs are very objective measures that can be quantitated and is very correlative with what we consider to be clinical outcomes, which hasn't been formally studied in terms of PROs. But there are objective findings, including the hemoglobin and albumin levels that are often low, that do correlate in our

studies with these endoscopic and histological scoring systems that I think have a lot of value.

I'll also comment about the transcriptome analysis, which is a very robust, objective, empirical analysis of a number of different pathways, including ways of measuring mast cells as a surrogate. And these do strongly correlate with endoscopic findings and histological findings, and there are very distinct parts of the transcriptome that have those correlations.

There is a lack of data on the correlation with the PROs. The PROs are currently being developed, and validated, and further defined for the non –EoE EGIDs, but I do suspect that these parameters will also show strong associations.

I want to finally say that in the case of EG, CEGIR has developed strong evidence, and it's been validated that there are peripheral blood biomarkers that can be useful for following patients. In addition to the blood eosinophilia, which is correlative particularly in EG, we do know that there is particular cytokines like TSLP,

eotaxin 3, and IL-5 levels that are elevated in EGP patients, and they do correlate with eosinophils, intestinal and stomach. They also are variable depending upon the disease activity.

So these can be used, and we need to study them more, but we are optimistic that they will also be used to correlate with symptoms.

DR. HIRANO: I think there was a question, Marc, following up on that about the peripheral eosinophil count, and I know clinicians do use that in the patients where it does correlate, but it's not every patient that has that correlation between histopathological activity and peripheral eosinophilia, but when it does, it can be a non-invasive way to follow disease. There's a question about office-based technology such as the esophageal string test and Cytosponge, which have been validated for eosinophilic esophagitis but not for gastroenteropathy or enteritis.

Dr. Gonsalves, you have your hand raised?

DR. GONSALVES: Yes, thank you. I just wanted to add to that conversation about some of

those other metrics that Dr. Peterson had raised in reference to the ELEMENT study, which was brought up earlier today.

In the studies through CEGIR, we did see some changes, and significant changes, in those metrics. Specifically the EG-REFFS score did improve significantly after that intervention, in addition to the histology; as well as the EG HSS, we also saw an improvement in that peripheral eosinophilia, as well PRO metrics that were used in other CEGIR outcomes, such as the SODA and PROMIS scores.

So there are a lot of things that are seemingly starting to correlate with treatment that would be important to follow, so thank you.

DR. DELLON: I wonder if I could sneak in with one additional comment, because this is great. And I think just even in the last few minutes, we're hearing about the rapid development of data to kind of bridge the first session to this session now, where we were talking about all the clinical and histologic features and now the appropriate

endpoints to use.

I feel that we've presented a lot of data where we actually do know the symptoms, the patient's subtypes, what the histology looks like, the chronicity of the disease in particular and how these symptoms persist over time and don't wane. To me, it seems like we have a lot of information about how to select a population for study in a clinical trial.

So I'm wondering, again, about some of the comments that we're hearing about not the natural history information, and what specifically might we need to help increase that and know who to put in a trial because, to me, it seems like we could relatively easily select appropriate patients for trials right now.

DR. LYONS: Certainly, and I think that this is a point in time where we do have a wealth of information and we're keeping pace at this point. So when we say more natural history data is needed and more characterization is needed, really we're referring to outcome measures for a bit, as well as

I'll refer you back to our initial presentation; that yes, we do have a good body of building literature, information, and data, as well as lots of dedicated folks who have been doing research and are evaluating, and implementing, and developing new tools and metrics to use for these assessments.

We're still waiting for some consensus histologic criteria as a metric that we know the most about. We are working through what is supportable from the existing literature given the varied nomenclature that has been used in the past, as well as this heterogeneous population.

When you look at an individual patient, it is much easier to tell whether or not that patient is getting better or getting worse. And you bring it to the broader population where there may be heterogeneous symptoms or heterogeneous progression or response to treatment amongst those symptoms.

So bringing that all together with the work that's being done here, I feel like we are making great strides in moving the field forward at a very rapid pace. However, these are some of the gaps

that we hope to address effectively during this workshop and during additional opportunities for collaboration.

I would just applaud this group for being so willing to share their expertise, their perspective, and really work together in terms of how this needs to be shaped, or formed, or looked at from different perspectives to make it for regulatory use to really ensure that we are doing what we need to do for these patients. And that when we do have an approved therapy -- hopefully that day comes soon -- that we know that therapy is effective for the disease and the condition that they have, is safe, and that you, as well as patients, can be well-informed about the effects and the risks of taking that therapy.

I'm sorry. I know we're running a little over, but we do want to get to a common theme that came through the Q&A before we wrap up this panel discussion, and that's with Dr. Kovacs.

Could you please comment a bit on the recommended approach to developing a COA for a

disorder such as EGID, where individual patient symptoms can vary? Can you expand on that just a bit before we wrap up for the day?

DR. KOVACS: Sure.

I would mention first that FDA does encourage leveraging existing research and existing instruments and PROs that are out there if they are applicable. That would begin with conducting open-ended interviews with patients, concept elicitation and trying to figure out what are the meaningful and important symptoms that they have that they would like treated, and then also cognitively testing the skills to make sure that they're fit for purpose for that use in that target patient population.

It is challenging with these rare diseases to know what concepts to include as a COA endpoint in a clinical trial, so we do encourage leveraging the published literature, engaging clinical experts, collaborating with FDA, gathering qualitative evidence from patient stakeholders, patients, caregivers, and clinicians, and

understand what's most meaningful to these patients.

Then also very important is a thorough understanding of the drug's mechanism of action; what disease-related symptoms or signs are expected to improve, or normalize, or stabilize with the treatment in particular and what is considered meaningful to patients in terms of improvement or stabilization; also interviewing patients and finding out what constitutes, from their perspective, what is stability, what's worsening, and what's meaningful improvement.

In terms of an endpoint, figuring out what to use as an endpoint, maybe focusing on what's most widely characterized, what's most common and meaningful to patients in that particular subgroup of EGID patients, and what would be expected to improve or stabilize within the duration of the clinical trial so that you could actually show a treatment effect for a drug approval; and focusing on whether the symptoms are episodic or chronic and if it's frequency or severity of symptoms that's

most meaningful to patients.

Just really quickly, an example, if patients have a 7 on a pain scale of 0 to 10 in pain, and they have it every single day for 7 days at baseline, and then at the end of treatment, they have a 7 of pain on a 0 to 10 scale only one day out of the 7 days but the other 6 days are like a 2 or 3, if you're looking only at the worst severity score across that week at baseline and end of treatment, you're going to get a 7 at baseline and end of treatment, and you're not going to show a treatment effect.

So you really need to find out is it frequency, is it severity, and what is the most meaningful to patients and how you can show treatment effect and have a successful trial.

One last thing is that well-designed natural history studies do provide an opportunity where you can evaluate a variety of clinical outcome assessments that could ultimately ease through clinical trials, and those can be conducted either independently or through partnerships with patient

organizations. Thanks.

DR. LYONS: Thank you.

That is a lot of great information, and we can build on that and build on this rich discussion and dialogue that we've had here, all focused on assessing benefit and how that can be leveraged. I think the panel discussion was very vibrant, so we thank you all for that.

At this point in time, if we don't have any quick follow-up, closing comments from any of our panelists, I'd like to turn it over to Dr. Kowalik to provide our closing remarks for the day.

Closing Remarks – Matthew Kowalik

DR. KOWALIK: Thanks, Erica.

Well, thank you, everybody. I think this was a really -- I'm trying not to use the word "great" -- great workshop. Before officially closing the workshop, I'd like to just say a few closing remarks.

Today we had the pleasure to hear from a variety of stakeholders in order to try and achieve our goal of having a collaborative discussion on

some of the key issues related to clinical development of treatments for eosinophilic gastrointestinal disorders beyond eosinophilic esophagitis.

As a recap, during Session 1, Dr. Dellon discussed the evolving understanding of the pathogenesis of EGID and the dutiful work he and others are performing to promote a standardized nomenclature for EGID and how important this is to establish a common language in order to advance our understanding of these disorders.

Dr. Collins discussed the histopathologic features of EGID and reviewed some of the knowledge gaps that exist in defining what are normal and abnormal numbers of eosinophils in each segment of the GI tract.

We then heard from Dr. Gonsalves, who described the current understanding of the signs and symptoms and the natural history of EGID, highlighting some of the similarities and differences between EGID involving different segments of the GI tract.

Session 1 closed with Dr. Talley regarding the importance of considering alternative etiologies for gastrointestinal mucosal eosinophilia, and we had a really lively panel discussion and Q&A.

Then as we just heard during Session 2, we heard from multiple stakeholders on the assessment of clinical benefit. We heard from Ms. Smith, who kicked things off sharing her perspective as a patient living with EGID. Dr. Kovacs then spoke on the FDA perspective and defined treatment benefit in clinical trials, and we had Drs. Peterson and Menard-Katcher present on the clinician perspective for adult and pediatric providers, respectively. We then had another excellent discussion, as you all heard and just finished, so we thank all of our panelists for participating today.

I'll just share it was very inspiring for me, and I think for everyone, to hear from all of the various stakeholders that were represented today and to see just how much energy, resources, and expertise are being used to advance this field.

Although there are several knowledge gaps that we identified during our discussion today, and more research and data are needed, we also learned how quickly the field is evolving and how quickly the community is addressing these gaps in knowledge.

Our hope is that this workshop will serve as a springboard for further discussion and research to fill in these remaining gaps to advance the field here at the FDA, and I think it's safe to assume the community as well is very excited about the future in EGID, particularly as the science evolves.

We remain committed to working with patients, patient advocacy groups, academia, the clinical practice community, and industry to advance the field and bring safe and effective therapeutics to patients.

If you participated in a GREAT workshop for eosinophilic esophagitis several years ago, and as we heard, many participants involved here today did, you may recall we started the workshop with a

quote. So today I'll end our workshop with a quote from Soren Kierkegaard who said, "To dare is to lose one's footing momentarily. Not to dare is to lose oneself." So I'd just like to encourage all of us to continue being daring and advancing the field of EGID and address this area of need.

With that, I'd like to close by expressing my sincere gratitude to everyone involved with this workshop. Thank you, everyone, who participated in the workshop, and thank you to all of our presenters, moderators, and panelists for your time and expertise.

Thank you to our co-sponsors from the AGA, ACG, CEGIR, NASPGHAN, AAAAI, and BIO, and a special thank you to our patient representative and all the patient advocacy groups, and patients living with EGID today.

I personally want to thank Drs. Jessica Lee, Juli Tomaino, Erica Lyons, Sarrit Kovacs, and Jay Fajiculay from the FDA for your tireless efforts putting together this workshop. And one last note is that tomorrow we will have a second day of our

GREAT VI Workshop to discuss celiac disease, so please register and join us for that.

Adjournment

DR. KOWALIK: With that, I close the workshop and say goodbye, and thank you, everyone, and have a nice day.

(Whereupon, at 3:12 p.m., the workshop was adjourned.)