FOOD AND DRUG ADMINISTRATION

CENTER FOR EVALUATION AND RESEARCH (CDER)

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

Virtual Workshop on

Celiac Disease

Thursday, July 22, 2021

9:00 a.m. to 3:21 p.m.

Meeting Roster

Dawn Adams, MD, MS

Vanderbilt Medical Center

Amanda Cartee, MD

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Prista Charuworn, MD

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Stephen Lagana, MD

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Benjamin Lebwohl, MD, MS

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Daniel Leffler, MD, MS, AGAF

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Francisco Leon, MD, PhD

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Center For Celiac Research and Treatment at MGHfC

Edwin Liu, MD

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Suna Seo, MD

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The Royal Melbourne Hospital

Ritu Verma, MD

Comer Children's Hospital

Lynne Yao, MD

U.S. Food and Drug Administration

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(10:03 a.m.)

Opening Remarks – Suna Seo

DR. SE0: Hello and welcome, everyone. My name is Suna Seo, and I'm a clinical team leader within the Division of Gastroenterology at the FDA. It is my privilege and pleasure, on behalf of my division director, Dr. Jessica Lee; deputy director, Dr. Juli Tomaino; deputy director for safety, Dr. Joyce Korvick; and the entire Division of Gastroenterology, to welcome and thank you for joining us today for our VI GREAT, which stands for Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics Workshop.

In fact, this is our second GREAT workshop on celiac disease, and we are thrilled to see So many participants in attendance from across such a wide variety of stakeholders, including representatives from academia, the clinical practice community, industry, FDA, and especially our patients and patient advocacy groups.

Building on our previous GREAT III workshop

on celiac disease from 2015, the goal of today's workshop is to further our discussion on the overall approach to drug development in celiac disease that includes an assessment of both clinical symptoms and histology.

We plan to focus on three main areas for today's workshop: the histologic endpoints to assess treatment benefits in patients with celiac disease; regulatory framework for pediatric growth development in celiac disease; and the role of gluten challenge in clinical trials. We hope that despite the limitations of a virtual environment, this will be a forum for an open discussion between stakeholders to facilitate drug development.

As a regulatory agency, 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; and within the FDA, the Division of Gastroenterology is a part of the FDA's Center for Drug evaluation and Research.

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're available to patients.

We'd like to note that this workshop is intended to provide a format for collaboration, information sharing, and scientific discussion of how to address key issues in the clinical development of treatments for celiac disease.

Although we encourage participants to share their experience and expertise for the benefit of the group discussion, please 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 or agreements reached.

As you see on the agenda, this workshop is divided into three sessions. All three sessions will begin with a few presentations that will provide the background and set the stage for the following panel discussion and Q&A portion, which will be focused on the strength of the available

data and the areas of persistent knowledge gaps for which additional research is needed.

We're most excited for what we hope will be a lively dialogue during the panel discussions and Q&A sessions. To facilitate the discussion, we encourage you to use the Q&A box on your screen to post your questions for a topic for the panel discussion throughout the presentations.

We'll try to have as many questions answered during the panel discussion and Q&A session, but please note that we may have limited ability to answer questions submitted in real time during the Q&A session and encourage you to submit the questions prior to the scheduled breaks in each session.

Before we get started, I would like to express my sincere gratitude to the co-sponsors of this workshop and to the steering committee members who helped to make this event come together. The co-sponsors include the American College of Gastroenterology; American Gastroenterological Association; and the North American Society for

Pediatric Gastroenterology, Hepatology, and Nutrition.

Each group, including pharma and bio, nominated representatives for the workshop steering committee, and the members of the steering committees have worked hard over the last seven months to make today's workshop a success. They took time from their busy schedules to get on numerous teleconferences, create today's agenda, and review the presentation topics together. We're truly grateful for their collaboration and the time that they committed to this effort.

I would also like to take this opportunity to recognize the dedication and leadership shown by our FDA staff who have worked tirelessly to plan this workshop. I would particularly like to recognize Dr. Irene Lavine; Dr. Juli Tomaino; Dr. Jessica Lee; Dr. Andrew Dodson; and Captain Kelly Richards for their commitment, diligence, and meticulous attention to details, as well as the FDA public meeting support and information technology teams for their assistance coordinating and hosting

today's virtual meeting.

Before we launch into our first session, which will focus on the histologic assessment in the evaluation of the underlying disease and treatment benefit in celiac disease, Dr. Irena Lavine will provide us with a broader overview and present the FDA perspective on Consideration for Drug Development in Celiac Disease.

Dr. Lavine is a clinical reviewer 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. Lavine has worked in a variety of therapeutic areas within gastroenterology, including inflammatory bowel disease, irritable bowel syndrome, chronic idiopathic constipation, and of course celiac disease.

I will now turn the presentation over to Dr. Lavine.

Presentation – Irena Lavine

DR. LAVINE: Thank you, Dr. Seo, for your

kind introduction.

Good morning. I will be talking about Considerations for Drug Development in Celiac Disease from the FDA perspective. This is our standard disclosure statement and I have nothing to disclose.

The purpose of my talk is to discuss where we have been and where we are going with drug development in celiac disease. First, I will discuss the regulatory framework for establishing substantial evidence of effectiveness, which guides our work; then I will discuss highlights from the previous gastroenterology regulatory endpoints and advancement of Therapeutics III, or GREAT III workshop, on celiac disease in March of 2015.

Finally, I will discuss considerations for drug development in celiac disease, including the patient population, trial design assessment, assessment of clinical benefit, and pediatric considerations. My introductory talk will provide regulatory background and context for the sessions of our workshop today.

Since I'm giving the regulatory perspective on the considerations for drug development in celiac disease, I'm going to use the first couple of slides to review the laws and regulations that guide the regulatory framework.

The 1962 drug amendments to the Federal Food, Drug, and Cosmetic Act required establishment of effectiveness of a drug as a prerequisite for marketing approval. Effectiveness is established by substantial evidence.

So what is substantial evidence? It is evidence consisting of adequate and well-controlled investigations, where it has been concluded by experts the drug will have the effect it purports or is represented to have under the conditions of use. This requires that studies are designed well enough to distinguish the effect of a drug from other influences such as spontaneous change, placebo effect, or biased observation.

Substantial evidence of effectiveness comes from evidence from adequate and well-controlled trials. Characteristics of adequate and

well-controlled trials include a clear statement of objectives; appropriate control for comparison; appropriate selection of patients with the disease or a risk of the disease; baseline comparability; methods to minimize bias; appropriate methods for assessment of response; and appropriate methods of analysis.

A key goal of any clinical development program is to demonstrate the clinical benefit of the therapy. So what is clinical benefit? Clinical benefit is a favorable effect on a meaningful aspect of how a patient feels, functions, or survives as a result of treatment. It should be meaningful, measurable, and interpretable.

The observed benefit is described in labeling as a claim using words that represent the concepts measured and they should also be meaningful and understandable to patients and prescribers.

Today we are building on a workshop from 2015 to focus on the approach to endpoint

development in celiac disease. This workshop is organized by the FDA and co-sponsorship with many organizations, including the American Gastroenterological Association; the American College of Gastroenterology; the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; and the North American Society for the Study of Celiac Disease. A workshop summary resulting from the workshop is shown on this slide, and I will discuss highlights on the next slide.

For those of you who are not familiar with GREAT, the purpose is to provide a public scientific forum to consider issues related to drug development in gastroenterology, including the patient population, selection of endpoints, and clinical outcome measures to assess treatment benefit.

In addition to a GREAT workshop on celiac disease, we've also held GREAT workshops in other disease areas, including several on inflammatory bowel disease, eosinophilic esophagitis, pediatric irritable bowel syndrome and functional

constipation, and liver diseases.

There are three primary topics that were discussed during the GREAT III Workshop. When defining the patient population in a clinical trial, it is important to ensure that the signs and symptoms experienced by patients are indeed due to active celiac disease and exclude other causes that mimic celiac disease.

We discussed the clinical benefit is demonstrated through improvement in the disease-related GI signs and symptoms and small intestinal histology. Finally, we discussed potential roles of celiac serologies in clinical trials, including using celiac serologies as part of the disease diagnosis for enrollment.

It is important to note that celiac serologies have been cleared by the Center for Devices and Radiological Health only as an aid in the diagnosis of celiac disease. Serologies have not been cleared for monitoring disease progression or disease response in a clinical trial.

Another focus of the GREAT III workshop was

incorporating the patient voice in clinical outcome assessment development. The FDA held a listening session with patients with celiac disease and caregivers on February 20, 2019 to better understand the celiac patient perspective.

Topics discussed included symptoms that most impact the daily lives of patients and caregivers and the type of potential treatments for celiac disease that patients would be most interested in taking. Patients were generally open to the idea of a treatment for accidental exposure to gluten such as cross-contamination in food. If such a treatment was available, the patients indicated they would continue to maintain a strict gluten-free diet.

Patients were generally not open to the idea of a treatment intended to be taken regularly that does not promote healing of the underlying disease. Patients generally expressed they were not willing to ingest gluten for the purpose of a clinical trial. I have provided the FDA link to the summary from this listening session if people are

interested in reading more about the topics discussed.

In the next few slides, I will outline some considerations that may be helpful to design clinical trials in patients with celiac disease. In general, randomized, double-blind, placebo-controlled trial design promotes interpretability of data since there is currently no approved pharmacologic therapy available for active comparison.

The intended use of a drug -- for example, products intended for adjunctive treatment to a gluten-free diet or monotherapy -- should inform the overall trial design, including the selection of the target patient population. In addition, enrolled patients should meet prespecified minimum requirements for severity of clinical signs and symptoms and histology to allow for observation of improvement due to the treatment during a trial.

The trial duration and timing of efficacy assessments should be guided by the anticipated onset of action in a time frame in which the

desired treatment outcome is expected to be observed. For drugs intended to be administered chronically, we recommend ensuring adequate exposure to the drug during the trial to allow for characterization of the long-term safety profile and durability of response.

Clinical benefit in celiac disease is measured by improvement in signs and symptoms via patient-reported outcome, or PRO, assessments and histology assessed by endoscopy with biopsy. What is a patient reported outcome assessment? This is an assessment based on a report that comes directly from the patient without interpretation. PRO assessments can measure patient's symptoms, signs, or an aspect of functioning related to a disease.

The other component of clinical benefit in celiac disease is a histologic assessment. As there is no generally accepted histologic scale for use in clinical trials, we recommend exploring changes in a variety of histologic outcomes and scales which incorporate evaluation of villous atrophy, crypt hyperplasia, and lymphocytic

infiltration. The histologic assessment will be the focus of Session 1, and we will discuss different approaches then.

There are various ways to assess benefit and some trials may include a gluten challenge. An active area of debate is when and why is it necessary to include gluten exposure in a clinical trial and the desired data cannot be obtained otherwise. Important considerations include the dose and duration of gluten exposure that elicits an immune response, timing and types of assessments, and safety monitoring, and you will hear more about this during Session 3.

Another important area for discussion today is on the unmet needs of pediatric celiac disease, and this is the focus of Session 2. The goal is to encourage the planning of pediatric development programs much earlier in the process. To facilitate development in pediatric patients, we often rely on extrapolation of efficacy.

Extrapolation of efficacy is an approach to improve efficiency and success of pediatric drug

development. It relies on a series of evidence-based assumptions that reference adult or other pediatric trials and targets pediatric populations that will be expected to have sufficiently similar disease course and expected response to therapy.

When designing clinical trials in pediatric patients with celiac disease, important considerations include to understand the mechanism of action of the drug and its target on the pathophysiology of disease. For example, is the underlying pathophysiology and response to treatment sufficiently similar between adults and children?

Is it different for infants, children, and adolescents? Is the exposure-response sufficiently similar between adults and children? Are the core signs and symptoms that define the disease similar between adults and children? Would a clinically meaningful outcome be similar between adults and children? What is the age range of pediatric patients who might benefit from the therapy? What

uncertainties and/or limitations are there in existing data and about the pediatric population? We will be discussing these considerations in Session 2.

In summary, early planning in the drug development process is critical to meet the challenges associated with defining the target population and outcome measurement. We need to identify clinically meaningful, measurable, and understandable endpoints based on improvement in both key signs and symptoms as well as the underlying disease.

Frequent communications and collaborations among the FDA, industry sponsors, academic investigators and clinicians, and patients will likely result in successful development of celiac disease treatment. This is the goal of today's workshop, to have a scientific discussion about drug development in celiac disease.

I would like to acknowledge a few individuals who contributed to the development of these slides. Thank you. I will now turn the

presentation over to Dr. Suna Seo and Dr. Dawn Adams, who are the moderators for Session 1.

Dr. Seo is a clinical team leader in the Division of Gastroenterology and Office of Immunology and Inflammation, within the Office of New Drugs in the Center for Drug Evaluation and Research at the FDA. Dr. Seo oversees a variety of therapeutic areas within gastroenterology, including celiac disease, inflammatory bowel disease, irritable bowel syndrome, chronic idiopathic constipation, and short bowel syndrome.

Dr. Dawn Adams is an associate professor of medicine and gastroenterology at Vanderbilt Medical Center. She's the medical director for the Vanderbilt Center for Human Nutrition and created and leads the Vanderbilt Celiac Disease Clinic. Her clinic and research interests are celiac disease and intestinal failure.

DR. ADAMS: Thank you, Dr. Lavine, and it's my honor to participate in the session and to introduce our first speaker, Dr. Lebwohl.

Dr. Ben Lebwohl is the president of the

Society for the Study of Celiac Disease. He is an associate professor of medicine and epidemiology at Columbia University Medical Center, where he serves as the director of clinical research at the Celiac Disease Center. Dr. Lebwohl will be reviewing an approach to monitoring disease through histological assessment in clinical practice.

Presentation – Benjamin Lebwohl

DR. LEBWOHL: Thank you, Dr. Adams, and thank you to the FDA for recognizing the need for this workshop. This is an exciting time in the world of celiac disease for our community, given the growing number of non-dietary therapies that are in the process of being investigated; and also particularly to the FDA staff for their careful and deliberate development of the agenda for today's workshop. I think we're really in for a productive exchange of ideas and opinions.

I was asked to speak about monitoring disease through histologic assessment in clinical practice, and I'll do so as a gastroenterologist who takes care of adults with a specialty in celiac

disease. I'm going to limit this presentation to histologic assessment on follow-up, not to the role of histology in the diagnosis of celiac disease, simply because the focus of this workshop is one on endpoints and potential response to therapies.

I would also say I do this as a gastroenterologist who takes care of patients, but also as an investigator who's been studying the causes and consequences of persistent intestinal damage, or villous atrophy, for a number of years.

We should start by looking at some histologic images. Shown on the left is normal duodenal mucosa and shown on the right is atrophic villi. You can still make out some semblance of villous architecture, but they're short, they're blunt, and this is a patient with celiac disease.

The direction goes from left to right if someone with celiac disease eats gluten, but it also goes from right to left once that person with celiac disease goes on a gluten-free diet. That's usually what happens and that's what we anticipate to see, but it's not always what happens because

not everyone heals.

The question is, do we need to know in clinical practice whether someone has healed or not? Well, if someone is still symptomatic despite trying to be on a gluten-free diet, a follow-up biopsy can be really clinically helpful because if someone is still symptomatic, we're not sure whether the culprit for those symptoms is gluten or something else: concurrent irritable bowel syndrome, some other food intolerance.

There's a long list for so-called non-responsive celiac disease, but if we see persistent villous atrophy, that is an indicator that gluten is likely getting into that patient and causing ongoing damage.

We also use it as a way to either diagnose or rule out refractory celiac disease, which is a rare subset of people with non-responsive celiac disease probably occurring in fewer than 1 percent of everyone with celiac disease, characterized by persistent clinical evidence of malabsorption, evidence of no ongoing gluten consumption, and yet

ongoing intestinal damage and inflammation. The follow-up biopsy is key to making or ruling out that diagnosis.

But there are also people who are asymptomatic, who are on a gluten-free diet, and we and they may want to know what their histology is doing over time, and there are a few reasons. One is to assess dietary adherence.

We like to say there's always someone out there who's stricter than you. All people with celiac disease have to make choices with regards to the extent that they are taking to avoid gluten. And the question is, is their current level of dietary adherence sufficient? And if we do a follow-up biopsy and their villi have normalized, that means that that patient, with regard to the current degree of precautions, is actually sufficiently avoiding gluten, at least from a histologic perspective.

There is also a potential role in triaging people for more intensive dietitian follow-up. Access to a dietitian expert in gluten-free diet is

the linchpin of management of celiac disease, and yet, first of all, not everyone has access; and second, after an initial consultation, it's not so clear the degree to which someone would be following up with a dietitian, and the patient who has persistent intestinal damage, persistent villous atrophy, might benefit from a more intensive assessment with that dietitian.

There's also emerging data that patients with persistent villous atrophy may be at increased risk of long-term complications in celiac disease, and so risk stratifying patients that way may be useful, even in a patient who is apparently asymptomatic.

How do we monitor people with celiac disease or on a gluten-free diet when we want to know how are they responding? I would argue there really are four pillars. One is symptoms. Symptoms are of crucial importance because ultimately we want to have patients feel better and have a good quality of life; so we assess them. We ask how they're feeling. And even though PROs are not the focus of

today's workshop, that of course is a central consideration in terms of any endpoints.

We also want to know, does our dietitian on their assessment believe that the patient is taking adequate precautions to avoid gluten? After all, symptomatic response is non-specific, and there are people out there with celiac disease who may continue to consume gluten at substantial levels and yet may not have substantial symptoms. So symptoms are clearly not enough, and we need to know whether these patients are taking sensible precautions.

We also use serologies. And even though Dr. Lavine correctly points out that this is not FDA cleared as a way to monitor gluten-free diet or response to gluten-free diet, in clinical practice we frequently do this. We follow patients' serologies because we anticipate that with adoption of the gluten-free diet, these serologies will decline and in most patients normalize, typically over the course of about a year after initial adoption of the gluten-free diet.

Finally, histology is for many of us an important way to monitor the response to the gluten-free diet. Histologic response, or normalization of villous architecture, likely will take longer than these other responses, a symptomatic response or serologic response. It is also not a universal response, and yet we find that it can be very helpful in both symptomatic and asymptomatic individuals.

I should acknowledge at this point that the role of follow-up biopsy in the management of celiac disease remains an area of uncertainty. And if you look at clinical guidelines with regard to monitoring celiac disease, you will not find firm guidance, and towards the end of this presentation, I'll quote one of those guidelines. So there really is a fair amount of variability between practitioners with regard to whether and when to do a follow-up biopsy.

One reason to do a follow-up biopsy is that there appear to be consequences of persistent villous atrophy. Shown here are the results of

five studies, all population-based studies, all consisting of individuals in Sweden who underwent a biopsy confirming a diagnosis of celiac disease, and then had a follow-up biopsy anytime between 6 months and 5 years after their initial biopsy.

In these studies, we compared people with persistent villous atrophy classified as Marsh 3 or greater to those with normal villi, so-called Marsh 0 or Marsh 1 or 2, increased intraepithelial lymphocytosis with or without crypt hyperplasia. We wanted to know whether there are any significant outcomes associated with persistent villous atrophy, and shown in the column labeled hazard ratio are these risk findings. A ratio greater than 1 indicates a greater risk of the outcome in question and less than 1 indicates a lower risk.

You can see that when we looked first at the ultimate outcome, mortality or life expectancy, there was no association between persistent villous atrophy and mortality, nor was there association with that finding in ischemic heart disease, or any obstetric outcomes among women who had a follow-up

biopsy and then became pregnant at an interval shortly thereafter.

But we did find that there were two outcomes that were significantly associated with persistent villous atrophy. One was lymphoproliferative malignancy, lymphoma, and this was a 2.26-fold increased risk or increased hazard among those with persistent villous atrophy on follow-up compared to those who healed on follow-up.

In fact, when looking purely at the absolute risk of lymphoma among those who healed on follow-up and comparing those to the general population, there was actually no increased risk compared to the general population among those who healed.

The other outcome that we found that was of increased risk among those with persistent villous atrophy was hip and other likely osteoporotic fractures. I should say these data were recently updated. We again looked at mortality published in JAMA in April 2020 and again when following patients through 2016 in Sweden in the modern era,

in which mild disease might be diagnosed in this era of more avid serologic testing. We still found no association between persistent villous atrophy and mortality.

We also recently updated the lymphoproliferative malignancy work, and we actually cast a wider net and looked at all cancers, and the only cancer that appears to be an increased risk of developing among those with persistent villous atrophy remains lymphoproliferative malignancy and that the hazard ratio was, again, very similar. That was recently published in Clinical Gastroenterology and Hepatology.

So there may be a role for follow-up biopsy for risk stratifying with regard to morbidity, and shown here is an algorithm of incorporating follow-up biopsy in the risk stratification and triage of individuals with celiac disease.

This is the experience of a group in Cambridge, England who report on 391 of their patients who underwent a follow-up biopsy at a

median time of 11 months after initial diagnosis. What they found was that 57 percent at 11 months actually had normal villi. But what I would ask you to focus on is what happens after that biopsy. Why do a test if you're not going to change your behavior based on the results of that test? And that's exactly what they recommended doing.

Among those who had ongoing villous atrophy at first follow-up biopsy, they were then reassessed by their dietitian and underwent a further duodenal biopsy 12 months later. The results of those third biopsies were really spread out, but before those third biopsies were done, patients were advised to either review their diet and try to clean up areas of potential gluten exposure -- that was if the dietitian found that there were areas of vulnerability -- or among those patients who have persistent villous atrophy and yet the dietitian did not find any area of potential contamination or cross-contact with gluten, they were put on a so-called super-sensitive diet. And you're going to be

hearing more about such a diet, the so called gluten contamination elimination diet, in Dr. Leonard's talk later on today.

So after that initial follow-up biopsy, depending on the dietitian's assessment, that determined the degree of enriched efforts to avoid gluten that were undertaken. Now, even people on the super-sensitive diet did have ongoing villous atrophy, but this is a way of illustrating that that first follow-up biopsy is a way to further risk stratify and triage patients to more intensive ways of following a gluten-free diet.

So when should we do a repeat biopsy? Well, there's a lot of uncertainty here, but in this analysis of a clinical trial of a follow-up biopsy that enrolled people at follow-up after at least one year of celiac disease, among people who had persistent symptoms, you can see that among those who had celiac disease for less than two years -- and I should point out this is among adults -- 50 percent had persistent villous atrophy. But after two years and beyond, no matter

how far you followed them, that rate declines to closer to 30-35 percent or so.

So it does appear that the natural course of healing among adults happens to take perhaps longer than a year, but after two years you don't typically see more gradual healing.

What about other ways to monitor whether people are being exposed to gluten and have persistent atrophy? Very recently published was a multicenter study in Spain and people were biopsied two years out. Fifty-three percent had persistent villous atrophy. An important predictor of persistent atrophy was age. You can see shown here that the majority of people older than 30 had persistent atrophy, but the majority among those under 30 had healed by then.

Now, the majority were deemed to have excellent adherence by an expert dietitian, and yet when measuring for gluten immunogenic peptides in stool, the majority had some evidence of gluten exposure, and these authors actually found no association between whether gluten was found in

their stool and the finding of persistent villous atrophy.

I should point out that other studies, prior smaller studies, of gluten peptides did find some degree of correlation between gluten exposure in stool or urine and persistent atrophy, but it does appear that these new technological ways of measuring gluten are measuring really small amounts of gluten, which might not be sufficient to cause ongoing intestinal damage.

This recent editorial discussing the potential reasons to biopsy or reasons not to biopsy basically goes through the different factors at play. Among someone with persistent symptoms or among a patient who's keen to know that they are doing what they need to be doing with regard to gluten avoidance, a biopsy will be helpful. But among patients who feel well, who have serologic negativity, they've normalized and they feel that they're being really adherent, the question of whether to do a biopsy is a matter of debate.

Then if someone has ongoing villous atrophy,

it's a question of, is it that they are being exposed to gluten, that they're super sensitive to gluten, or perhaps they're one of the minority of patients with celiac disease who are reacting immunologically even to pure oats.

So there's a lot of uncertainty surrounding the implications of histology, and yet we are learning that age is a very important predictor of histology and that children are more likely to heal than adults, particularly older adults, so we'll be hearing shortly about pediatric considerations.

What we do know is that symptoms are a very poor predictor of whether someone is healed or not. In this post hoc analysis of a clinical trial of one non-dietary therapy, we looked at people at baseline who were symptomatic in this trial and found that among people who had bloating, abdominal pain, and nausea, they were actually less likely to have persistent villous atrophy than people who did not report these symptoms.

So the presence of these symptoms are not a reliable predictor of persistent villous atrophy,

nor are serologies. In this systematic review by Dr. Silvester and colleagues, among people who had an elevated tissue transglutaminase on follow-up, you can see the sensitivity for that and specificity, where I would argue is unacceptably low as a marker of persistent villous atrophy.

So ultimately, what does it mean to have well-controlled celiac disease? Well, think about the four pillars. Symptoms should be improved or resolved. The dietitian needs to believe that the patient is adequately adherent. There should be serologic normalization, or at least near normalization, during that first year when serologies are coming down; that's frankly difficult to interpret. There should be histologic recovery, but because it can take two years on average for villi to normalize, it is difficult to interpret that during those first two years.

You will be hearing more about the ways we score histology, but in clinical practice we often speak of the Marsh score. It's widespread on pathology reports, and when we speak to colleagues

and patients, Marsh 3, indicating villous atrophy, sometimes denoted as villous blunting in a pathology report, is useful, because if someone has a pathology report on diagnosis, anything short of Marsh 3, we're concerned. Maybe it's not celiac disease, because any biopsy score short of that is non-specific for celiac disease.

When thinking about follow-up histology, we think of that as a surrogate for healed versus not healed, but I should say we're leaving a lot of data on the table in clinical practice. We don't use the continuous gradations. We really think of it as Marsh 3 versus not, and we ignore a really critical piece of data that's out there because we're not sure how best to incorporate it, the presence and quantity and type of increased intraepithelial lymphocytosis.

You'll be hearing more from Dr. Robert shortly about the villous height to crypt depth ratio. The benefit of this is that this is a continuous measure, so particularly when thinking about endpoints and trials, there can be a lot more

analysis if you look at this continuous response; though I would direct you to this review by Adelman and colleagues that maps villous height to crypt depth ratio to the traditional Marsh score used in clinical practice.

So finally I'd say that I offer a follow-up biopsy. I typically offer it at two years, but clinicians will vary, and one to three years is most typical. It's not mandated by guidelines, and most recent American College of Gastroenterology guidelines state that it is reasonable to do follow-up biopsy in adults after two years, after starting a gluten-free diet, to assess for mucosal healing.

If someone has healed, it offers validation of the patient's current precautions, and if there is persistent atrophy, it suggests -- it doesn't guarantee but it suggests -- the presence of ongoing gluten exposure.

In clinical practice, we dichotomize, healed versus not healed. But we should acknowledge that, truly, there is a continuum, and the villous height

to crypt depth ratio is a way to measure that continuum. And with that, I thank you for your attention and look forward to the panel discussion.

DR. SE0: Thank you, Dr. Lebwohl.

Next, we will go on to Dr. Jocelyn Silvester. Dr. Jocelyn Silvester is an assistant professor of pediatrics at Harvard Medical School, director of research for the Celiac Disease Program at Children's Hospital, and courtesy staff at Beth Israel Deaconess Medical Center, also in Boston. Her research relates to the diagnosis and management of celiac disease with a particular interest in what happens after the diagnosis of celiac disease is made.

Thank you, Dr. Silvester.

Presentation – Jocelyn Silvester

DR. SILVESTER: Thank you very much, and thank you for bringing our community together for this meeting. I'm very much looking forward to our discussions on how we can collectively move our field forward because I think this is a very exciting time.

To start off with, I have a few disclosures all related to celiac disease. In terms of this talk, we're going to take a step back because in pediatrics we actually talk more about why do a diagnostic biopsy than follow-up biopsies, although both are relatively controversial.

I want to address the issue of mucosal recovery in pediatrics and some of the knowns and some of the unknowns; talk a little bit about why kids are different; and how this is going to have implications for clinical practice and research, and then ultimately clinical trials.

I think in this respect, history is perhaps constructive, and if we look at how we diagnose celiac disease in children, we really have changed things a lot since the first recommendations in 1979, which recommended three biopsies. The concept here at that time was primarily young, symptomatic children were being diagnosed. They would have initial biopsy on gluten. They'd then be put on a gluten-free diet to see symptomatic and histologic recovery, and then they would be put

back on gluten in order to see relapse.

Now, there are obviously some challenges with this. Particularly when you have a 1979 quality, gluten-free diet, getting people back on a gluten-free diet can be challenging. So in 1990, the criteria were officially revised, the third biopsy was scrapped, and the second biopsy was restricted to those less than 2 years old because of the concern that in this age group, cow's milk protein allergy can be an important item on a differential diagnosis and hard to distinguish; so this is part of the reason for looking for reversibility with gluten.

In 2012, there was perhaps the biggest change and paradigm shift in how we diagnose celiac disease, which has significant implications for our discussion today. This is really driven by the discovery of serology, particularly tissue transglutaminase and endomysial antibodies as a biomarker of celiac disease. So we're now moving on to more disease-relevant measures than simply looking at what the histologic effects of the

disease are.

This is complicated, but don't worry; we're not going to go through it all. The main points are that rather than focus on histology, the focus is on symptoms. There are different algorithms for those who have symptoms and those who do not have symptoms. Autoimmunity antibodies is a main criteria for stratifying, and genetic risk because we have learned since 1979 about genetic risk for celiac disease.

The take-home message here is that in those who are symptomatic with very high tTG levels and a positive endomysial antibody on a second test, as well as susceptible genetics, the recommendation was that they could go gluten-free without the biopsy.

Now, one of the few good things to come out of 2020 was an updated guideline, and this is much simpler. Symptomatic and asymptomatic are grouped together, they're no longer divided, and the requirement for genetics has been removed. So now there are recommendations to diagnose celiac

disease solely on serology regardless of symptoms.

This clearly has significant implications for how we manage celiac disease when we start to think about follow-up biopsies. The obvious one is if the initial diagnosis is made by serology, then the follow-up biopsy may be the only biopsy that is performed, or the first biopsy; so then it's difficult to compare without a baseline.

As well, follow-up biopsy is not currently routine and it's more likely in those who may be a little bit different; so those who have new or persistent symptoms, those who serology is elevated, or particularly -- and I think this is an important thing to think about -- those who have other conditions in which routine follow-up endoscopies are a generally accepted part of treatment.

You think about eosinophilic esophagitis, which I know many people have been thinking about a lot this week, it's quite well accepted that even very young children could have several biopsies over the course of a few months in order to

determine the treatment. So I think while we are all excited about the prospect of diagnosing celiac disease with a biopsy, it's also important to remember that there are very different standards when we start thinking about different gastrointestinal diseases.

I want to briefly talk about some data, more for the implications for what we're doing and what we know than the data itself. This is a cohort from Mass General Hospital and Boston Children's Hospital of children who had a follow-up biopsy, children with celiac disease had a follow-up biopsy, over a three-year period.

What's interesting is the N is only 103. Combined, these centers followed thousands of children, but the vast majority did not get a follow-up biopsy. So this is a very incomplete picture of what's happening for children with celiac disease. As you can see, the main indication for the biopsy was persistent symptoms, followed by new symptoms, and there is a good proportion who are having follow-up of esophagitis.

On the right, you see the histology, which is reported as Marsh 3. As Dr. Lebwohl noted and I think Dr. Robert will talk about in more detail, how we think about histology clinically is much less sophisticated than how we think about histology in clinical trials, in that the reporting is often less rigorous and this has implications for how we think about improvement.

The main point here is that about 20 percent had persistent Marsh 3 lesions, which is similar to the numbers presented by Dr. Lebwohl and potentially a better result than we see in adults. I think it's important to note when we think about the earlier studies that prompted changes to the guidelines, the way that biopsies were being done was different, so that may also affect our ideas of historical rates of mucosal recovery.

If we look at the next slide, I think there are many proxies for serologic endpoints. And clearly, if most children are not getting a follow-up biopsy, then these are really what we're relying upon clinically, and I think they all have

limitations, which we'll have more time to discuss later.

I'd like to think about why are children different than adults and what are some of the reasons why some folks might be routinely doing follow-up biopsies on their adult patients, and this is much less common and certainly not universal in pediatrics.

I think the most important reason is that endoscopy in pediatrics is a more significant undertaking than endoscopy in adults, and this is not because of the endoscope or the procedure itself necessarily, so much as the fact that pediatric procedures are typically sedated, and we're learning increasingly that there are impacts of sedation on the developing brain.

So concerns about this makes us more cautious about putting children through procedures, although I would note that most of the data is on procedures longer than an hour and an upper endoscopy tends to be much shorter.

Again, there are many children with other

conditions who are getting much more frequent biopsies than our patients with celiac disease. There's also a question of the risks of more biopsies in smaller children.

So when thinking about these considerations, I think what's really important and really exciting, and what we need to think about in designing clinical trials is that technical innovations can really change what we do and the risks.

This is another way of thinking about villi. I think we think about histology as a way of looking at villi, but we actually look at villi before we even take a biopsy. On the left, you see some images that are taken using a high-definition endoscope with optical filters, and you can see clearly that there is resolution between those who have villi and those whose villi are flatter.

On the bottom using capsule endoscopy, which is a swallowed pill, which means that there's often no sedation, in the center you see images from confocal laser endomicroscopy, so this involves an

endoscope that has additional microscopic and laser on it and allows us to get images but leaving the tissue intact, and is another way of thinking about what's happening in celiac disease and visualizing what happens in celiac disease. It's perhaps less commonly used but has been shown to correlate with histologic findings.

On the right, this is not a Crosby capsule of old. This is a newer tethered capsule that's being developed by Dr. Tearney over at Mass General, and this is potentially going to revolutionize how we think about celiac disease and how we follow up because this technology is very small.

It's about the size of a vitamin. It's designed to be able to be performed on children who are unsedated, and it's been performed in settings where they don't have the same degree of support that we typically have in North America. There are all sorts of different things you can put in these capsules in order to get a glimpse of what's happening in the intestine.

On the left you see some spectral enhanced confocal microscopy and then on the right you see some optical coherence. As you can see, you can get an idea of villi. You can actually start to see epithelial cells. And this is very different to think about than what we're used to thinking about because we often think about villi in terms of histology, but I think we need to think about what are we really assessing when we look at villi. There's a whole other step, which is once we have the biopsy, how do we look at the villi, but I'm going to leave that topic for Dr. Robert.

To summarize briefly, in pediatrics, increasingly the follow-up on a gluten-free diet may be the initial biopsy and not a follow-up on an initial biopsy. We aren't performing a lot of biopsies, so there's a lot of reliance on clinical signs and symptoms, but this is not standardized. So as a consequence, there's lots we don't know about signs and symptoms of pediatric celiac disease, particularly as many patients don't follow up.

The rate of mucosal recovery on a gluten-free diet in children on a modern gluten-free diet with many of the foods available today is uncertain, but it's probably not a hundred percent. If we look to the future, technological advances may definitely shift things. I think as we think about evaluating therapies, we need to think about how we evaluate disease because these evaluations are a great opportunity to refine our measures, not only to learn more about the disease but to improve our clinical practice.

With that, I will pass it along. Thank you.

DR. ADAMS: Thank you, Dr. Lebwohl and Dr. Silvester, for your excellent reviews of incorporating the biopsy in clinical practice.

We will now discuss specific histological characteristics that define disease activity by Dr. Robert. Dr. Robert is an internationally recognized gastrointestinal pathologist and a professor of pathology medicine in the human and translational immunology program at Yale University School of Medicine.

She's been working in diagnostic and clinical research in celiac disease for 30 years and is the lead author of guidelines for the diagnosis of celiac disease and refractory sprue. She served as the chief scientific officer for the nonprofit advocacy group, Beyond Celiac, and founded the Yale Celiac Disease Translational Research group.

Dr. Robert?

Presentation – Marie Robert

DR. ROBERT: Thank you so much, and thank you to the FDA for putting together this day. I am an academic gastrointestinal pathologist as mentioned, and I have not to date participated in measuring the histologic response to therapeutics in clinical trials. I think that may be the reason I was asked to provide an overview of the topic of histology today because I don't have a horse in the race, so to speak, as of now. I trust that those with experience in measuring histology and clinical trials, who are on the webinar today, will contribute their knowledge during the discussion

period.

Nothing that I'm presenting today represents the FDA's recommendation for how to measure histology in a clinical trial. In fact, nothing is actually set in stone. As was mentioned, there are good practices and then there are still open questions about what is the best way to measure histology to show responsiveness and what that means. So just please keep that in mind, and if you're sharing these slides with others, just remember that this is not a recommendation per se.

What we have here is the spectrum of histology in celiac disease. on the top left is normal duodenal mucosa. The finger-like projections are the villi going up and the little tubes going down are the crypts. So if you were to look at this so called villous height crypt depth ratio in the top-left panel, you see it would be for 3 to 5 villous height to crypt depth, perfectly normal.

If you move along to the right, panel B, that would be mild blunting, Marsh 3A, for example,

Marsh-Oberhuber 3A, C would be moderate, and D, there's actually no villi that severe. So the villous height crypt depth ratio is actually zero in this. You cannot appreciate at this magnification the intraepithelial lymphocytes, yet they are increased in panels B, C, and D, and that forms a part of the Marsh.

We've already heard about celiac disease activity indicators from Ben and Jocelyn, including symptoms, titers, et cetera, and we're going to focus in these few minutes on duodenal mucosal histology. It's already been acknowledged that there's an imperfect correlation between clinical data and the morphology, however, I think we all agree that histology will always be a useful element in the toolkit of activity status indicators in celiac disease. Yet, as Jocelyn indicated, the future holds promise for more things aside from histology.

An example of the disconnect between histology and other markers is this patient. In panel A is the patient at diagnosis, completely

flat mucosa. In panel B, more than a year on a gluten-free diet, the mucosa has recovered and looks essentially normal with some nice, finger-like projections, and yet the tissue transglutaminase IgA antibody titer was 3 times normal.

So what is the expected histology at diagnosis and follow-up? Just to start from basics and get us on the same page, in health, normally the villous height to crypt depth ratio is greater than 3 to 1, and intraepithelial lymphocytes, abbreviated as IELs, is on the order of less than 25 per hundred enterocytes.

At the first diagnosis of celiac disease, the majority of patients have a diminution of the villous height to crypt depth ratio and increased IELs, often up to 40 or more, very obvious at low power per hundred enterocytes.

At follow-up, at least one year on a gluten-free diet, there are three possible outcomes with the biopsy. There could be improvement to the normal range; there could be improvement but still

abnormal, the so-called continuous variable that Ben referred to, and that abnormality might consist of an abnormality of villous height, crypt depth ratio, et cetera, an abnormality of IELs or both, and in that scenario, the first step is to question dietary adherence and work on that; or there could be no improvement or deterioration, and the question again becomes dietary adherence and rarely refractory celiac disease.

So the question that we're all wanting to consider today among several questions is how to grade the change and define remission or improvement in a clinical trial, or even in life, in celiac disease, from the baseline diagnostic biopsy to the something else, either gluten-free diet or an intervention.

So in discussion with many key opinion leaders who have been active in trials and treat patients for years, I think there's general agreement that we really want to eschew the Marsh score for this purpose and dissociate the villous architecture from IEL counts and treat them as

separate data points. There are a number of good reasons for this, but one of them is that intraepithelial lymphocyte recovery lags behind the return of villi to normal. Even when a patient is asymptomatic or with the normal tissue transglutaminase, the IELs may still be increased beyond 25 per hundred.

That sort of begs another question that's not the topic today, is what is the functional significance of some of these IELs? Are they still having the natural killer phenotype and doing the bad things or maybe they're quiescent and they're not active? And remember, too, that intraepithelial lymphocytes are normal in the small intestine and throughout the small and large intestine to a degree of up to 20 or so per hundred enterocytes.

So it's a little bit different than counting eosinophils in eosinophilic esophagitis when, really, we're not expecting to see any in health, or crypt abscesses, for example, another inflammatory change in inflammatory bowel disease.

This is just a snapshot. It's a busy slide, and I'll take you through it briefly; some data from a study that is in preparation that I lead with Dan Leffler. This was a study of 183 patients from 14 centers who had an initial and a follow-up diagnostic biopsy more than a year out. In 142 of those patients, they were following a strict gluten-free diet.

This table shows in a snapshot their improvement over time from the first to the second biopsy. If we go to the far left, its age, all patients, children 17 or under and adults; and we have a breakdown of younger children and older children as well that I won't talk about today.

Then across the top is proximal duodenum or distal duodenum and a Marsh that improved from, let's say, any blunting in March 3A to C to no blunting; and with IELs, that it decreased and what percentage of patients did it decrease from abnormal at diagnosis to normal in the follow-up. So we're looking at improvement to near normal.

In all patients, only about 20 percent of

patients in the proximal and distal duodenum still had villous blunting at follow-up following a straight gluten-free diet, but half, or just a little less than half, had increased IELs still after a year or more of following a strict gluten-free diet; so that's the lag of the IELs behind the villous or Marsh score.

Then in children, it's quite interesting. This has been referred to already, but we also confirm in this study that children improved after a year on a strict gluten-free diet to a greater percentage. A greater percentage of children improved compared to adults, and this was significant, in both Marsh and IELs.

Well, what is Marsh? We keep talking about Marsh, and it's actually the Marsh-Oberhuber modification. This is very good for qualitative assessment in clinical diagnosis, although not everybody uses it. The type 3 is where we get to this destructive lesion, but it's a combination of considering -- if you go across the top column, intraepithelial lymphocytes, crypts, and the villi,

and you put all that together to come up with these types 0 through 4.

There have been other workers who have looked at this and come up with other schemes, and the main difference is that if you go to the right for the Corazza and the Ensari, they lump together mild and moderate blunting into a grade, so there's partial villous blunting and severe villous blunting. This is all fine, but these were not developed for assessment of therapeutics.

So let's dig in now and understand what has been done so far and what is done today in the clinical trials that are ongoing. I call this the nitty-gritty of endpoints, getting pretty granular here. There are several things to consider: location and number of biopsies.

In general, what one has seen in the published reports is that workers are taking between 4 or 6 biopsies all the way down to what we call D2 or the post-ampullary part of the duodenum; just not the first part but the more distal parts, and we call them D2 or D3 only. There's a general

agreement to avoid the first part of the duodenum sometimes called the duodenal bulb or the pre-ampullary region.

I'll just present, as someone who doesn't have a horse in the race, a contrarian view that we just want to make sure we all remember that in clinical practice, the duodenal bulb and the pre-ampullary portion is actually always involved at diagnosis. It's the first sight to see the gluten, and sometimes it's the only site to show diagnostic abnormality.

So we know at diagnosis we do want to take some biopsies, and that's in the guidelines, from the first part of the duodenum. It doesn't mean we have to do that in a trial. I'm just presenting as an independent person in this a contrarian view to consider.

Each biopsy fragment is usually put in a separate container so they can be dealt with down the road here; fixation in formalin. There are other fixatives that can be utilized -- I won't get into that today -- at least for 8 hours but not

longer than a few days, and certainly not longer than a week.

In terms of handling the tissue, it's very important for clinical trials, especially, that the trials -- and this has been done -- use a centralized number of laboratories, one, or just a few laboratories, for what we call embedding the tissue and sectioning the tissue to reduce the variability and to achieve the best what we call embedding in actually paraffin wax. That way, you get these nice histology slides, some of the pictures we just showed, that allow for good orientation.

What we're talking about is that the villi are standing straight up, what's left of them, and that the crypts are going straight down, and they're connected, and you can see that; so we talk about the villous crypt unit. In general, at least three perfectly oriented units are achieved in a single biopsy for evaluation.

This is just an example of what leads me to wanting to point out about the importance of the

bulb certainly in diagnosis just so we understand this. I've shown you here a real sample I had at diagnosis of a child with Downs syndrome who also was being evaluated first time for celiac disease. Biopsies from the first part of the duodenum, including the bulb and all the way to D2 or 3 were put in one container.

You can see I've labeled them since I can't use a pointer, and there's one on its side that I have the word "flat" next to, sort of in the bottom middle. And even though on its side, you can appreciate looking at this side that it's a smooth surface. There's nothing sticking out. Where it says "flat," that's the surface, and it's a straight line going down and crypts that are pretty well oriented.

So it's a Marsh 3C, and that actually can be interpreted, and we won't talk about the IELs at this magnification; whereas if you go to the one that's normal, this is same patient, these are tall villi, reasonably oriented, and there were no increase in IELs; it's completely normal. Up at

the top, there was a middling piece that had some normal height, 3 to 1 ratio villi, and maybe some that were a little blunted, and that was also present in this specimen.

That's just a point that celiac disease at presentation can show a diminution from the proximal to the distal and some patchy distribution, and that's why clinicians take as many biopsies as they do.

Once we've collected the tissue and embedded it so carefully, what are we doing at the microscope for evaluation? It could be thought of as potential endpoints and trials. I'm presenting here things that are used currently in a variety of ways.

I see in studies that one does collect the villous height to crypt depth ratio in at least 3 villi per sample, et cetera, and also counts the intraepithelial lymphocytes as separate data points, and I think this is very important. They collect data only in well-oriented villi. I've already mentioned at least three. Maybe they count

more if there are many more villi that are well oriented to get really the full breadth of measurements. I believe there's a standardized approach -- this should be very important -- to counting the intraepithelial lymphocytes.

This can be done -- again to get into the nitty-gritty detail here -- with an immunohistochemical stain called anti-CD3 antibody, which stains T cells, versus our pink and blue stain called the Hematoxyln and Eosin stain. I think in the future there may be automation for this. This is currently available and it's maybe done or not done. It's certainly fine to do it either way. It's a little easier with automation.

Then there are methods of selecting and how to count. If something is flat, one might be counting along that flat surface. If there are villi, one might count just the villous tip or the side. As long as one is in agreement and doing things the same across the trial, there can be more than one way of doing this and scoring each biopsy fragment separately.

But what's interesting, as an outsider to trials, is to think about, in addition to some of these things, that one could do a range of villous height crypt death or average across all the samples and think about this. Again, I don't think Marsh or other scoring systems that are really qualitative and not quantitative are appropriate for clinical trial use.

Other considerations and potential exploratory endpoints for the future include what is the time interval? What should it be between the initial entry to the trial and following the intervention?

Since we've been hearing that not only one year but maybe one really needs two years, certainly in adults, before one can really see the full response to something, it's hard to reconcile that with a trial design that can succeed, but maybe ideally on the order of some months between the pre- and post-trial biopsy.

Now this depends a lot on the trial design. It could be unrealistic for some trials. I think

it also depends on whether or not there is a gluten challenge in the trial. In a gluten challenge, maybe one can get away with shorter intervals, whereas without a gluten challenge, one might want to have a longer interval to see whether there's an improvement or not.

Then how are we going to define improvement, deterioration, or equivalency between time points? Is it a continuous variable, an absolute change, or a percent change, and are we going to have predetermined set points and just yes/no? The villous height crypt depth ratio is now greater than 3, and it wasn't before, and we don't care how much greater than 3; we just say yes/no, et cetera.

Another challenge is if you think back to that first picture I showed with very tall villi and then the crypt going down, as you're doing the measurement, for those doing it, we know that there can be a challenge of understanding where does the crypt end and the villous begin if you're doing the villous height crypt depth ratio, and I think that can be challenging. But I understand from some

data that that might be soon published, that there may be some technique that might be helpful in showing that cutoff very clearly.

What about other histology elements? What about villous height alone or villous width, or what about comparing proximal versus distal duodenum? These are all things that I think can be discussed.

Then beyond the H&E, it will be very interesting in the future to consider the functional status of the IEL since they seem to lag behind and patients are feeling well maybe with these still increased IELs; to look at their functional status both in diagnosis and in follow-up biopsies.

There are techniques that are absolutely real time like multiplex immunofluorescence to co-localize markers and see what's in that T cell; or measures of other things in the mucosa generally, not even just the intraepithelial lymphocytes, but certain cytokines, IL-15, IL-2, et cetera; and other inflammatory cell types, are

they important; and the techniques that are so used today on a daily basis in so many areas in medicine like RNA seq, proteomics and transcriptomics that might develop signatures for disease states that are complementary and go beyond.

So I'm hoping that the combination of histology and deeper analyses may maximize information that one can get from a biopsy and maybe even become a blood test if useful.

To that end, this is a table from a paper with multiple authors, including Dr. Leonard and Dr. Silvester, where they measured in a gluten challenge study a bunch of markers, not just villous height crypt depth and IELs, but also things -- if you look at the far-left column -- like the proliferation rate of the inflammatory cells, how many gluten-specific T cells where there, and cytokine interleukin-2 measurement within the mucosa. The darker the color, the more correlation so that under both doses, there's a big red dot next to IL-2, and that's the column for intraepithelial lymphocytes;

so they are finding a correlation between some of the other measurements and histology.

There are just two more slides. I just want to pause for a moment to contrast trial work and trial histology reporting with clinical practice. What can pathologists be expected to report in a patient on a gluten-free diet, or in the future, who's routinely taking a medicine to help them with their celiac disease?

In the U.S. -- and this may be a little bit different from Europe and other countries -- many pathologists are not using Marsh per se, but they're reporting mild, moderate, or severe blunting with or without a Marsh score, more of a descriptive report. That's because we often don't have the information with our scads of biopsies coming in every day that, hey, this is a proven celiac patient. Sometimes it's just question, celiac.

So you wouldn't apply a Marsh score to something you didn't know was celiac, and there are so many other things, especially medications and

immunodeficiency disorders that lead to duodenal inflammation. So a descriptive report gets the message across and IELs might be reported as normal or increased.

Now what can one do, then, if one is asked to, knowing you're dealing with a celiac patient? Well, if biopsies are available, as work-a-day pathologists in the hospital, we can compare pre- and post-treatment biopsies using our usual methods. No one in routine practice is getting out the ocular micrometer and measuring villous height crypt depth. That's not really going to happen. Also, requests to give a precise IEL count in clinical practice, there's basically all sorts of challenges of the uniformity of approach, where to count and how to count.

This is my last slide, and I'll just end and hope that the discussion with so many experts on the call will lead to further progress on these points. But my high-level summary points would be that I view this topic as having three buckets, one considering the histology in celiac disease and the

use of a duodenal biopsy; there's clinical practice, taking care of a patient; there are clinical trials and developing a means to measure responses; and then there's research with the biopsy to address knowledge gaps and advance patient care so we can maybe do things differently in the future.

Ideally, clinical trials should collect data in a variety of ways to maximize the scientific takeaways and to advance the field, and also to perhaps find creative ways to detect that important endpoint.

I think one can have predetermined histologic endpoints but still be nimble to correlate other data points that may come out in the analysis, such as your range versus an average, or multiple sites, or molecular techniques with the patient reported outcomes and other clinical endpoints and to see what signals are important.

If possible, especially when there's not a gluten challenge in the trial, it might be good to maximize the time interval to the follow-up biopsy

to allow the mucosa time to register that response, and I'm sure there are pros and cons to that. In the future, I hope we'll go beyond the H&E of light microscopy for some of these activity measures. Thank you very much. I look forward to the discussion.

DR. SE0: Thank you, Dr. Robert, and thank you to all of our Session 1 speakers.

We will now take a 10-minute break before we transition to our panel discussion and the Q&A session. We are running a few minutes behind, but that was all very valuable time spent. Right now it's 10:17. If we can all get back by 10:25, we will resume here at 10:25. Please come back.

(Whereupon, at 10:18 a.m., a recess was taken.)

Panel Discussion and Q&A

DR. SEO: Alright. It's 10:26, one minute extra. Welcome back, everyone. I hope you've had a chance to stretch your legs and get your eyes off the screen for a few minutes. We're all eager to begin the panel discussion session.

If all panelists for Session 1 can turn on your videos, that would be great. In addition to our Session 1 speakers, Dr. Lebwohl, Jocelyn Silvester, and Mary Robert, and moderators Dr. Dawn Adams and myself, we're pleased to welcome the following panelists.

Panelists, when I say your name, please briefly introduce yourself.

Dr. Prista Charuworn?

DR. CHARUWORN: Yes. Hi. My name is Prista Charuworn. I'm an executive medical director in the inflammation therapeutic area at Amgen. I'm also an adult gastroenterologist.

DR. SE0: Thanks.

Dr. Steve Lagana?

DR. LAGANA: Hi. I'm Steve Lagana. I'm a GI pathologist at Columbia University Medical Center, and I work closely with colleagues in the celiac center, including Dr. Lebwohl.

DR. SE0: Dr. Irena Lavine?

DR. LAVINE: Hi. I'm a medical officer in the Division of Gastroenterology at the FDA.

DR. SE0: Dr. Edwin Liu?

DR. LIU: Hi. I'm a pediatric gastroenterologist at the Children's Hospital Colorado, part of the Colorado Center for Celiac Disease.

DR. SE0: Thank you.

Ms. Kelsey Smith?

MS. SMITH: Hello. I'm Kelsey. I'm a celiac patient. I was diagnosed six years ago, and I live in Washington, DC.

DR. SE0: Wonderful. Welcome. Thank you so much for joining.

We have received several questions from the attendees and we will begin with one of those questions. This question is for Dr. Irena Lavine, and hopefully we can clarify this really quickly before we delve into further discussion on topic here.

The question was, is a biopsy of the small intestine necessary, as blood tests for immunoglobulin levels can be obtained?

DR. LAVINE: Hi. Thank you. Just to

clarify, a serology isn't cleared by the FDA for monitoring disease and really hasn't been evaluated for regulatory purposes as far as what represents a meaningful change, and whether normalization reflects histologic healing or improvement, or even longer term outcomes.

So while it may be used in clinical practice for different purposes, from a regulatory standpoint and for the purpose of clinical trial, it is not cleared by the FDA for monitoring disease progression or really any response to treatment. So just to clarify, we just really don't have the data to support what is a meaningful change in terms of serology.

DR. SE0: Alright. Thank you.

If we can move on to our second question here, this was touched on by Dr. Lebwohl's presentation. We'll begin by asking you to address and maybe further expand on your comment, and then we'll ask Dr. Liu, and then we'll open it to the floor for the rest of the panel for further comments.

The question is, we just heard that the patients will have variable histologic healing and patients not show improvements for months and even years.

Dr. Lebwohl, you mentioned that maybe one to three years might be an appropriate time frame for follow-up histology, but based on available data, if you were going to evaluate whether a patient is showing signs of histologic improvement or healing in response to the gluten-free diet, when and why would you perform the endoscopy?

DR. LEBWOHL: So it's important to clarify that rates of damage from gluten are much faster than rates of healing. So a celiac who starts eating gluten, for example, in the context of gluten challenge, you may see changes after a couple of weeks, but a newly diagnosed celiac patient who goes on a gluten-free diet, it takes much longer for you to see that reverse. It's just something to recognize.

In terms of how long to follow patients in a trial, it really depends on which direction you're

going. If you're studying newly diagnosed patients and you are studying a product that might, we hope, accelerate healing, we have to follow these patients for months at least. I would imagine 6 to 12 months would be the window I'd be thinking about. If on the other hand we're testing a product that protects against damage, that can be a much shorter time scale. That could be potentially just a few weeks of a gluten challenge.

DR. SE0: Dr. Liu?

DR. LIU: I'd agree with Dr. Lebwohl on this. We're assuming that the mechanisms of healing of the intestine are the same as the mechanisms behind, for example, preventing injury in the intestines. And going that direction, for example, doing a gluten challenge will get results much faster.

So if you're looking at endpoints looking at healing from somewhat active disease, I think the data suggests that you're looking at one year or two years for more complete information. Granted, you can look at intermediate markers, but for more

definitive outcomes histologically, you need to wait that long. So I've always been a little bit more of an advocate, I think, towards the gluten challenge aspect in terms of preventing injury.

DR. SE0: Yes. We'll be addressing the gluten challenge component on Session 3, so stay tuned.

Would any other panelists like to comment?

DR. CHARUWORN: Yes. I just want to make just a quick comment. The patient population that we're really looking at addressing at this time in clinical development are really patients who are not just recently diagnosed with celiac disease and newly placed on a gluten-free diet, but these are patients who've been diagnosed for a while now, who have been on a gluten-free diet for many years, and many of these patients might still have villous atrophy or changes.

So the rate of change for this population will likely be very different for those who are just newly dually diagnosed and started on a gluten-free diet. In some ways you are enriching

possibly for a population that might be slower to respond histologically, so we just have to take that into consideration as well in the clinical trial setting.

DR. LIU: I think that's a great point there. I think it depends on the drug that you're studying, too. If you're looking at a drug that's targeting gluten exposure, that may be different than a drug that's actually targeting immunologic aspects in these kinds of patients.

DR. CHARUWORN: I think one of the big variables is what is driving healing in patients with chronic disease? Is it persistent gluten exposure, and once you deal with that in some ways, the patient will start healing; or is there something else, or the biology is really different that's dictating healing within chronic disease?

DR. SILVESTER: I think that has a big impact on how you might use biopsy as an inclusion criteria because if you're selecting the people who do or do not heal, we don't know what the reason those people being different is, and you might be

selecting functionally different populations.

DR. CHARUWORN: It also makes, I think, designing clinical trials very hard. As was mentioned, there are no therapeutics right now in celiac disease, and there's still, I would say, just a lack of information about histology, especially within the population that most companies are currently studying in, which is non-responsive celiac disease.

So how long do we run those studies? What changes are we expecting? It depends a little bit on the mechanism of action, but I really would say I don't think we're really understanding what's going on just yet.

DR. ADAMS: So on that point, our next question is regarding what we're looking for in histology, so we'd like to hear from Dr. Lagana, in addition to what Dr. Robert spoke about.

Can you please comment specifically on how you generally are assessing histology and what aspects of histology are you considering as important changes, including any data available to

support these measurements?

DR. ROBERT: I'm sorry. Who did you want to answer that? Dr. Lagana?

DR. ADAMS: Let's hear Dr. Lagana's opinion first. Thank you.

DR. LAGANA: Sure. Well, it's a great question, and it gets to the heart of what we do when we evaluate a small intestinal mucosal biopsy. I could talk about that for the remainder of the day and everyone would be angry at me, so I'll try to be brief about it.

The first thing that I think Dr. Robert covered quite well is that you have to find a well-oriented piece of small intestinal mucosa, so you want to make sure that you have a good data point to start with before you start thinking to -- before you get into the minutiae, you better make sure that you're starting with a good sample.

So you start there. You find yourself a well-oriented piece where you see the muscularis mucosa oriented on one end and the villous tips on another end, if there are villi, or at least the

mucosal surface on the other end. That gives you a chance to evaluate the height of the villi as well as the depth of the crypts to see if they are in a normal configuration or not.

I'd say that is a massive distinction because villous atrophy, I think as a GI pathologist, I come into contact with a lot of cases of intraepithelial lymphocytosis, and as Dr. Lebwohl said, that's a non-specific finding. We see it in various conditions, including very common ones like proton-pump inhibitor use, or H. pylori infection of the stomach.

However, villous atrophy is rare. We don't see that 10 times a day. When someone has real villous atrophy, that means they've had a pretty significant insult to the intestine, so that is step one.

Step two is evaluation of the inflammatory cell component, and that includes determining if there is intraepithelial lymphocytosis or not. If there is, what is the distribution of that? There's some thought that if you have villi,

there's some thought that IEL clustering in the tips of the villi is more significant toward celiac disease than on the sides of the villi.

I'm perhaps a bit of a skeptic on that specific criteria, and maybe Dr. Robert will comment on how she feels about that one; and also making sure all the normal constituents are there, including plasma cells, which are absent in certain disease states that we see, especially in children; and finally, excluding infections and other findings like granulomas that might be present in Crohn's.

I would say here, we're at an academic medical center. We have a celiac disease center. So I personally will look at the biopsy, formulate my opinion of the histology in the way I just described, and then I do consider it my responsibility to look at the patient's chart and find out what is going on with this patient. What do we know? Do we know the serologies? Do we not know the serologies? Are there other reasons for them to have an intestinal insult like IBD or

something like that? Then I formulate the diagnosis at that point.

So I describe the histologic findings, I research the patient at least to some extent, and then I synthesize for my report, and that's my approach.

DR. ADAMS: Dr. Robert?

DR. ROBERT: Yes, sure. I basically agree with everything that Dr. Lagana said, so I won't repeat but just add a couple of little nuances. Even the blunting, it's seen in common variable immunodeficiency bacterial overgrowth, environmental enteropathy, and in checkpoint inhibitor and other medication use.

As people who practice, as Dr. Lagana does as well, GI pathology, gastrointestinal pathology in an academic center, we are understanding that we have to consider the breadth of disease, and we do. So even the blunting, it's not specific at all. There's nothing in the histology of celiac disease that is specific for this disease. That's why it always has to be correlated with serology and other

clinical parameters.

My approach is very similar. I think of it as three compartments, and this is what I teach to the residents and fellows. Number one is architecture. Number two is the epithelial layer, both IELs and other forms of injury that can happen to the epithelium, muco-depletion and other fussy stuff. And the lamina propria is the third, and that's where a whole bunch of other inflammatory cells are, and vessels, and other things. Otherwise, I agree completely with what Steve said.

DR. SE0: As a follow-on to that, could the panel comment on the impact of inter- and intra-operator variability on the interpretation of the histological finding from follow-up biopsies?

DR. ROBERT: Well, as a pathologist in this, I'll be happy to start the discussion and hear about others. It goes back to what I think Dr. Lagana said earlier, is the proper orientation. If we're doing things at the light microscope, they're mostly qualitative and you can add some measuring devices in there, but a lot of it is

qualitative.

So there is room for intra-observer variability and we have to guard against that. That's not unique to celiac; that's true in a number of inflammatory conditions, probably more so than malignant conditions. One has to deal with good material that's properly oriented, and then one has to be trained in the field to understand what you're looking at. That's just to get us all to the same starting point.

Aside from that, another source of variability is evaluating different -- if you're having two reads, the reads might be happening on different parts of the sample. There's much less variability if you're saying, "These are the three villi I'm counting. This is what I got. What did you think of these three villi?"

In this 14-center study that I mentioned briefly, there were 13 pathologists evaluating materials, and we sent around digitally and intra-observer variability assessment test, and I was nervous. These are all expert GI pathologists,

and yet I was so pleased.

Now, it's as good as it gets, well oriented, this is the piece to count. I didn't give them what villi but what fragment to count, and our kappas were 0.7 and above among 13 people; and 0.7 for those who wonder what the heck that means, the closer to 1 you are, that's perfect. And you never get to 1, so it's really quite good.

Let me stop there and invite others to comment on this question.

DR. LAGANA: Yes, I agree with everything Dr. Robert said. I would say that a couple of things help us in this regard. One is that small intestinal biopsies are incredibly common. In a typical sign-out day, you might see 20 or more small intestinal biopsies. If you're biopsied at a place with high volume, there's a good chance that the pathologist investigating your sample has quite a bit of experience evaluating these types of samples and should be fairly good at judging at least the big-picture distinctions.

My people disagree about whether something

is Marsh 3B or 3C. Yes, that happens all the time. But generally, I rarely disagree with my colleagues as to whether or not the villous architecture is normal or blunted. That's an unusual argument for us to have.

You know, medicine and pathology is a human endeavor, so yes, there are going to be disagreements. They're going to be people who are better or worse than others. I'm always very impressed with my colleagues. We all take our jobs extremely seriously, and we have ways of handling difficult cases. We'll share cases amongst our group and get second opinions.

So can you get intra-observer variability to zero? No, but I think for the most part, it's pretty reasonable.

DR. ROBERT: I think in a trial, trials are not practice, so you can control a lot and get to very careful measurements with agreed-upon techniques with only a few observers. I'm not worried about this for trials.

DR. LASAGNA: I think digital pathology

would help with what Dr. Robert was just saying. For a trial setting, you can very easily digitize a slide and then you can annotate with your measurements. You could have consensus there. There are a lot of tools that maybe aren't practical for day-to-day patient specimens, but for a trial are perfectly reasonable.

DR. SILVESTER: I think the other thing to do is to look to our colleagues in other specialties and recognize that in an area like cancer, there's much more being done with the same biopsies. This is why we really need exploratory endpoints in clinical trials.

As Dr. Robert was saying, are these IELs functionally the same when they're increased? Is there an IEL marker that we could be staining for? Is there more information we can get that's going to give us more an idea what's happening and also that's easier for a pathologist to interpret?

So I think we really have to remember that what we have now, that state of the art does not need to be state of the art. And as we learn more

about celiac disease, we probably need something we don't yet have in order to really understand how these therapies are working.

DR. SE0: Thank you for that comment.

DR. LAVINE: I was just going to agree with what Jocelyn said. I think, as we've highlighted so far today, that we're still learning about how a lot of these histologic outcomes and scales really perform, and that is really why we need to collect more data on how to interpret these outcomes and how they could potentially be used in a clinical trial setting.

So I'm trying to collect as much data as possible and as a variety of outcomes as possible, would really help push the field forward.

DR. CHARUWORN: I just want to add, I think in a clinical trial setting, I do agree that it's a more controlled setting. Usually we'll have one pathologist and more of a standardized process. I think when you do compare two time points, I think it becomes an issue, especially if this change -- the patchiness of the disease might also

play a role as well.

DR. LAVINE: Very good point.

DR. SE0: Yes, these are all excellent points.

We are going to switch gears a little bit and move on to our next question, and this is for Ms. Kelsey Smith, our patient representative.

If you can provide your perspective on whether you would be willing to undergo an endoscopy at the start of a trial and another endoscopy later in the trial after treatment to check whether your intestines have improved or healed.

There are multiple questions in the Q&A box asking for your experience and your thoughts on this.

MS. SMITH: Yes. I actually was part of a clinical trial for a while, and I agreed to undergo a biopsy. So just putting that out there, if you are part of a clinical trial, you have made the decision that you want to be moving research forward. So someone who has already agreed to that

trial is more likely to say, yes, I'm willing to undergo these things because I don't feel good.

I think the baseline here is that if you have celiac disease and you're going to be part of a clinical trial, it's either because you still don't feel good or you know that other people still don't feel good. For so many years, we've been told just go on a gluten-free diet and you'll be fine, but that is not actually the case for so many of us.

So what we're really looking for is just to feel better. Regardless if that means I have to undergo a biopsy so that you can learn more about it, I want to feel better, especially with how much back and forth about what is actually showing if you are healed, or if you're better, or what does better mean.

Better for me means I feel better. It means I don't feel sick at the end of the day. It means I don't have brain fog, so I can go to my job the next day. So while you're looking at all these clinical endpoints that are really important for

the long-term development of research and celiac disease, from a patient perspective, we will undergo a biopsy if it means that your trial can better understand the underlying things that are happening in my intestines.

But I really just want to feel better. I don't want to have to worry about whether by villi have all of these different changes. I know when I'm feeling better, and that is the critical aspect from my perspective.

In the past, my first biopsy I had, my next doctor said -- I moved across the country, and the follow-up doctor said, "Well, I don't agree with that reading from your first doctor, so I'm going to have to do another endoscopy to verify that." I think that that's pretty typical across patients in that we hear, well, this doctor said this and had these pictures, but I see this, so I want to keep trying or I want to keep looking because you're still having these symptoms.

So for me, if I'm feeling better, from a doctor and from a clinical perspective, no, I don't

want to undergo that biopsy. I don't think it's necessary to have to go into a hospital, and take a day off, and do all those things if I'm feeling better. If I'm not feeling better, that might look different.

DR. ADAMS: Ms. Smith, thank you for that. Just branching from that data collected from Beyond Celiac, it shows only about 40 percent of adults are willing to participate in biopsy as part of a clinical trial in a sample of over 4,000 patients with celiac disease.

I'm curious on other members of the panel's opinion on whether or not increased need for biopsies is going to be a significant barrier for clinical trial participation.

DR. SILVESTER: So in Canada, along with Dr. Duerksen, we have a cohort in Manitoba where we recruited people at diagnosis, and we've been following them, and part of the study is an optional two-year follow-up biopsy. Now these people are selected because they agreed to participate in an observational study, but the

take-up rate for the follow-up biopsy has been about 80 percent.

So I think it's important to note that there are people who do want a follow-up biopsy. And even in my pediatric practice, when I discuss the diagnosis and the follow-up plan for my patients, often one of the first questions that parents ask is, "So when is the follow-up biopsy to make sure my child is getting better?"

So I think part of our role as clinical trial investigators is to ensure that if patients are going to be asked to provide biopsies, that it's appropriate and it's actually going to advance the science. I think taking the time to explain to patients and communicating to patients is what we need to do because, as Kelsey mentioned, I think patients who participate in trials are very generous and they are willing to do what is asked of them to help move science forward.

DR. LASAGNA: I agree. I would say among adults patients, follow-up biopsy is not a major deterrent in terms of trials. Some are even eager

to know about the quantified self and that extra data. The gluten challenge is another story entirely, but I know we'll discuss that later here.

MS. SMITH: And just to Jocelyn's, Dr. Silvester's point, if you tell us why and we can have a good understanding, and we're brought along in the process, that makes a huge difference in our willingness to enter into something as invasive as a biopsy, especially if you're recruiting for a study.

If you're recruiting for a study and it just says you have to have multiple biopsies and there's not really an understanding of why, then a patient is going to be much less willing to undergo something like that than if you can show the data of why it's important, where you're coming from, what you're looking for, and how it will actually impact the overall results of your trial.

DR. ADAMS: Ms. Kelsey, I just want to second what you said. I think you said it very nicely. But just for the greater group, the reason that the histologic assessment is so important is

because we really need to understand what the effect of a treatment is on the underlying disease. So we know in celiac disease, a lot of the signs and symptoms can be non-specific and they can overlap with many other GI conditions.

So we really need that histologic assessment to understand the treatment benefit of a drug and also to ensure that we don't continue to give ineffective treatments to patients who are not responding. So just for the greater group, those are sort of the reasons and the rationale why we feel the histologic assessment is so important in the evaluation of drugs for celiac disease.

DR. LAGANA: I think, again, just from another pediatric perspective and more from a clinical standpoint, certainly in pediatrics, some folks are moving a little bit further away from the initial biopsy to diagnosis since they're doing more serologic diagnosis. But I think that the families that I work with have been more willing to consider repeat endoscopy, not when they're feeling better -- they don't feel like there's a need for

that -- but when they're still having symptoms, but also another group of the individuals who are asymptomatic. So they've never had symptoms, they don't experience any symptoms when they get exposed, and they have no idea how well they're doing. So a lot of those individuals have expressed the interest for a follow-up biopsy to show that they're actually doing well.

DR. SE0: Maybe I will bring up another question up to the floor on a related note, again for Ms. Smith.

Would you be willing to take a drug that may make you feel better but doesn't necessarily heal the underlying inflammation?

MS. SMITH: Yes, absolutely. There is no doubt in my mind I would take that drug if it had gone through testing or I was in a clinical trial. As someone with celiac disease, I understand where the research currently lies. I get that we haven't been doing research to the level we may have been doing for other conditions and other chronic lifelong autoimmune conditions that people might be

undergoing.

So I know that there isn't currently a magic pill that I can swallow that will allow me to go out and eat gluten all day and be fine. I just want to feel better. That is the biggest endpoint for me, is that celiac disease can have a major impact on my day-to-day ability to go to work, to hang out with my friends, to go out with my family, and to do things in a holiday setting that other people don't have to worry about. And if I know that I'm just going to be able to feel better right now, that is enough for me.

I recognize long-term that there needs to be more research and there needs to be an endpoint that you are healing the intestines and that there is a reduction in inflammation. But from a patient perspective, celiac disease impacts our lives in a major way, and we need something that will allow us to continue going day to day even if we're on a gluten-free diet.

I've been on a severe, strict gluten-free diet for six years, and I can tell you, it still

impacts me. I still get sick, and I know when I'm getting sick from something, and being able to have a drug that can reduce those symptoms would be life-changing.

DR. CHARUWORN: I just want to add, I think we're still kind of early in developing therapeutics for celiac disease, especially understanding of any endpoints such as histology. I think we're still collecting information on this, particularly in specific target populations.

I do understand the need to collect the data, and to understand the data, and to understand what is meaningful change with that data and how to design a study around that. I do think, though, it is a bit early to consider this an efficacy endpoint, but I understand where the FDA is going. We're just lacking information at this time.

DR. ADAMS: To follow up on that, for the prescribing physicians on the panel, how do you feel about prescribing a medication that would treat symptomatology but not treat underlying inflammation?

DR. LAGANA: That would make me nervous. Dr. Lavine said this is about, well, what is this drug doing to the body. I see it really as a surrogate marker for safety in the long term because you're not going to be able to trial or know about what something's long-term risk is on lymphoma, et cetera. So if there were a drug that made patients feel better but caused persistent villous damage, I'd worry about a long-term safety condition.

DR. SILVESTER: I think I would agree. The intestine doesn't have a lot of ways of communicating, so symptoms typically in intestinal diseases don't correlate well with histology or other biological endpoints. So as a prescribing clinician, I would be concerned that I was giving something that I thought would make my patient better clinically and feel better, but also that inflammation was being addressed.

DR. LIU: From a pediatric standpoint, again, I would be nervous as well, and I might consider such a drug on an as-needed basis but

certainly not something that would be used, for example, on a regular basis.

MS. SMITH: I think that Dr. Liu makes the right point here. I'm not looking for a magic pill that I would take every single day so that I feel better. I can understand hesitancy from the long-term perspective, but also there isn't anything else that we're using right now to treat that inflammation.

So as a doctor, it's not like you're missing out on finding another pathway or producing something else that's going to reduce that inflammation. We don't have that at this time. I think long term, especially because there are so many patients with celiac disease across the country, one day we will get there. But in the meantime, there's not something else that we're using to reduce inflammation or that can make that impact. There are clinical trials and there is research happening that is addressing that and that is looking into that, and there's more every year as we have more of these panels, and more of these

workshops, and more of your colleagues that are picking up that mantle, so to say.

DR. SILVESTER: I think none of us explicitly said it, but it's also important to note that there are two different types of approaches to therapy for celiac disease. One is an alternative to a gluten-free diet and one is in addition to the gluten-free diet. I think how you evaluate those and how you assess them is very different. So I think it's hard to answer these questions with context of what therapy is meant to do.

MS. SMITH: To be clear, anyone with celiac disease will continue following a gluten-free diet. Once you figure it out, honestly, you are hesitant to go away from it, even in a clinical setting, which we will address. But I think in addition to any of these drugs, I would continue following a gluten-free diet, and any patient with celiac disease who's already figured it out would agree with that.

DR. CHARUWORN: I also would say I think I completely agree that you probably don't want to be

on the therapeutics, especially if there's a concern that the disease, underlying disease, will be getting worse. I completely agree that's not appropriate.

In some ways, I think this was brought up in the last GREAT meeting about the use of histology, at least for this time, as more of a safety endpoint.

DR. LAGANA: I would just be curious. I'll pose this as a question maybe to the group. But is there a road to significant symptom alleviation that doesn't run through reducing inflammation?

(No response.)

DR. LAGANA: Just thinking of it from a pathophysiologic perspective, it seems unlikely that you would find any therapeutics that would be really clinically efficacious, but the intestine is still getting ripped up by inflammation.

DR. LEBWOHL: I'd say that dermatitis herpetiformis, which is sort of like a very close cousin to celiac disease, celiac of the skin some call it, there is Dapsone. There is a drug that

really helps the cutaneous manifestation. And I'd say that even among people who've figured out the gluten-free diet, some such patients, anecdotally, when offered that drug will start to eat gluten.

So there you might have significant alleviation of at least of cutaneous manifestations but ongoing intestinal inflammation. The analogy is not perfect, but I think that the possibility exists.

DR. ROBERT: Would there be a different answer to the question about using a drug, whether the drug is aimed at inducing tolerance versus affecting the absorption of gluten? Would that affect your answer or does it matter?

MS. SMITH: I think if there was something that was telling me, okay, we need to test this out to see if you can tolerate gluten, I think to some of the comments that have been made, honestly that is more frightening than just treating symptoms, just because of the research that has been done that points to the damage that does happen. And to all of your points, as soon as you ingest gluten,

it can take as little as a couple of weeks to start doing further damage, which can then lead to things like cancer, lymphoma; we're very aware of that.

So I think if the instructions were, hey, if you continue on this gluten-free diet, you can also take this drug which can help reduce your symptoms, that's different than take this drug and you can kind of maybe ingest gluten along the way.

If down the line there's research that points to not causing further damage to your intestines, that would be amazing. But I think the hesitancy would absolutely be there. And in someone who's followed a very strict diet for a number of years, coming off of that diet because there's a drug that says you can ingest gluten would be a little scary.

DR. ADAMS: I have one quick last question for Kelsey Smith. Can you comment on the correlation between the biopsy findings that you have had with your symptoms? I think that also gets to Dr. Lagana's question, too.

MS. SMITH: When I had my initial biopsy, I

was very sick, and the biopsy results showed that I had severely atrophied villi. I had very high levels in my blood. I didn't feel good all the time. I passed out a lot. I would get full after one bite of food, so I stopped eating a lot. I was very shaky. I had a lot of the pretty severe symptoms.

Once I went on a gluten-free diet and I felt better when I came here to DC, I had a follow-up biopsy. It had been about 0.4 [ph] years since my diagnosis and my villi had definitely returned to a more normal state. In that in time, at that time when I had that biopsy, I was feeling better in terms of my celiac specific symptoms.

DR. LAVINE: I think to wrap up this discussion, a lot of the discussion we just had shows why we value both improvement in signs and symptoms as well as histology, because we know that some patients may have to correlate together, but others may not. And we really want to look at both measures, as well as many other exploratory endpoints as well. But we really want as broad of

a view as possible as to what the drug is really doing on both signs and symptoms as well as the underlying disease through histology. So I think that's really why we look at both quite significantly.

DR. SE0: Yes. Thank you for all this valuable discussion on histology. It is still a little bit of a knowledge gap for all of us, but I think we're moving on in the right direction and getting there, and we really thank you for all of your great comments during the discussion today.

We're going to switch gears and move into our second session that's planned for the day, and I will introduce our next two moderators for Session 2.

Dr. Lynn Yao is the director of the Division of Pediatrics and Maternal Health in the Office of New Drugs, Center for Drug Evaluation and Research. She is board certified in both pediatrics and pediatric nephrology and has been with the FDA since 2008.

The Division of Pediatric and Maternal

Health oversees quality initiatives which promote and necessitate the study of drugs and biological products in the pediatric population and improve collection of data to support the safe use of drugs and biological products in pregnant and lactating individuals.

Dr. Adams, would you introduce our second co-moderator, Dr. Ritu Verma, please?

DR. ADAMS: Yes. I'm honored to introduce Dr. Ritu Verma. She's a pediatric gastroenterologist and professor of pediatrics at Comer Children's Hospital at the University of Chicago, and she has been in the celiac space for at least 20 years. She is the medical director of the Celiac Center at the University of Chicago, as well as the president-elect of the Society for the Study of Celiac Disease. She also has two children with celiac disease. She's passionate about improving the quality of life of children with celiac disease, as well as the families that support them.

DR. SE0: Dr. Yao and Dr. Verma?

DR. VERMA: Good morning, good afternoon, and good evening, whichever part of the world everyone is in. I of course made the big mistake of speaking while I was on mute, so sorry about that.

First of all, I want to thank the FDA for setting up this workshop on a very, very important disease and very close to many people's hearts, and more important I think having pediatrics at the table. I don't think we get invited to the table often, so thank you much for bringing us, and I do have the honor and pleasure to co-moderate with Dr. Yao.

Just a word for the attendees, can you please submit all your questions via the Q&A box? We will be looking at them, moderating them, and then we'll hopefully try and answer as many as we can in our Q&A session later; but you can continue to send us questions throughout.

I have the distinct pleasure of introducing our first speaker. Again, I think I'd like to just thank all the speakers and the panelists that we'll

introduce later.

Dr. Mona Khurana is our first speaker, and she is board certified in general pediatrics and a pediatric nephrologist who joined the FDA in 2009. She initially worked as a medical reviewer in the FDA's Division of Non-Prescription Drug Products in the Center for Drug Evaluation and Research.

She then moved to the Division of Pediatrics and Maternal Health as a medical reviewer in 2015 and has been a pediatric team leader there since 2016, where her efforts have primarily focused on working collaboratively with review divisions in the Office of New Drugs to promote pediatric drug development in all therapeutic areas.

Her topic today is really discussing the extrapolation of the efficacy and regulatory considerations.

Dr. Khurana?

Presentation – Mona Khurana

DR. KHURANA: Thank you so much, Dr. Verma.

Good morning, everyone. You heard a little bit about pediatric extrapolation during the first

session, and I'll be expanding on this concept from a regulatory perspective and sharing how this scientific approach when used appropriately has the potential to streamline pediatric drug development. I don't have any disclosures to report.

Let me start by noting that FDA holds pediatric programs to the same standard for approval as adult drug development programs. This standard consists of the demonstration of substantial evidence of effectiveness along with collection of enough safety data to be able to assess if a given drug's benefits outweigh the risks for the proposed indication.

It's also important to recognize that FDA is required to exercise flexibility and to use scientific judgment when determining the amount and type of evidence that would be needed to meet the approval standard for individual drug development programs.

As previously mentioned, while FDA has generally interpreted the requirement for demonstrating substantial evidence of effectiveness

to be based on conducting at least two adequate and well-controlled trials in the affected population, there are circumstances, specific circumstances, when this requirement could and has been matched through other types of evidence.

The need for this type of flexibility is particularly critical for pediatric development programs, which are often faced with unique feasibility and ethical and operational constraints. The increasingly global nature of many of these programs adds another layer of complexity because of geographical differences that may often also need to be addressed.

Pediatric extrapolation is one scientific approach which can be used to overcome some of these challenges. The dictionary definition of extrapolation is an instance of inferring an unknown from something that is known.

The term "extrapolation" is actually used in different ways in the regulatory setting and really depends on the context of use. The concept of pediatric extrapolation specifically was formally

introduced by FDA in a 1994 regulation which allowed for pediatric approval to be based on the extrapolation of efficacy from adequate and well-controlled trials that were done in adults, provided that the agency had concluded that the disease, the course of the disease, and the effect of the drug were sufficiently similar between the adult and pediatric populations.

In such cases, the drug could be approved for pediatric use without controlled pediatric efficacy trials as long as pediatric PK data had been collected to confirm the pediatric dose and enough safety data had been collected to adequately characterize the safety of the drug in the pediatric population.

Since the 1994 regulation, FDA's thinking about pediatric extrapolation has continued to evolve and has moved away from thinking about the ability to extrapolate as a yes or no answer and more about falling within a continuum based on what we know and what we understand about how similar the disease and the treatment response are likely

to be between the adult and the target pediatric populations.

This approach focuses on identifying where the critical knowledge gaps are and what type of clinical data might be needed to fill those knowledge gaps to optimize the success of a pediatric program without compromising the standard needed to achieve drug approval.

The ability to extrapolate should really be based on how much confidence there is and the quality of the adult efficacy data, how relevant the adult data are to the target pediatric population, and also on the quality and quantity of data available to support the assumptions of disease and treatment response similarity between the two populations.

The assessment of disease similarity should focus on how similar the disease pathophysiology, the diagnostic criteria, and clinical manifestations and progression are between the adult and the target pediatric population. This requires a good understanding of the natural

history of the disease in both populations, as well as of any disease modifying factors which might result in different manifestations of the disease in either population.

Factors potentially resulting in a different treatment response in the pediatric population have to also be considered, and these typically include any expected age-related differences in drug disposition, expression of the drug target, and then the clinical response.

Another important component of this assessment, and I think has been the subject of some discussions in Session 1 as well, is understanding whether or not the primary efficacy endpoint used in the adult trials is relevant to the target pediatric population.

If the adult endpoint is relevant and the dose exposure-response relationship of the drug is well characterized in the adult population and expected to be similar in the target pediatric population, then all of this information can be used to identify a pediatric dose that achieves

similar exposure as this dose found to be effective in adults.

If the adult endpoint is not relevant to the target pediatric population, than extrapolation could still be acceptable if a relevant biomarker is identified that has relevance to the pediatric population and can be measured in both populations, and also the relationship between that biomarker response and the clinical outcome of interest is well characterized in adults.

This is one of the reasons why thinking about pediatric extrapolation early during drug development becomes important; so certain trial design elements could be incorporated into the adult clinical program if needed to support pediatric extrapolation down the line.

This is a useful framework of questions to ask when reviewing the available evidence to help identify where the knowledge gaps exist. First, how relevant is the existing information about the disease and the treatment response in adults to the pediatric population? What assumptions are being

made in assessing the similarity of both the disease and treatment response in both populations? How confident are we in those assumptions? It's really the degree of confidence in the assumptions that will dictate what additional pediatric data might be needed.

Once the knowledge gaps have been identified, then efforts can really focus on what additional pediatric data would be needed to fill those gaps to support pediatric approval of a drug.

If you look at this figure, it's falls along a continuum. On the right side, you can see there's a high level of certainty in the disease and treatment response similarity between adults and the target pediatric population, and if there's evidence to support a similar dose-response relationship between the two populations, then pediatric PK and safety data may be enough to support pediatric approval of a drug.

In the same context, if you move to the middle of this figure, there's still a high degree of certainty in the disease and treatment response

similarity, but the dose-response relationship is thought to be different in pediatric patients, and the pharmacodynamic data, along with pediatric PK and safety data, might be needed to support pediatric approval of a drug.

Along the left side of this continuum, if there are too many uncertainties about similarity of the disease or the treatment response, an extrapolation may be possible, and you may need one or more pediatric efficacy trials to support pediatric drug approval.

It's really this targeted, data-driven approach that helps ensure that pediatric patients are participating in clinical trials that are necessary and that have specific objectives that will inform regulatory decision making. Appropriate use of pediatric extrapolation in this way can ultimately help achieve timelier access to safe and effective therapies for pediatric use without having to enroll a large number of pediatric patients in clinical trials.

I just wanted to end by noting that FDA has

successfully applied this framework for pediatric extrapolation in other therapeutic areas such as for the treatment of HIV, for partial onset seizures, and then most recently for patients with dilated cardiomyopathy and heart failure. In each of these areas, appropriate use of pediatric extrapolation has really streamlined drug development, leading to pediatric approvals with fewer enrollment of pediatric patients in clinical trials. I think that's it. Thanks very much for your attention.

DR. YAO: Thank you, Dr. Khurana, for that terrific review of pediatric extrapolation.

We are now going to switch gears just slightly. I am very honored to present to you Mr. Tyler Friedman. Tyler hails from Greenwich, Connecticut, and he is a 17-year-old rising high school senior. We have invited Mr. Friedman here today to discuss his experiences with celiac disease.

Tyler was diagnosed with celiac at 11 years of age and he's had to navigate living with this

condition all throughout his childhood and early teenage years. We are very anxiously awaiting his talk, and he will be providing his first-hand descriptions of what it's like to live with celiac disease and his views on goals of treatment.

Thank you again, Mr. Friedman, and the floor is now yours.

Presentation – Tyler Friedman

MR. FRIEDMAN: Thank you so much.

As early as first grade, I'm able to account scenarios in which school would be filled with discomfort and agony. I was a stereotypical child who dreaded school, but as one who is dealing with a disease in which they knew nothing about.

On a somewhat daily basis, I was overwhelmed by abdominal pain, nausea, vomiting, and chronic diarrhea. With no explanation as for why I was feeling the way that I was feeling, the symptoms persisted as I kept feeling my body, which I later discovered to be its own attack.

What didn't persist on the other hand was my reliable attendance at school, either having to be

called out as a result of my symptoms or countless doctor appointments trying to decipher what was wrong with me. Some might say it was a less than an ideal situation to be in as an elementary school student.

Eventually however, with the help of Dr. Peter Green and the Celiac Disease Center at Columbia, I was finally able to pinpoint the source of my dismay. Initially leaving the appointment bearing this new label of celiac, I was unaware of all the changes in which I needed to make in my life.

At the time of my diagnosis, celiac awareness was tremendously less than what it is today. All that I had to guide me was the short and simple basics: no wheat, barley, or rye; truly only the blockbuster warnings.

Even on the train ride back to the apartment, I remember being hit with my first gluten bombshell. In an effort to lift my spirits, I was promised some sushi, my favorite meal of all time. Little did I know the roll I ate religiously

had wheat inside of it as a starch filler to hold it together. Hearing the news, my eyes were opened right up, and not just from the tears of losing one of my favorite foods.

With gluten making its way into other ingredients that are countless to name, it is truly scary to look back and see how little information I had to navigate this new way of life. Fortunately, however, in addition to my health being saved, my diagnosis led to the discovery of celiac disease within two of my relatives, an added bonus to my own diagnosis, if you will.

Comparing where I was prior to my diagnosis to where I am now, the difference is remarkable. By strictly adhering to the gluten-free diet, I was able to rid myself of all the symptoms which limited my day-to-day life, which for the record is not a luxury that all individuals with celiac disease are fortunate enough to obtain, as seen earlier.

However, a lasting effect I was faced with was my growth being stunted. While able to help

alleviate my other symptoms, the gluten-free diet wasn't able to reverse the effects, but luckily I was able to turn to growth hormones. While the hormone salvaged my height to a solid 5'9" -- that all of you will have to just take my word for it due to virtual circumstances -- it became another daily burden that celiac was responsible for, now having to inject myself nightly with hormones in order to make up for a normal process that celiac disease has affected.

Additionally, as a result of strict adherence, any unintentional gluten contamination currently magnifies any symptoms I had prior to being gluten-free since this type of food was now so foreign in my body for such a long period of time. While it isn't concerning day to day, any unfortunate contamination results in tremendous consequences that are unbearable to experience.

Because of its keystone in ruining my health, the gluten-free diet was not a choice but a must, however, it is definitely not flawless. While there are much better mainstream gluten-free

alternatives present today, at the time of my diagnosis, all gluten-free substitutes led me to try foods that weren't just free of gluten but taste.

While that in itself was a struggle, countless servers at a multitude of restaurants made me question my security of eating out, often mistaking celiac disease for simply trying to avoid carbs or follow the new food trend of the month, not having the slightest clue regarding the colossal symptoms and internal damage that being contaminated would cause. This added heavily towards my apprehension in eating out.

Because of this new lifestyle and additional apprehension, there's no question of the significant amount of socializing I lost out on. All spontaneity was gone. It was more of a process synonymous to, "Let me read the menu," the night before, or "I'll have my Mom call and talk to the kitchen beforehand," et cetera, et cetera. It was nothing like grabbing a meal at the diner with my teammates after a flag football game or going to

grab lunch with friends on the weekends. It was simply a lost outlet at the time.

Firstly though, I was more distressed by the increasing anxiety of actually deciding to go out and eat. In many instances, it even got to the point to which my fear of being unhappy or coming across as high maintenance caused fights between my parents and I. They simply wanted the best and safest meal for me, while I simply wanted to order just the same as everyone else and not be a burden to the wait staff or kitchen. In complete honesty, these [inaudible – audio fades] are still not completely absent, even today.

While that is stressful in my hometown, it is all further magnified when eating out of town. My greatest challenge at this was my eighth grade class trip to Washington, D.C. It was 4 days and 3 nights of me being completely responsible for what I was eating. Refusing to put my faith in all the school's accommodations, my Mom and I had packed a whole suitcase full of food and requested a room with a refrigerator in it.

While I definitely hated being singled out with my requests and large suitcase, that effort tremendously aided my comfort level in figuring out what to eat while away from home. Especially as part of an entire grade going to restaurants and food courts, there isn't that time to be the kid with the dietary restriction, asking them to change their gloves, or change their pans, or asking about the way something is prepared.

In hindsight, the trip was actually far less intimidating by having the suitcase there, but making the extra preparations were not just inconvenient; it diminished my excitement towards the supposed highlight of my middle school career.

Similarly, vacations also now succumb to that diminishing excitement that being gluten-free brings. Going on trips anywhere from 3 to 10 days in a place completely foreign and expecting to fully take care of your health needs is daunting to say the least. Even if one is able to take on necessary precautions and plan ahead, the comfort level truly never sets in until after the meal is

over and personally no symptoms are detected. And until that point, anxiety sets in regarding whether or not this is going to ruin my vacation, my night, or more importantly, my body.

This leads me to, arguably, the worst part being gluten free, which is slipping up. With so many factors out of your hands, it is almost impossible to guarantee your meal's safe. With a possibility of cross-contamination occurring in extreme circumstances such as a flower in the air or oats grown in the vicinity of wheat, gluten is bound to enter your food at some point within your lifetime. That's not to say that going that extra mile and doing your best isn't worthwhile, because without a doubt it is; it's just relying on your expectations to adjust for this possibility.

There is such a confidence that goes along with the contamination, and my personal experience is much of the anger I expected to feel towards restaurants was absent and instead turned towards myself, bashing myself about why I decided to trust this place and what else I could have done to

prevent this from happening. It's a vicious second-tier symptom of getting contaminated.

Yes, as I mentioned earlier, being someone who is gluten free, I already went through that initial fear of trusting others with my health. I've gone this far in doing so. So putting that same trust again and again will just continually bolster my experience and comfort level.

Now there's this new mentality effect. I've been through all these crappy experiences, these restaurants can't mess up in any way that I haven't already experienced and figure out a way to counteract. It all relies on the courage to make the effort to actually put one's trust back inside a kitchen beside your own which, believe me, is way easier said than done.

Being a rising senior in high school, though, there are far more social events that I care to admit. The last thing I want to do at set events is put another aspect into the hands of someone else, much less risk the possibility of getting sick and having a fun social time ruined.

Rather than build up the courage I so confidently shared two seconds ago, I often end up trying to subside my hunger by eating beforehand and afterwards in the comfort of my own home. But there's no long-term application for that, especially when my new home base would be my college dorm next year, which brings me to a special challenge unique to the kids with celiac disease, which is the college process.

On every college tour, the dining halls are always breezed over because for people without dietary restrictions, there's nothing stressful or life-changing about the meals that you're going to be eating, and worst case scenario, the food is bad and you go into town or order takeout.

Yet, being responsible [indiscernible] -- all three meals a day plus any snacks for the entire school year, that's a substantial amount of food. Now not only does that food have to be gluten free, but has to be both tasteful and diversified. Only when you imagine yourself eating chicken and broccoli for the next 160 days for

3 meals a day are you truly able to understand the importance of a college's ability to accommodate.

Similarly, another issue that is far less discussed is the use of alcohol with high school and college, which again isolates individuals with celiac. Not only is their peer pressure to drink, but also this mentality that if kids with celiac drink enough alcohol, then they experience nausea and vomiting, regardless, while not missing out on these bonding opportunities.

While I most certainly am not condoning underage drinking, I refuse to ignore it as a serious concern for those with celiac. By not being able to participate with other kids your own age, there's a lack of connection there and another form of social isolation aside from dining, with the only other alternative being to choose a damaged [indiscernible].

Going to parties and watching everyone around you drink is definitely memorable for deciding whether or not you want to go out next weekend or the weekend after that. It's a

double-edged sword for kids with celiac and will likely have a major impact on the ease in which they and myself integrate into college.

With that being said, there's no reason in this day and age for individuals with celiac to be at such a social disadvantage. A monotherapy option would ultimately be ideal in remedying this issue. I personally know a great handful of people with celiac, including myself, who would do just about anything to go back to a regular way of life.

Regardless of what the future of the field looks like, as long as gluten continues to damage my body, there won't be a time in which I forget about it or fail to accommodate for it, which leads me to a potentially more relevant option, adjunctive therapy with a gluten-free diet.

While obviously not ideal due to the continued adherence of a gluten-free diet, it can definitely be helpful in relieving some of the stress and anxiety around eating. Being able to have this backup sense of relief for those times where contamination occurs, that's completely out

of one's control, may be the game changer to one's comfort level.

I know that some of the anxiety or physical side effects of possibly eating gluten can be lessened or avoided completely. The power that celiac has over my decisions would shrink exponentially, no longer dictating each and every one of my choices and allowing me to once again reclaim eating as a potential highlight within my life. Thank you.

DR. VERMA: Mr. Friedman, thank you very much for being so open and honest about your journey. I feel for you, and I hope that workshops like this having research folks and clinicians will make the journey better for you and for other patients as well, so thank you so much for sharing your journey.

We'll move on to our next speaker, Dr. Maureen Leonard. She is the clinical director of the Center for Celiac Research and Treatment at Mass General Hospital for Children and an assistant professor of pediatrics at Harvard Medical School.

She is an NIH-funded physician/scientist whose work is focused on utilizing a multi-omic approach to predict celiac disease onset in at-risk children.

This doesn't give full justice to what Dr. Leonard does, but in the interest of time, I will hand it over to Maureen.

Presentation – Maureen Leonard

DR. LEONARD: Thank you, and thank you for the invitation to speak, and thank you to the FDA for dedicating this time to children with celiac disease.

I hope this presentation will help you appreciate the signs and symptoms that children with celiac disease suffer from, and Tyler did an amazing job with that, and I hope that I can convey some of the difficulties in managing and treating children with celiac disease.

For many years, celiac disease was considered a pediatric gastrointestinal disorder which presented between 9 and 24 months of age with complaints such as abdominal pain, diarrhea, bloating, weight loss, and irritability. However,

the development of non-invasive, accurate, diagnostic serological tests allowed for screening of large populations of people for celiac disease, and this led to the recognition that celiac disease is truly a systemic autoimmune condition.

For children with celiac disease, this means that they share many of the same signs and symptoms that adults with celiac disease have, in addition to other signs specific to pediatrics. These include short stature, which may affect up to one-third of patients; delayed puberty, which may be found in up to 10 percent of patients; dental enamel defects; and behavioral changes that have a potential to significantly impact social development and learning. These signs in children are particularly notable because they may lead to lifelong deficits if not identified and treated.

Today, patients with celiac disease look very different from the depictions in the text, and they may not have the signs of malnourishment or irritability like this child who was identified as having celiac disease as part of an ongoing

prospective study.

It's not just that we're recognizing the heterogeneous presentation of celiac disease; recent literature supports the clinical observation that pediatric celiac disease has changed. The majority of children are now normal weight at diagnosis and nearly 1 in 5 have overweight or obesity. The minority are now underweight.

Studies suggest that symptoms in histology may be less severe when compared to 15 to 20 years prior and children are older at diagnosis. This graph shows the mean age at diagnosis from 1970 to 2015 in Sweden, and there are other studies that support the finding that the mean age at diagnosis has increased from somewhere around 2 to age 8 or 9.

Extraintestinal manifestations are common. These are symptoms such as anemia, fatigue, skin rash, headache, joint pain, and others. They can be the presenting symptom in children. They're equally prevalent at diagnosis in children and adults, and there's some research to suggest there

may be a slower rate of improvement in children that present with these symptoms.

We know that the incidence and prevalence of celiac disease is rising globally, and this is true for children as well. For example, the Mayo group showed that there was an increase in incidence of celiac disease in children by nearly 3-fold between 2002 and 2014. Other studies have documented a rise in prevalence, including a 2-fold increase prevalence over a 20-year period in school-aged children in Italy.

In an ongoing screening study run by Dr. Marisa Stahl and Dr. Ed Liu, which has screened more than or nearly 10,000 children in Colorado, estimates that up to 1.9 percent of children in Colorado may have tTG positivity.

To illustrate what we see in clinic, I wanted to share with you some of the common ways that children with celiac disease present to our clinic and take you through some of the first year of their treatment to discuss some of the challenges we face.

In a typical morning in our specialized celiac disease clinic, we may see a 12 year old with decreased height velocity; a 16 year old with delayed puberty and rash; an 18 year old with fatigue, headache, and constipation; and a 3 year old with a family history of celiac disease.

As Dr. Silvester discussed, when celiac disease is suspected in a child, we typically measure the total IgA level in IgA tissue transglutaminase, and then there are two diagnostic approaches. The first, which is guided by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, is if there's a positive IgA tTG, then a diagnostic. endoscopy is suggested. And if we have the findings consistent with celiac disease, we confirm the diagnosis.

Our European colleagues have another approach where if tTG is greater than 10 times the upper limit of normal and an IgA anti-endomysial antibody is positive at a second time point, we can also make the diagnosis of celiac disease.

According to the patient's presentation and family preference, and a number of other factors, either of these options may be utilized.

So these patients referred to our celiac center all came with a positive IgA tTG, the first sent by the endocrinologist, the second after suggestion by the dermatologist, and in the last two cases by the primary care physician. After a discussion about how to confirm the diagnosis, the first three had an endoscopy with biopsy that confirmed the diagnosis of celiac disease and the last utilized the European criteria to also have a confirmed diagnosis.

Regardless of how the patient presents at diagnosis, how long they've been sick for, what their symptoms are, and what their age is, the treatment is the same. Within two weeks of getting the information, we begin teaching the patient about the gluten-free diet and we try our best -- of course with the guidance of our dietitian who's leading this part, we help them learn how to navigate and minimize cross-contact.

The gluten-free diet is incredibly difficult and almost impossible for children who really just want to blend in with their peers. They may be embarrassed to talk about having celiac disease, which can lead to gluten consumption or cross-contact exposure, and they may not comprehend the long-term consequences of the disease.

For young children who are less than 5, they may not mind bringing their own food to a birthday party or bringing their own food to other events, but this becomes more stressful as children get older. If they choose not to bring their own food, then we're putting the treatment of their serious autoimmune condition in the hands of other individuals that may not be trained on a gluten-free diet.

For some children, not being able to buy school lunch, or have food after an away basketball game, or have special food at an outing is very stressful, and I think Tyler did a great job talking about the concerns about the transition to college and not being able to share in those social

experiences, and sharing those cheaper foods that sometimes we think about at college with pizza and beer.

For our children with celiac disease and their families, we typically see them in our clinic three months after diagnosis and again at six months. At that point, we talk about their symptoms and how they're feeling. We repeat labs, including the tTG, and we provide more education about the gluten-free diet.

Typically, at the six-month visit, the tTG remains elevated in all patients, but it's typically lower than it was at diagnosis. It's this point where we also get a chance to really talk to our patients and hear about how they're doing on the gluten-free diet.

Our first patient, who was otherwise feeling well and was found to have celiac disease due to this decreased height velocity, tells us that he's more bothered by the gluten-free diet than his stature at this time. He wants to eat the same food that the other kids are eating at school and

he wants to be able to get fast food after away basketball games. And while his parents pack him other options, he is eating some gluten; so he continues to eat some gluten daily.

Our second patient has an improved skin rash but has become quite anxious about exposure to cross-contact and is so worried about eating potentially gluten that she is restricting her social interactions and her diet.

Our third patient at six months isn't feeling well. They have transitioned to college and they're not sure if that's because they are not responding to the gluten-free diet or they may be getting some cross-contact at school. And again, they mentioned that there are very few options at college to eat.

I just want to bring this up to show you that celiac disease really requires a multidisciplinary team. I think we all appreciate that a dietitian is absolutely essential for patients with celiac disease in helping them navigate the gluten-free diet because they are

administering their own treatment. But psychologists, psychiatrists, and social workers, all of these are very important for our patients, too.

For example, our first patient would really benefit from a dietitian who can give them more options for the gluten-free diet. Our dietitian would help give other options for the gluten-free diet and a psychologist could work with the patient to talk to them about the long-term consequences of celiac disease, which if they continue to eat gluten may not be reversible.

Our second patient also requires additional help from a psychologist and psychiatrist to talk about the restrictive eating patterns. Even our fourth patient, who is doing well, will require a dietitian and a lifelong relationship with them as they navigate various stages of childhood.

As we address these issues, we find some patients are feeling better; others are not. Others never had symptoms; they had the signs. So how do we monitor improvement or establish

remission in children?

I'm happy that I have the same four pillars as Dr. Lebwohl. Of course we monitor symptoms but, again, not all patients have symptoms, and studies have shown that symptoms don't necessarily correlate with mucosal damage. We also gain valuable information from our dietitian assessment, but it's not standardized and it's not available at all centers. It's an important piece of information we need, but we need more to establish remission.

We've already heard that serology tests aren't validated and multiple studies show that they're not accurate in predicting mucosal healing or dietary adherence. Finally, we have mucosal recovery, which was discussed in detail in our first session. Dr. Silvester discussed, again, this is what we aim to achieve in other disorders, but this isn't mandated in celiac disease and we don't know the timing or when it's necessary.

We know that non-responsive celiac disease and persistent enteropathy is common in adults, but

the data remains limited in children. As Dr. Silvester discussed, a lot of the data we have is from the 1970s with different endoscopic techniques and with children that are younger than they are now.

Our data today suggests that the frequency of persistent villous atrophy is somewhere between 4 and 19 percent after somewhere between 1 and 2 years on a gluten-free diet but, again, we need more information. A recent study out of Boston Children's showed that there may be a frequency of non-responsive celiac disease of 15 percent in children.

We don't know the consequences for this. It's possible that the consequences may be similar to children with undiagnosed celiac disease, and thus issues related to growth failure, nutritional deficiencies, and altered school performance, but we don't have that data.

When we check in with our patients after one year after diagnosis, we're still thinking about, again, how we establish remission in children with

celiac disease. Our first patient is continuing to eat gluten and we continue to counsel them.

For our second and third patient, a repeat biopsy may be helpful in establishing remission for our second patient. And our third patient, we may think about it because they're not feeling better to look and see if celiac disease is still active or if there's something else going on; and likely wouldn't be the case for our fourth patient or, again, as Dr. Silvester mentioned, it would be their first biopsy if that is the case.

Even if we do find persistent villous atrophy, we don't have any FDA approved treatment options for celiac disease or non-responsive celiac disease in children. We do offer the gluten contamination elimination diet, which is a very strict diet with a goal of eliminating any cross-contact and where people are asked to eat essentially only fresh foods. That is not an option for everyone. It's not an option for college kids. It's not an option for our second patient who already has restrictive eating

patterns, so it's not a great option. We also may use budesonide, again, off label as it's not approved for patients with celiac disease, but that's something we tend to use at times when needed in pediatrics.

So in thinking about how children and adults with celiac disease are different -- and I hope we can talk about this more in our discussion later on -- I think it's important to remember that children and adults with celiac disease may follow the same pathway to diagnosis, or maybe a different path, and they're started on the same treatment.

A lot of the signs and symptoms are similar, but they often change or differ according to age; with our younger children seeing abdominal distention, growth failure, appetite loss, and pain, and in our adults seeing other signs like anemia, osteoporosis, and symptoms of diarrhea and bloating.

While the older data suggest that most children heal, that was, again, on a population that was diagnosed quite early, and our recent

literature is somewhere between 4 and 20 percent that don't heal. So our data is limited, and I think this is an area we need to continue to work on, but from what we know, adults may be more likely to have comorbid autoimmune conditions, non-responsive celiac disease, and persistent enteropathy.

To summarize, some of the key signs and symptoms that differ between children and adults with celiac disease would be growth deceleration or growth failure; delayed puberty; and some behavioral changes that could impact social development and learning.

Children may not understand the long-term consequences of celiac disease. They may not be able to independently execute the gluten-free diet, and there are long-term implications for this related to growth, social development, and school performance.

It's important to recognize that there are different challenges for patients with celiac disease throughout childhood. For young children

less than 5, their caretaker provides all of their food but they have the potential to possibly try and grab other food; while for adolescents, the challenges at school and socially are significant.

So we do need more accurate biomarkers to monitor disease. We need to have a better understanding of non-responsive celiac disease and persistent enteropathy in children and we need alternative treatment options because I think they could be very impactful for our young children. Thank you.

DR. VERMA: Thank you so much, Dr. Leonard, for that very comprehensive talk on pediatric celiac disease. I'm very impressed with the need for a team approach and the presentation of similarities and differences between adult and pediatric celiac disease; so thank you so much for that presentation.

The last presentation of this session will be given by Dr. Christopher St. Clair.
Dr. St. Clair is a reviewer in the Division of Clinical Outcome Assessment within the Office of

New Drugs at FDA, and I might just mention parenthetically that he is one of my favorite colleagues at FDA.

Dr. St. Clair works with clinical teams and sponsors on issues related to development, validation, and interpretation of clinical outcome assessments with a focus on measurement issues in gastroenterology, rare diseases, and pediatrics. Dr. St. Clair's presentation this morning will focus on -- now that we've heard about pediatric celiac disease -- how do we define that clinical benefit for the purposes of pediatric clinical trials.

So the floor is now yours, Chris. Thank you.

Presentation – Christopher St. Clair

DR. ST. CLAIR: Thank you. I am so thankful to be here to wrap up this session and lead us into the panel discussion. As you heard, I'm going to be talking about clinical benefit in pediatric clinical trials for celiac disease. I'm a clinical outcome assessment reviewer at FDA, so naturally

I'm going to focus on clinical outcome assessments. The standard disclaimer, this presentation reflects my own views and should not be construed to necessarily represent FDA's views or policies, and I have no conflicts of interest to disclose.

I'm going to start off by defining clinical benefit, and then I will discuss selection of clinical outcome assessments and interpretation of the outcome data, with an overview of both quantitative and qualitative methods to assess clinical benefit and clinically meaningful change.

I'm going to start off by revisiting a definition of clinical benefit that we heard this morning in opening remarks, which is a positive clinically meaningful effect of an intervention, meaning a positive effect on how an individual feels, functions, or survives.

Feeling and functioning are concepts that are measured by clinical outcome assessments, which I'm going to call COAs rather than biomarkers. Patient-reported outcome, or PRO, measures are a common type of COA that usually directly comes to

mind, but in the context of pediatric studies, we also need to consider caregiver-reported outcome assessments, particularly if we're looking at enrolling young children in a clinical trial.

COAs intended to support regulatory decision making and labeling claims should be well defined and reliable in their specific context of use. We also use the term "fit for purpose" to describe this.

We look at various qualitative and quantitative evidence to see if a COA is fit for purpose, and I'm going to give an overview of the key components I think that fall within that.

First, we look for content validity. If we're thinking about a PRO questionnaire, let's say as an example, this means that the questionnaire would measure concepts that are relevant and meaningful to the patients, or the caregivers if it's a caregiver questionnaire, and that the instrument itself is understandable and usable by those patients or caregivers.

The evidence is usually established through

concept elicitation and cognitive interviews in patients or caregivers, as well as of course input from clinical experts and measurement experts. This component is primarily qualitative in nature. Then we look at measurement properties of the COA instrument. These include psychometric analyses such as reliability, construct validity, known-groups validity, and so on. This is quantitative information.

We use the instrument in a trial, and we want to know what kinds of changes in the COA scores are considered clinically meaningful to the patients and/or the caregivers. There are both quantitative and qualitative ways to look at meaningful change, which I'll discuss further.

But before I get into specifics about meaningful change, I want to also highlight some unique measurement considerations for pediatric studies. As I said, we're not necessarily assuming a PRO assessment is the most appropriate type of COA to use for all the patients. We have to consider PRO assessments and caregiver-reported

outcome assessments, depending on the intended study population. For older children and adolescents, a PRO assessment may be appropriate, but for younger patients, the caregiver-reported outcome assessment might be needed.

So depending on the nature of the study, it may be appropriate to include both, but the key point is this is something to discuss with FDA early on in the drug development process so you can plan to have those instruments ready for use in your pivotal studies.

If pediatric PRO assessments are proposed, they should undergo testing in a representative sample of patients prior to being used in pivotal trials. This includes interviews in the pediatric patients to ensure that the components of the PRO instrument, the instructions, the questions, the response options, and so on are all relevant and understood by those patients.

It's important to test it in the age group that you actually intend to study because, of course, the PRO assessment that's appropriate for

12 year olds may not be appropriate for 8 year olds, or 6 year olds, and so on.

ISPOR has a 2013 task force report that provides a really great overview of pediatric PRO considerations, and of course this report does not necessarily represent the views of the FDA, but it does provide a very thoughtful overview of the topic, so I recommend a read there.

Now let's get into meaningful change and talk about interpretation of COA data with a focus on how to interpret meaningful changes in COA scores. I think the key word is "meaningful" in the sense that statistical significance alone does not indicate whether individual patients experienced meaningful clinical benefit. We have to actually look at what kinds of score changes are perceived as being meaningful using information provided by the patients or caregivers.

We recommend anchor-based methods as the primary method to assess meaningful within patient changes and COA scores. Anchor-based methods are a quantitative approach, and I'll explain further in

subsequent slides. But I also want to bring up the point that qualitative data, such as results of exit interviews in patients or caregivers, can also provide incredibly useful information regarding clinical benefit and meaningful change.

So ideally, a strategy that includes both quantitative and qualitative approaches can provide a really robust picture of clinical benefit and meaningful.

Back to anchor-based methods; what are they? On a high level, anchor-based methods involve comparing changes in scores from one COA measure, such as let's say your PRO questionnaire, to responses from an external or anchor measure. This gives you different ranges for the PRO scores that each correspond to different levels of disease severity on the anchor or different levels of improvement or worsening on the anchor since beginning the trial. The results of anchor-based analyses can be represented in various ways such as eCDF curves, which I'm going to have an example of in an upcoming slide.

We recommend including multiple anchor scales in clinical trials because no single anchor scale is perfect, but these are really important analyses. As I said before, anchor-based analyses produce ranges of scores, so having multiple anchors can help you pinpoint maybe more precisely what range of COA scores indicate clinically meaningful benefit.

In terms of the actual anchor scales, we recommend including at least a global impression of severity scale which assesses disease severity over the assessment period of the sign/symptom COA like the PRO questionnaire that it's intended to anchor.

The preferred response scale for this anchor is a verbal response scale, which would mean response options such as none, mild, moderate, and severe. But we also recommend including a global impression of change scale that assesses change since beginning the study; again, a verbal response scale but the responses will be something like much better to much worse with a neutral option in the middle.

Consider also including anchor scales from multiple perspectives such as one from the patient perspective, one from the caregiver perspective, and one from the clinician perspective. Again, the additional information helps to pinpoint or triangulate the clinical benefit.

Here is a generic example of an eCDF curve -- I know I used the term earlier -- from a patient global impression of severity scale. I'm not going to spend too much time on this, but I think it's a useful illustration just to familiarize with it. In this case, the X-axis represents the COA score changes from baseline. Moving toward the left in this example indicates improvement and moving toward the right indicates worsening.

Each curve that's drawn there represents a level of change on the anchor scale. The orange curve in the middle is for patients who showed no change on the anchor and the dark blue line to its left is one level of improvement, such as going from a rating of severe to a rating of moderate,

and the light-colored line on the far left indicates two levels of improvement such as going from severe to mild.

Anchor-based analyses are really only as good as anchor scales that are being used, so it's very important to start these discussions with FDA early and let us look at the anchors you propose, and seek concurrence with us on the anchor scales before using them in a study.

Here are a few essentials for a good anchor scale. First, anchor scales should be easily interpretable. This basically means that the response options should be clinically distinct, and moving from one response option to another should represent a clearly distinct change. For this reason, we recommend verbal response scales. We don't recommend visual analog skills or numeric rating scales for anchors because it's more difficult to interpret for meaningful change.

The second point is that anchor scales should measure similar concepts as their target , COA endpoints. Anchor scales that are overly

general, like an anchor that ask patients to rate their overall health or something kind of broad like that, are not really interpretable or sufficiently interpretable because the patient's impression of their overall health likely includes factors that are unrelated or very far removed from the signs and symptoms of disease that the drug is actually intended to treat.

The third point here is that anchor scale recall periods should be consistent with the assessment period of the target COA endpoint. For example, if you're using a daily PRO diary for measuring signs and symptoms and the endpoint is based on an average of scores over seven days, then you'd want to use a 7-day recall period for the anchor scale so it matches up with the PRO diary endpoint.

Back to qualitative approaches that I mentioned earlier, qualitative methods are also useful for interpreting meaningful change. Clearly, as we've seen today, patient and also caregiver narratives are really powerful.

Qualitative data can be a rich source of context and detail regarding patients' experiences during the clinical trial and observations from the caregiver. Patients really have the opportunity, in that case, to describe clinical benefit in their own words using real examples from real life.

We usually recommend this in the form of exit interviews conducted soon after patients complete the double-blinded portion of the trial. Waiting too long after a double-blind period increases the likelihood of bias or recall error. Unblinding could have occurred since then and so on.

Exit surveys are also an option in some cases, but in this context, interviews are usually more informative. However, again, this is something to discuss with FDA early so we can help you plan the most appropriate and informed approach. Qualitative data I think are always useful, but even more so if there are potential issues with anchor-based analyses such as if not so great anchor scales were included in a study or,

commonly, if sample sizes are small.

Some examples of what exit interviews can explore are how a patient's condition changed, or even didn't change, during the trial, and also collect the context around any changes in the patient's environment, or diet, or gluten exposure that may have happened during the trial that may or may not have affected outcomes but it's important context.

Exit interviews could also look at whether an observed change was meaningful in terms of improvement or worsening, and if so, what exactly that improvement or worsening looked like in terms of signs and symptoms. But of course, again, as we've heard today, celiac disease can have a devastating effect on daily living, socialization, and the activities you can participate in. Interviews are a great way to capture those narratives and learn what's really important to the patient and what changed or didn't change over the course of the trial.

I've only been able to touch on some

important issues at a surface level today, so I would really encourage you to look at our guidances that relate to patient-focused outcome measurement. We have a 2009 PRO guidance, as well as newer patient-focused drug development guidances that are still being developed and released. I highly recommend referring to these guidance documents for a deeper dive into the quantitative and qualitative approaches that I've been able to touch on today.

To conclude, quantitative and qualitative approaches both provide evidence to support COAs and inform determination of clinical benefit and meaningful change, and they're pretty powerful when used together.

It's so important to talk with FDA early regarding your strategy to assess clinical benefit and meaningful change. As I just showed, we have a number of helpful guidances that cover these topics in greater detail, so definitely worth the read. I believe that concludes my presentation. Thank you.

DR. VERMA: Thank you so much, Christopher.

We are headed for a very short break, and my

understanding is that we will plan to reconvene in exactly 7 minutes at 12:15; so just a short enough break to get up and take a stretch. We'll reconvene at 12:15, and we'll proceed with the panel discussion for Session 2. Thanks, everybody.

(Whereupon, at 12:09 p.m., a recess was taken.)

Panel Discussion and Q&A

DR. VERMA: Good afternoon. Welcome back. I'm sure somewhere it's good evening. It is 12:15, and we don't want to really step into anyone's lunches or any other meals.

It is our pleasure to introduce the panel. First of all, I'd like to welcome back our speakers, Dr. Khurana, Mr. Friedman, Dr. Leonard, Dr. St. Clair, and of course my moderator, Dr. Yao. I will introduce the panelists, and after I say your name, can you please briefly introduce yourself, and then we can get into the questions. And I'm going to apologize. I probably will not say your name correctly

Dr. Charuworn?

DR. CHARUWORN: Hi. Prista Charuworn -- [inaudible – audio gap].

DR. VERMA: We may have a little glitch there.

FEMALE VOICE: Yes, I lost her as well.

DR. VERMA: Okay. So we will continue --

DR. CHARUWORN: -- I'm an adult gastroenterologist.

DR. VERMA: Thank you.

Dr. Fasano?

DR. FASANO: Hi. I'm Alessio Fasano. I am a professor of pediatrics, MGH for Children, and Harvard medicine, professor of nutrition at the T.H. Chan School of Public Health, and the director of the Center for Celiac Research and Treatment, MGH.

DR. VERMA: Thank you very much and welcome.

Mr. Beckett Hardin?

MR. HARDIN: Hi. My name is Beckett. I'm 12 years old, and I was diagnosed with celiac when I was 6.

DR. VERMA: Welcome, Beckett, and your mom,

Ms. Kathy Hardin.

MS. HARDIN: Hello. I'm Kathy Hardin. I'm a speech language pathologist and very proud to be Beckett's mom.

DR. VERMA: Thank you so much for joining us.

Dr. Seo?

DR. SE0: Hello. I'm Suna Seo. I'm the clinical team leader in the Division of Gastroenterology at the FDA.

DR. VERMA: Thank you. And of course, thank you for setting this actual workshop.

And last but not least, Dr. Stahl?

DR. STAHL: Hi. I'm Marisa Stahl. I'm an assistant professor of pediatrics at the University of Colorado and a pediatric gastroenterologist and clinical researcher at the Colorado Center for Celiac Disease.

DR. VERMA: Thank you so much.

Welcome, everyone. I just want to take the liberty here as being one of the moderators and setting the stage. I think when we think about

pediatric celiac disease, there are so many factors. There's the child, there's the family, and there's the parent; and of course we have the clinicians and the researchers.

When we think about where does pediatric celiac disease go and where do we look from a next therapy or adjunct therapy standpoint, we first have to think about how do we make diagnosis, what are the signs and symptoms that are different, different age groups, and Dr. Leonard has really elicited that very nicely in her talk.

Then the big question that has been going on from this morning is what are the diagnostic tests and what's the healing; what is the quality of life, the quality of life of the patient and the quality of life of the families; and whether you're symptomatic or asymptomatic?

So I think we need to keep all this in mind as we think about pediatric celiac disease. What I would like to do is jump off with this question to, first of all, the physicians.

Dr. Khurana gave a really nice discussion

about pediatric extrapolation. Could you comment -- and maybe we'll start with Dr. Fasano -- in your clinical experience and available data, what are the differences or similarities between adults and children, and how do we support the extrapolation; or should we not support the extrapolation and think about medications, so on and so forth, in pediatrics in a different way?

Dr. Fasano?

DR. FASANO: Ritu, as you mentioned already, celiac disease is a family affair, so it doesn't involve only the patients; it is affected by the entire family. Now, this is 10 times more in pediatrics because, of course, the involvement is much stronger in the family, to the point in which sometimes the entire family embraces a gluten-free lifestyle in the household to facilitate this transition that is not easy.

The symptoms, as you heard already, are similar but not identical to the adults. For what we understand, the pathogenesis is the same, so

potential targets could be the same.

The impact is tremendously more impactful in pediatrics depending on the age. Of course when you talk about sleepovers and birthday parties, and transition to college, the major change is when you become an adolescent, in which you want to blend with your peers and you don't want to appear different, and has a tremendous social, personal, and intellectual impact to the entire ordeal.

Nevertheless, I believe that there is enough similarities for which I believe that there is definitely a possibility to catch on what we have learned from adult clinical trials, and they can be extrapolated to pediatric trials.

DR. VERMA: Thank you.

Dr. Leonard, Dr. Stahl, and Dr. Charuworn, anything that you would like to add to that in terms of comparisons and differences between adult and pediatrics; and your thoughts in terms of do you think that we should be in pediatrics, at least in extrapolation, or should we think about something on our own in different age groups?

DR. CHARUWORN: When I think about extrapolation, I think I have to focus first on the target population, and whether the target population that we're evaluating in adults also exists in kids and what's the parallel between the two.

I know we're jumping to extrapolation per se, but I hope we also have time just to talk about what are the possible target populations in the pediatric age group and whether they're there at a prevalence or they're there -- and I think that's easier in some ways to start thinking about the similarity of the disease because it really depends on what group you really want to focus on.

DR. VERMA: Thank you.

DR. KHURANA: I echo that. I think if we're talking about extrapolation, pediatric extrapolation, I think that is an important first step, is to think about what is the adult subpopulation that's being targeted for drug development; starting there and then thinking about how relevant the corresponding pediatric population

might be to that adult subpopulation.

I think one of the speakers earlier mentioned that it's not the newly diagnosed adults that are being targeted for drug development; it's really those who've had established diagnoses with persistent villous changes. So what's the corresponding prevalence of the pediatric population that's impacted chronically and how representative are they of the adult population?

DR. LEONARD: I think we have to think about children, again, in maybe more than one group because we have the teens that are facing a lot of the same challenges with cross-contact that adults are facing, and then we have this younger population where, again, the family controls most of the food intake.

So looking at these a little bit differently I think is important, and trying to understand the frequency of non-responsive celiac disease across childhood would be important.

DR. CHARUWORN: I completely agree, and I think one of the things that was mentioned at the

start of the workshop today was to identify knowledge gaps. For us in pharma, we rely a lot on the published literature on what are the unmet needs, the characterization, and the epidemiology. I have to say there's such a paucity of data within the pediatric age group and just separating out the adolescents, the children, and the younger population.

DR. STAHL: I would echo what others have said in terms of pediatric extrapolation. I think in Colorado, one unique experience that we have had is with more population screening and screening of high-risk patients. I think some of these individuals may be more asymptomatic, or maybe not, or have more subclinical presentations.

I would challenge when we're thinking about clinical trials and these families are interested in participating, I would challenge us to think about how to plan for that and whether there is more of a pediatric extrapolation with that patient population or if we should be planning other trials with them, and also thinking about disease

interception and prevention when we're thinking about these patient populations.

DR. VERMA: Thank you, Dr. Stahl.

I'll come back to your question about how to design clinical trials, but I'd like to find out -- and I'm sure everyone wants to know -- from Beckett.

Beckett, I'm sure you've been hearing the whole morning what has been going on. What are your thoughts? I know you heard Dr. Leonard talk about various symptoms. You yourself experience symptoms. What would you want?

MS. HARDIN: What would you want to feel better and what would that mean to you?

MR. HARDIN: To feel better, maybe like a medicine that would reduce some of the symptoms when I eat gluten. If it gets really well, then I might say it completely neutralizes the effects of gluten or we somehow figure out how to take gluten out of bread or things that contain gluten to make it gluten free without losing this.

DR. VERMA: So you would go for any option

that's better than where we are now; is that what you're saying, Beckett?

MR. HARDIN: Pretty much. As long as we make some further advancements, I'm ok with that.

DR. VERMA: Thank you.

And maybe your mom has something else to add as well?

MS. HARDIN: Just as Beckett started when he said when I eat gluten -- especially during COVID, we subscribed to a strict gluten-free diet. Beckett very thankfully is -- he has a very strong reaction, so that instinctive, "Oh maybe I'll just have a Twix bar" or something like that is not something that his system could tolerate in any way, shape, or form because he just gets so incredibly sick.

But it would be ideal if there was something, of course, that was happening at the, really, biological level. But at this point we need something for symptom relief, and if I can just share a quick story.

During COVID, we were not eating out. We

felt like we were particularly successful with a strict gluten-free diet and Beckett was really having chronic diarrhea. We went into our gastroenterologist, and myself, my husband, our GI doc, who's great, we all thought it was anxiety-based, and it happened every Monday morning. We said, "Beckett, are you nervous about going to school?" And he's like, "No, I'm not." And we thought he just wasn't in tune with symptoms of anxiety as an 11 or a 12 year old.

It turned out that a spice packet that we had been using that used to be gluten free and then they had added a gluten-containing ingredient without labeling it, we'd been using it for the past year, every Sunday night in family spaghetti sauce. So guess what? Every Monday morning, Beckett had chronic diarrhea.

It wasn't that we weren't trying to do everything in the best way that we could, but obviously it was affecting both his mental health, missing school, embarrassment about having to turn off the camera for online school; not a

misdiagnosis, but it took us time to figure out what was going on, and that was particularly challenging.

So anything that we could do to have those symptoms be better, that directly improves that familial quality of life and Beckett's quality of life.

DR. VERMA: So besides being a mom, you had to be a detective as well. I think that everyone who is part of taking care of children with this or have children with celiac disease, that's part of what we unfortunately need to do right now. I agree with you that we do need something else as well.

Tyler, what are your thoughts in terms of from a symptom standpoint? You've heard a lot about talking about histology, pathology, biopsies. What are your thoughts and what would you share from your age groups?

MR. FRIEDMAN: I'd say that my age group, I have a lot of friends and people that have celiac disease in my life. Once people get to around

16 years of age or older, I feel like everyone has a good understanding of what they need to do to be safe and adhere to a strict gluten-free diet. But I will say that biopsies, and other histologies, and all these other solutions are interesting if they can lead to more long-term solutions rather than the gluten-free diet and with the gluten-free data.

As for me personally, since it eliminates symptoms, it is effective, but for those who don't have the symptoms eliminated with the gluten-free diet, I feel like those processes are necessary to further develop a safe and effective method for all people with celiac, not just those that are symptomatic or asymptomatic, and whether those are cleared up through a gluten-free diet or not.

DR. VERMA: From your standpoint, just as a discussion, would you say if you had to do biopsies as part of clinical trials, your age group, and if Dr. Leonard approached that, she came to you and approached you with that question, what would your answer be, and I guess your parents as well?

DR. FRIEDMAN: I think that for a biopsy, at first I think most families will be hesitant because it is a procedure. But then I think when you look at the fact that there is such a knowledge gap and there needs to be some progression to make some significant developments, families will have to converse and realize to be part of this generation of people with celiac disease that can live their lives how they want to, then there needs to be some who take these risks and go through this.

But I will say that in the trials, when there are chances of contamination, that is probably less likely to occur because I myself would definitely try and stay away from a contamination at all costs. With the clinical trials, having that risk if the medicine will be working or not and effective in limiting the symptoms, I think that people my age, and me in particular, would be more hesitant to that.

MS. HARDIN: Could I add to that?

DR. VERMA: Absolutely.

MS. HARDIN: As a parent, I'd be interested.

Beckett, would you be willing to have a biopsy?

MR. HARDIN: If it was to further the research for finding a medicine for gluten, but I'm not quite sure if I would do it or not; depending on how much research would still make me do it [indiscernible].

MS. HARDIN: I think, for me, just from listening to the workshop today, earlier at the very beginning, there were some concerns raised with anesthesia and pediatrics. We didn't really get to that in the second pediatric session, but I think that's something that most parents would be very concerned about.

I'm also concerned, and we heard that there's the smaller pediatric population and how many patients and families would not engage in a trial with a biopsy. I'm not sure that Tyler and I are necessarily the most representative of the full celiac community because we are here as advocates and trying to advance the research.

Personally, my mom has celiac disease. My son has celiac disease. What I would like to see the most is a successful trial, one where we can recruit the number of patients we need and that we could see something that's hopefully showing some degree of clinical and meaningful change as Dr. St. Clair was talking about.

That's something where I would worry about having a trial design where we couldn't recruit enough patients, and then that pipeline for where we may be moving to in the future stops. So that's a fear of mine.

DR. FASANO: I see many issues with a clinical trial in pediatrics involving a mandatory or a necessary endoscopy, some that are shareable with the adults. It would make sense if we would have strong evidence that the pathogenesis in kids versus adults is different, and we do not.

So in terms of gaining information by doing an endoscopy compared to adults, at least for the data that we have so far, we don't have that information. Like in adults, of course the

endoscopy with the biopsy is objective analysis, so again you have to have a good pathologist with a good orientation of these slides to have the proper interpretation. We know that in double-blind studies, even very skilled pathologists, they don't have a hundred percent concordance in reading.

But the main problem that I see in pediatrics compared to adults, I will have a hard time justifying a gluten challenge in pediatrics. So I see more a clinical trial for the non-responsive kids or, again -- we have two examples here -- something that gives a peace of mind or safety net, because when you are home, you know that you can control everything unless you have the boo-boos that we just heard, and somebody changed the recipe and put the gluten in there, but it's on [indiscernible – audio gap]. Therefore, the real-life trial is what is more important in pediatrics.

I here have my last concern on the matter. You heard that establishing an enteropathy with a gluten challenge is something that is rather quick,

and hopefully rather quick is the resolution if you use a drug to try to mitigate the problem. If we do real-time and real-life clinical trials in pediatrics, lacking adults, you know that the enteropathy can take months, if not years, to heal, how can we use histopathology as a possible outcome if this is not an [indiscernible]? Because you can be waiting [indiscernible] 2 weeks after the drug, in 5 weeks, 5 months, 6 months. Who knows?

So that's the reason why I personally believe that together with the fact that many kids now, they don't have a baseline endoscopy, it will be a little bit tough, really, to consider a must in pediatrics, and I see this as the bigger difference in adults.

DR. YAO: Well, thanks --

DR. SE0: If I may --

DR. YAO: Yes, go ahead, Suna.

DR. SE0: Yes. No, I wanted to thank you for that comment, Dr. Fasano.

We've heard from Ms. Kelsey Smith on question 1, and we've now heard from Tyler and

Beckett, and we appreciate all your input. I just wanted to throw another question back out into this session that we've already asked in Session 1, and that is to ask Beckett and Tyler both, would you be willing to take a drug that might make you feel better, but it might not necessarily heal the underlying inflammation?

MR. HARDIN: Well, I would kind of debate between it because it would be very helpful for me to feel better, but it would still cause the inflammation, and I would still kind of have stomach aches and diarrhea. I might try it a couple times just to see what it might do, but I probably wouldn't keep using it.

MS. HARDIN: What if it made you feel better and it did not make the inflammation worse; like the inflammation stayed there but you were feeling better? Does that make sense? It didn't make you worse.

MR. HARDIN: Well, then I might take it, but I would still be hesitant.

MR. FRIEDMAN: I on the other hand would

probably be more willing to take that because, for me, with my symptoms being directly correlated to when I have gluten, I would continue my regular gluten-free lifestyle, but then I would have a better sense of ease when going out to eat and when going to restaurants because I'd still be taking all the same precautions, but I just wouldn't have that extra thing in my head telling me, "Oh, don't do this because you're going to get sick," or don't go out there, and don't take all these risks. But because in reality we have to take the risks, I feel like this extra medicine would just be so helpful and giving me that extra peace of mind.

DR. VERMA: So Tyler, for you, if there was a medicine that you could take only, let's say, where you're traveling, as Dr. Fasano was mentioning, and where quality of life would become a big hustle because you have to carry your own suitcase of food, that you would eat gluten free but you could take this medication that would not give you all the symptoms, but you wouldn't worry if it continued to cause inflammation.

DR. FRIEDMAN: Correct, because obviously I'd try to avoid having contamination in general, so it wouldn't be as though it was doing anything other than helping me because my body would be exposed to gluten regardless if a contamination occurred, but I'd still try to maintain a completely gluten-free lifestyle.

DR. VERMA: So peace of mind and symptoms being better, that's from your age group.

But Kathy, what do you say?

MS. HARDIN: Having also many other pediatric friends and adults in the celiac community, I just want to draw some attention to something that did come up in the first session, that there was that concern that if there was this sort of therapeutic, that people with celiac would kind of go gonzo and just start eating anything in sight.

Of course with any medication, there are people who do things that are not good for them, but overwhelmingly, I would hate to prevent something that could help so many people for just a

few kind of crazies who are going to kind of do their own thing anyway. So I would hope that the FDA, and everyone thinking about pharma and academics, can have confidence in the patients making the best choice for their own health and thinking about that majority of the community with celiac because that's just a huge game changer in terms of quality of life.

DR. VERMA: So really thinking about clinical trials with education, with having the input, obviously, from everyone, patients and all the stakeholders, I'm going to put Marisa and Maureen on the spot here.

As pediatric gastroenterologists, how would you feel in terms of if there was a drug that had been tried in adults or do you feel like you should have something for different age groups? So the less than 5, 10 to 12, over 14, that kind of age group, what are your thoughts on that?

DR. STAHL: I think there have been some scenarios for drugs that have been outlined that probably are more appropriate for pediatric

extrapolation. In the adult population, when you're eating out and you're worried about cross-contamination, that probably applies pretty well to our adolescents who are in similar scenarios. But I think for particularly our younger age groups, as others have said, you're dealing with a lifelong diagnosis, and it's a new diagnosis at this point, and I don't know how well that necessarily extrapolates to the pediatric population.

So I think there are definitely considerations based on when you are diagnosed, how old you are, what age group you're in, and what the indication for the medication is. Whether it's at diagnosis or because there are concerns for ongoing villous atrophy, which we've touched on as well, it's not necessarily the same in the pediatric population, and then are you dealing with adolescents, or school-aged kids, or even younger.

DR. YAO: Before, Dr. Leonard, you weigh in, I want to ask a question that is similar to what Dr. Ritu asked.

How do you feel, and the pediatric gastroenterologists on the panel, about a product that would relieve symptoms but not necessarily treat underlying disease? I'm curious about your thoughts there.

DR. STAHL: I think Tyler was very articulate in describing his impression of that and why he felt like he would be willing to take that medication, and I think had a really great understanding of the implications of ongoing inflammation and complications from that. I don't know that all of the children that we treat and see have that same understanding.

I guess one of my concerns with having a medication like that is that we're treating children throughout the course of their life span and at vulnerable times of transition, so when they're going to high school and maybe they're eating out more independently. If they don't have a good understanding of the importance of the gluten-free diet with a medication like that, I think it could really be dangerous.

DR. LEONARD: Yes, I would agree with Dr. Stahl in that I think there are many areas. First going back to the extrapolation, I think ages 13 to 18, our adolescents, a lot of the work may be extrapolated to them. I think the younger group is something that we really need more work in because, again, we think, and there's some data to suggest, that healing is faster, and there's greater healing in this group, and that there's less non-responsive celiac disease. But this is such an important group, too, because it's before puberty, and we have this potential to really help them, and get healing, and have them reach their adult height that they're meant to do.

We don't know yet if this is a problem and if this is contributing to growth problems, and I think we need to understand that before we can talk about whether things should be extrapolated to even the younger group because if we have the chance to impact growth, then we should be trying to do that in these younger populations.

Regarding the --

DR. YAO: Please go ahead.

DR. LEONARD: -- question about something that helps their healing, helps their symptoms but may not help underlying disease, I think it's a difficult question. But I certainly think that it would benefit many patients who, like Tyler, are going on a short trip.

If they're going on a short trip or, like we heard, when you're going on a vacation, one slip up by somebody else can ruin that time, or they may not be able to experience an abroad program at a certain place. So I think there could be some circumstances where it could be helpful.

DR. FASANO: I personally will say, to answer your question, no brainer. I would like to have a drug that will take care of both symptoms and inflammation. Inflammation doesn't equal histopathology evidence, thankfully. And thanks to the research in pediatrics, now we have a better understanding of the natural history of celiac disease. We have prospective studies, as Marisa was mentioning. We are learning a lot.

So I foresee in the near future a possibility of a combination of symptoms and biomarkers that will have almost a hundred percent possibility of value if there is ongoing inflammation in the gut. That will be much more informative when it comes to one of the two subgroups of conditions that we want to target, namely a new celiac disease that occurs in 20 percent of the pediatric population; in other words, kids that will still have symptoms despite the strict adherence to a gluten-free diet, and therefore the next push to take the inflammation out control.

But the second and much larger group that will eventually benefit from medications that will come in the pipeline is the one that wants to have a safety net. There, the inflammation is likely an issue because it's more a problem of cumulative cross-contamination over time that leads to the inflammatory process.

There is the situation that Beckett is experiencing and that Tyler has experienced. One

mistake -- and they are lucky by the way, and they have symptoms by the way, and they live a "miserable life," quote/unquote, in terms of quality of life because they're in that fear; take that fear out will be tremendously impactful in pediatrics.

Of course, everybody that lives a "normal," quote/unquote, life with no celiac, when they go dining or having a meal, it's just enjoy the conversation and the meal per se. People always see the disease as having this mental focus in making sure they are safe. Taking that out from the equation will be a tremendously impactful change for the better.

DR. SE0: Yes, we completely agree with you, Dr. Fasano, in that we would love to have a non-invasive biomarker. And we may be getting there, but right now we don't have any that's quite available and ready for regulatory use yet, and we're all waiting.

DR. FASANO: Yes, but again, what I mentioned in terms of the limitations to do an

endoscopy in pediatrics, that's, again, factual for all the reasons that were mentioned before. You know our kids are not small adults; there's a total difference.

DR. YAO: I know we're running out of time, but I do have a question that I think flows from the discussion so far. If we're going to move forward in therapeutics development and we're going to consider patients' symptoms in this paradigm, I'm wondering, Chris, if you could mention or give us some insight on how the patient community can help inform any kind, for example, of PRO development. How can patients be used to actually develop these instruments?

DR. ST. CLAIR: Yes, definitely. We don't currently have a fit-for-purpose signs/symptom measure, so if something like a PRO could be developed that really checks the boxes for what we need for regulatory decision making, that would be a huge advancement.

I would say as far as what the patient community can do is, really, being involved, and if

the communities can organize and really get the research together and come talk to us about if they intend to develop a PRO or something like that, that would support clinical trial endpoints.

I think coming to talk to us is a good first step always because, obviously, there are patients willing to give their stories. But getting that qualitative data, it's the foundation of it, but it's just the first step, and then we need a plan to actually test it statistically and use it in early-phase studies.

So it's definitely going to be a multi-year process before we have something that we can say is fit for purpose or supports labeling. But I think patient groups are really in a position to organize the patients and get the resources necessary to carry out that kind of research and, again, come talk to us because we are definitely willing to advise you at every step of that instrument development process.

DR. CHARUWORN: Yes, and I agree. I think this is an area that needs additional work in

pediatrics. I know we do have a valid PRO in the adults, but especially in peds, it's certainly an area that I think requires a bit of work.

DR. YAO: I have one clarification I hope we have time for, and then one final question, for me anyway.

Again, I'm really trying to wrap my head from our panel of experts here, what is it about celiac disease that you feel defines it differently in children, or some subgroup of children, compared to adults, or is it really, in terms of similarities, histopathology progression?

How different are we talking about between children and adults? I was hoping that maybe our pediatric gastroenterologists could comment.

DR. FASANO: If I can start, because I've seen both kids and adults, it's not much of a difference in terms of quality rather than quantity. In other words, the extent of the enteropathy may be different. The time of recovery for the enteropathy will be different. The symptoms may be different in terms of the intensity

and so on and so forth, but there is not much difference in terms of quality; the symptoms are the same. These two pathologies are the same. As I was saying before, as far as we know, the pathogenesis is the same.

I just want to make clear that we're talking about growing bodies, and everything that we do to them, it can affect that growth. You heard Tyler is taking growth hormones now to catch up and will be something that can have permanent consequences.

So that's the reason why I feel very uncomfortable with clinical trials with the gluten challenge in pediatrics. Again, it's going to be difficult. But other than that, I don't think there are substantial differences that make this a different disease compared to adults.

DR. YAO: Dr. Stahl, and then Dr. Leonard? I might even ask Dr. Verma as well, even though she's a moderator.

DR. STAHL: I completely agree with Dr. Fasano in the sense that the symptoms can be the same, especially as Dr. Leonard outlined so

nicely in her presentation. Initially, we had the description of smaller children who are very malnourished, and that's just not clinically what we're seeing in practice as much anymore. I think the presentation is much more similar at times to what we see in adults.

I think the potential in terms of a drug to really have that lifelong effect when you're diagnosing someone at age 2 or 3 is obviously different than what we're seeing in the adult population when you're diagnosing later in life, so we really have the opportunity to make a huge difference for these kids. But as Dr. Fasano was saying, there is the need to think about how it affects them throughout childhood as well and how that affects their growth.

I do think maybe one area that I touched on before that is maybe a little bit different in terms of what we're seeing, at least in our pediatric population here, are the kids who are screened because they're high risk or screened for population screening, and maybe seeing more who are

asymptomatic and the struggles around that with gluten exposures. It's different in terms of your level of potential adherence and quality of life if you're not having symptoms when you're exposed, but you're still worried about the inflammation; so kind of the opposite question of what you were asking us before in terms of the drug that helps with symptoms but not with inflammation.

DR. LEONARD: Yes, I agree with Dr. Fasano and Dr. Stahl. I think there are a lot of similarities, which I talked about in terms of symptoms and diagnosis. What we have less information about is long-term consequences and recovery. I think we need more information there.

DR. VERMA: I think the only thing I would add here and emphasize is growth is such a big thing for pediatrics. So that age when you're diagnosed and what you do beyond that is so significant. Then thinking about the child who's diagnosed at 2 years, what is their immune system like and what's the child diagnosed at 15 years of age.

I think those are the big differences that I would see in the spectrum of pediatrics, so not just pediatrics and adults, but more the spectrum of pediatrics and that we have a difference from someone diagnosed at 3 versus that. Even from a quality-of-life standpoint, it is so different when you are diagnosed at 3 versus at 15. So I think those are the big differences, but otherwise they're about the same.

DR. YAO: Terrific. I wanted to double-check. There was one last question that I think I'm going to table because it really has to do with trial design, and I think we're going to have a lot of conversation about trial designs and gluten challenge, et cetera, and when to enroll patients, pediatric patients, in the coming session.

Dr. Verma, any last questions or comments before we head to our slightly delayed lunch?

DR. VERMA: No, not really. I just want to thank everyone, and of course Beckett and Tyler for you to step forward and talk about your journey and

what everyone else is feeling.

I can tell you as a Mom myself with two children with celiac disease, I would like to see something more than the gluten-free diet. I think that it's time for us to do something for our children, and of course the adults as well. Let me not forget the adults. But as a pediatric gastroenterologist, it's time to do something, especially I think more so for that teenage, high school, going on to college tough age. We've got to do something there; so thank you.

DR. YAO: Indeed. I think what I heard as a summary from this session, which was tremendous -- thank you to all the panelists and presenters -- is that there is a need for development of therapeutics not just to treat the underlying disease, a disease that we know is chronic and is lifelong at this point, but also a need for potentially intermittent therapies or symptom therapies that can be used as needed when there is an exposure. So I think that there's a lot of room here for therapeutics development.

What I also heard from our panelists is there seemed to be a lot of similarities between pediatric and adult celiac disease, and that that old vision of what we had of large bellied little children who are wasting away is not the same celiac disease that we're seeing in 2021.

So with that, finally not to forget my FDA colleagues, the ideas of how we use PROs and how we use pediatric extrapolation, I think stay tuned, because after our lunch break, we're going to get, I think, more into that topic.

So thank you all for participating in Session 2. My understanding is that we'll have a shortened lunch break and that we would like to reconvene at 1:30 p.m. Is that correct?

DR. SE0: Yes, that's correct.

DR. YAO: Okay. Thanks, everybody. We'll see you again soon.

(Whereupon, at 1:01 p.m., a lunch recess was taken.)

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

(1:34 p.m.)

FDA Introductory Remarks – Juli Tomaino

DR. TOMAINO: Welcome back from lunch, everybody, for our final and third session. I'm Juli Tomaino. I'm the deputy director in the Division of Gastroenterology. It certainly has been an informative and lively workshop so far, and I anticipate that this session on gluten challenges will continue to foster an exciting discussion.

As we know, there's a great deal of interest from the community relating to inclusion of gluten challenges in clinical trials. We all share the common goal of developing safe and effective therapies for celiac disease, and collaborative learning opportunities such as this workshop are critical to success.

This session is intended as an open forum for scientific evidence-based discussion with participation from all stakeholders, including the patient community, clinicians, academia, industry, and FDA. I'd like to remind everyone that this

workshop is not advisory in nature and not intended as a forum for FDA to provide or receive advice.

We are looking forward to discussing the current role that gluten challenges plays in clinical practice and during clinical trials, as well as the knowledge gaps for future opportunities to move the field forward.

As you listen to the presentations and during the panel discussion that follows, an overarching theme will be to consider when would a gluten challenge be necessary, and if it is needed, how can it be incorporated in a thoughtful manner that will produce interpretable results that are not obtainable through other means and also ensure the safety of patients during that trial?

I'm now going to turn it over to my co-moderator, Dr. Amanda Cartee to introduce the speakers for this session.

DR. CARTEE: Thank you so much, Juli.

I think we're all very excited for this session today, and I would like to introduce our first speaker who will be speaking on gluten

challenges and unintentional gluten exposure and clinical practice.

Dr. Joseph Murray is a professor of medicine at the Mayo Clinic and has been engaged in celiac disease clinical care and research for over 30 years. He went to medical school in Ireland, completed his fellowship training at the University of Iowa, and is a consultant in gastroenterology and immunology at the Mayo Clinic in Rochester, Minnesota, where he leads the celiac disease program

Dr. Murray?

Presentation – Joseph Murray

DR. MURRAY: Thank you, Dr. Cartee, and it's my pleasure.

This is the opening of what I call a feast of gluten in this meeting. I'm going to talk about gluten challenges and unintentional exposure in clinical care. These are my conflict statements.

I'm going to talk about the clinical uses of a prescribed gluten challenge. Really, as part of the initial diagnosis of celiac disease in patients

on a gluten-free diet, historically, this was used to confirm the permanent nature of a gluten response in celiac disease, but that's no longer necessary, and it's really where there's uncertainty of diagnosis that this might be required; then I will turn my attention to gluten exposures in real life of patients with celiac disease.

We know the threshold for what's labeled gluten free has been set by the FDA and Codex. Alimentarius is less than 20 parts per million. There have been some excellent microdose studies, which are beyond what I'm going to talk about. We'll talk a little bit about frequency, causes, detection, and then of course verification of gluten exposures.

The current use of a gluten challenge for diagnosis is limited to those patients who are on a gluten-free diet. We know that diet reduces the sensitivity of serology, and if sufficient time has elapsed, even the biopsies.

Currently it's recommended that HLA

genotyping be done because of its very high negative predictive value and only those with the genotype can really be expected to have celiac disease. It should be a medically-directed challenge, and many patients of course refuse or might even be unsuitable for a challenge.

Some of the contraindications to a clinical challenge include a history of anaphylaxis to wheat or gluten; neurologic associations of celiac disease that can be quite severe and often don't reverse quickly or at all; and then there may be relative contraindications related to age critical to development, childbearing for example, or patients who report very severe or persistent symptoms with a prior short-term gluten exposure; and of course we really don't need to rechallenge the adult who was diagnosed as a child, who met the rigorous ESPGHAN criteria for biopsy avoidance-based diagnosis.

What are the expected outcomes or do we see with a gluten challenge? Well, symptoms often start quickly, within 6 hours after the first dose,

and they're both GI and non-GI symptoms. There is the issue of anticipation or a nocebo effect, and then, of course, complex foods may contain other items that might trigger symptoms and may not be specific for celiac disease.

We know now that serology is slow and uncertain. Histology and the development of histologic change is a trade-off between dose and duration. Do we go with a traditional high-dose gluten for 2 to 4 weeks versus a more moderate or gentle gluten challenge for a longer period of time?

A baseline biopsy, as we've already heard earlier today, might still show damage, and thus avoid a challenge if you can make the diagnosis on an initial pre-challenge biopsy, and of course it can be useful for comparison with a post-challenge biopsy. There is no baseline biopsy that clear pathologic changes must be obtained on the post-challenge biopsy in order to confirm a diagnosis.

This is an excellent study from Boston by

Drs. Leonard and Silvester and co., and I put this up only to illustrate that the symptoms occur with both moderate -- that's 3 grams -- or 10 grams of gluten, and this is occurs quickly. But only the 10 grams achieves reliable changes histologically at 2 weeks, suggesting that symptoms occur early. I put this up to illustrate this can be a limitation of being able to complete a challenge long enough in order to identify histologic change.

So moving on to the follow-up of celiac disease or how we think about gluten exposures, symptoms resolve in 1 to 3 months, is our typical expectation. Serology levels fall substantially by 6 months and are often negative and usually negative by a year.

Biopsies improve more slowly in adults than in children, as we've heard already, and a re-biopsy in 1 to 2 years may be performed in adults, but it's probably not mandatory in all patients.

Dietitian follow-up for adherence would be ideal but is rarely undertaken. Physician interest

and engagement is crucial, but in clinical reality, little or no follow-up is quite common, even in certain areas where there's excellent medical attention otherwise.

The recommendations for follow-up biopsies vary a little. Routine biopsies can be considered, however, they're not necessarily mandatory in patients doing well on a gluten-free diet if those patients lack increased risk of complications. They are needed in those whose condition does not respond to a gluten-free diet or who develop symptoms despite doing their best on a gluten-free diet.

Non-responsive disease, also known as slow-to-respond disease, is a patient with persistent or recurring symptoms despite a self-declared adherence to a gluten-free diet. It can be primary, no initial response, or secondary, where there's been a response, and this may affect up to 35 percent of patients seen in celiac centers. The symptoms are quite variable and they include both GI and non-GI symptoms.

There is a systematic approach that's been recommended to these patients. First, review the original diagnosis and make sure that they actually have celiac disease; then look at compliance by diet review, serology, and histology, and if it is an issue of gluten contamination, try to help the patients eliminate gluten; and of course don't forget additional diagnosis can also hang out with celiac disease.

What about gluten exposure in celiac patients? This excellent meta-analysis of all the studies looking at adherence to a gluten-free diet suggested adherence was achieved in about 75 percent of patients, but this is very variable with some studies suggesting as low as 25 percent. In one survey from the UK, we suggested that accidental was about as common as deliberate exposures to gluten, at least by patient report.

So how do they occur? Deliberate or knowing intakes are associated possibly with things such as taste, cost, and depression. Diagnosis in adolescents is especially problematic, and then

self-regulatory efficacy seems to be an important issue for exposure to gluten. Then, of course, accidental; it's very hard to avoid gluten, as we've already heard from our patient representatives about how difficult it is to avoid gluten in this gluten-rich environment.

The consequences of gluten exposure vary depending on whether it was a single event or short-lived symptoms and really not much of an excitement of the immune system. But as the gluten exposures get longer and longer, and indeed when it reaches decades of gluten exposure, then the consequences can be catastrophic for the patient with neoplastic transformation, severe neurologic injury, for example. So it is a spectrum of change over time and duration of gluten exposure.

How do we detect these? Most patients report them themselves. They admit to eating gluten even if they don't get symptoms. They will report accidental exposures based on symptoms that they experienced, but often collateral support for the actual gluten intake is not available. Perhaps

review of ingredients, admission by a food server, et cetera, might provide such collateral history clinically.

Objective patient testing is still fairly largely restricted to research circumstances, and we are really using serology and perhaps biopsies in symptomatic patients to identify those serologic or histologic consequences of gluten exposure.

Food analysis is really beyond what we're talking about today, but there was an excellent doggie bag study done by Dr. Silvester and colleagues, demonstrating a high rate of exposure to gluten in patients doing their best on a gluten-free diet.

Serologic monitoring is recommended at diagnosis, 3 to 6 months, 12 months, and then yearly thereafter or if patients develop symptoms. If it's persistently positive or one year or beyond on a gluten-free diet, it usually indicates gluten exposure and often predicts ongoing histologic damage.

Though serology lacks sensitivity for

damage, and of course the thresholds developed for diagnosis are not necessarily appropriate for healing or gluten exposure, there's a little data suggesting that a high-negative serology, or so-called detectable serology, may indicate a higher likelihood of damage than if the result is completely undetectable.

The management of sequelae, many exposures likely have little or no acute symptoms. Anti-diarrheals may help perhaps after the gluten has been cleared and after the first bout or two of diarrhea. Antiemetic drugs may be necessary for an acute exposure.

Reflux, dyspepsia, upper GI symptoms are common and may be managed symptomatically, and headaches, the typical relief of headaches with acetaminophen, et cetera. Weakness sometimes can lead to hypokalemia or dehydration, and rarely is hospitalization required for a celiac crisis in patients who are quite ill. Of course, long-term, it's managed by dietary intervention.

In summary, gluten exposures are common.

They're often recognized by patients. Consequences are variable and uncertain. Verification of the exposure has often been lacking, and in gluten challenges, symptoms often occur quickly, within hours, and histology may be dependent on dose and duration; for example, 2 weeks at 10 grams or 6 weeks at 3 to 6 grams.

Seroconversion is delayed for weeks of exposure, and symptoms often preclude a sufficient duration of challenge to be able to produce enough damage in clinical practice to make a certain diagnosis. Thank you.

DR. CARTEE: Thank you, Dr. Murray.

Our next presentation, we'll be learning more about the dose and the duration of gluten exposure that elicits clinical symptoms and signs.

Dr. Jason Tye-Din is a gastroenterologist at the Royal Melbourne Hospital and head of the Celiac Disease Research Lab at the Walter and Eliza Hall Institute in Australia. He runs a celiac research program and is committed to improving the advocacy and care of people with celiac disease.

Presentation – Jason Tye-Din

DR. TYE-DIN: Thank you, Dr. Cartee.

Thank you to the FDA for inviting me to be part of this very important workshop, and hello to everyone from Melbourne, Australia, where it's very chilly at the moment and very early in the morning. Please note my disclosures.

Gluten challenge has been used for a variety of reasons. We've heard very nicely from Dr. Murray its role in diagnostic evaluation. It's been very important in the understanding of the pathogenesis of celiac disease, and more recently in the preclinical development of novel therapies, and also clinical trials to assess these novel therapies, particularly when we're trying to assess protection from gluten-induced damage.

In the context of these clinical studies, gluten challenge is generally used at higher dose, for example, 3 to 6 grams, over a sustained period of time as opposed to a real-world setting, which may be intermittent exposure to gluten typically less than 1 gram each time.

There have been a large number of studies looking at the effects of gluten challenge in celiac disease that have used different amounts of gluten. Most have been from wheat; very few have been from barley or rye. But the doses and duration, the types of inclusion criteria, and readouts used have all varied.

This is a summary of some recent academic studies that have looked at gluten challenge and their effects on histology. You can see two figures here, the VHCD on the top and the IEL count on the bottom figure. These are means or medians from the publications just for the sake of clarity.

One of the striking findings that you can see here are that, at baseline, all of these studies had a VHCD below 3 and an IEL count over 25. Based on traditional criteria, this would suggest baseline disease activity.

Another striking finding, if you draw your attention to the 2-week trials by Dr. Leonard and Dr. Leffler, Dr. Leonard did show a very nice dose-response relationship between 3 grams a day

versus 10 grams a day -- so that's the blue line and the red line -- compared to Dr. Leffler's study, which was at slightly different lower-dose differences, which didn't show that difference. But he did note that at 3 days there were some early changes already present.

We can see a lot of the changes occurring by 2 weeks, but over a period of time you can see that inflammation does accrue, and you can see that on the lower graph with the rising intraepithelial lymphocytes.

This here is a summary of some more therapeutics trials from recent times which were performed under GCP conditions, so we can be confident these biopsies are well oriented and assessed by quantitative morphometry.

You can see very nicely in Dr. Lahdeaho's study, which had a dose ranging component there, that there's a very nice dose-response relationship, ranging from 1.5 grams up to 6 grams, and when that's plotted out, it's a very linear relationship. The authors did note that at

1.5 grams, the difference from baseline was fairly marginal. It was a weak effect, so they did end up going with a higher dose to ensure more consistency.

Again, we can see that most of the baseline values are below a VHCD of 3, and again we can see that there's an accumulation of damage with longer challenge duration.

The key messages, I think, from these last two slides are summarized there on this slide. Whilst there are several patterns that we can see relating to dose and duration, there still remains some heterogeneity between patients and studies.

Let's look at that in more detail. I wanted to focus initially on this issue of the low VHCD. I think that it's worth pointing out that a VHCD of less than 3 being abnormal has been based on very early work through general biopsies from healthy volunteers, but after discussions with people like Dr. Marco Mackey, he's reminded me that the actual cutoff for normal may be different using quantitative morphometry, and I think this is an

important point that will need to be discussed moving forward to establish the appropriate set points for normal.

Nevertheless, even if we accept a lower normal cutoff, we can see that there have been several clinical trials that have shown substantially lower VHCD, like the CeliAction study, which was admittedly symptomatic celiac patients, where 38 percent had to be a VHCD less than 2. But in a more recent RESET-CD Nexvax 2 trial of well-treated celiac patients from the United States and Australasia, there were 60 percent of participants at baseline who had a VHCD less than 2, and the majority of these participants had normal celiac serology.

The authors of this study highlighted also the fairly complex relationship, the nonlinear relationship between villous height and crypt depth, which changes depending on the continuum from healing to injury. I think this comes back to one of Dr. Robert's points around whether we talk about villous height crypt depth or just think

about something like villous height alone as a readout.

More recent studies have also shown that even in mucosal biopsies that look normal, there is an altered transcriptional profile. So what does this all mean?

Well, in a very important study performed on the patients who were involved in the 2-week gluten challenge study by Dr. Sarna, they showed that the histologic responders to a 2-week gluten challenge all had evidence of baseline disease damage; so tissue inflammation and higher levels of gluten-specific T cells in the actual intestine. And these are the cells that drive celiac disease; they're the causative cell. This has been supported by some other studies showing higher immune responses to gluten in those patients who had baseline disease activity.

So the implication may be that a longer duration of gluten challenge may be required to fully expand these gluten-specific T cells in order to get consistent mucosal changes.

Looking at these different causes of histologies, dose and duration are clearly important factors. Other issues include how do we measure gluten, and it's important to control for that. Currently, there's no international reference standard for gluten, so there's a real acknowledgement of the need to harmonize the analytical approach to measuring gluten.

Food matrix effects are likely to be very important and should be accounted for. We've heard very nicely about the role of where you get biopsies from; what we might take as the appropriate histologic parameters to measure villous atrophy; and how quantitative morphometry is performed and who's doing it.

I've touched on the issue of baseline disease activity, but there's also likely to be other issues like biological variation between patients, and that may be affected by the patient's HLA or other genetics and possibly even sex or age, although that's been less looked into; and then of course medications can have an effect as well.

This slide really is a summary of therapeutics trials and the examination of symptoms, and you can see here that there's been a range of different gluten challenge formulations, doses, and durations used in these studies. Some of them have used the placebo gluten arm as well, and the patient-reported outcome measures or the instruments used in these trials have also varied.

When we look at symptom readouts, there's some variability between what's being recorded, but what is quite apparent is that symptom onset is fairly rapid and it tends to increase over time. You can see here in some of the studies, these increase and then plateau. In one study it increases and then drops off. In terms of tolerability, generally well tolerated, but there were dropouts at certain doses, but it wasn't always consistently a dose-response effect for dropouts.

I'll draw your attention to the bottom study, which used a slightly different design to all the other studies in that it was a single-dose

challenge of 11 grams of gluten, which turned out to be around 10 grams that the participants were consuming.

They showed in that study that vomiting was a major feature; probably a result of the higher-dose challenge that was used. It's interesting to note that patient-reported outcome measures don't typically include vomiting as a measure. Nausea was also a very important readout that correlated more with gluten exposure than with a placebo gluten exposure. Symptoms would peak after around 2 or 3 hours of the gluten ingestion, so this was fairly rapid onset symptoms.

Let's look again at causes for heterogeneity. Again, we need to think about the dose and duration of gluten and think about food matrix effects and other issues around the taste and formulation of the gluten challenge. I think it's really important -- and this is to build upon some of the comments Dr. Murray made about patient-reported symptoms not always being driven by gluten.

Of course, patients have very real symptoms that are distressing, but we know that sometimes the genesis for these symptoms is not necessarily gluten. Irritable bowel syndrome occurs commonly in celiac disease, and that can be triggered by non-gluten wheat components like fructans, which is a type of fermentable carbohydrate, also known as a FODMAP.

So it's very important that we control for FODMAP contained in the gluten challenges, and we need more data on what do FODMAPs do in the absence of gluten when people with celiac disease consume them.

Another interesting finding from the Nexvax 2 trial is that when patients were asked what they were expecting to experience after gluten, it was often that they were expecting something like diarrhea. But when going through a double-blind gluten challenge process, it was actually very different what they ended up experiencing, and it was really only nausea and vomiting that were strongly linked to gluten

ingestion.

So it's very possible that the symptoms they were expecting may not reflect from past history true gluten-related symptoms. It possibly may in some cases for some patients, but at least for some other patients, it may reflect other issues such as irritable bowel syndrome.

So I think this is very important that patient-reported outcome measures do depend on patient report, and that's obviously very important, but I think that in the design of PROs, it's very important that we ensure that the symptoms being attributed to gluten are indeed being driven by gluten. Another point there is that a screening challenge can be quite useful to help define symptomatology.

In terms of in the nocebo effect, this is where a person is given a non-gluten-containing challenge but actually develops symptoms, and we have very little data on that. There have only been several studies that have employed a double-blind, placebo-controlled gluten challenge,

and also dr. Dr. Lahdeaho's study did it during leading [ph] as well.

It didn't seem to show a lot of effect, but I do think that there's more data that's required. Clearly, the nocebo effect will be impacted by the patient's level of anticipation of the likelihood of the gluten exposure occurring and the amount of gluten they may be exposed to.

One interesting observation, which again I think needs more data to support it, was that in the Nexvax 2 trial, when participants were given the same dose of gluten, again, 5 months later they actually developed more prominent symptoms than the first time. So there was a doubling in the number of participants who vomited with the same-dose gluten challenge the second time around, with a much stronger immune response as well.

So it raises the possibility of a boosting effect, and certainly that is sometimes anecdotally observed, but I think more data is needed on that. We also need more data on the effect of baseline disease activity on gluten-induced symptoms similar

to how it can impact histologic changes.

Immune readouts, they're not the basis for regulatory approval but can provide very important complementary data. Celiac serology does have a gluten dose-response effect, although this appears to be variable, as you can see with the references I've provided on the slide.

Gluten-specific T cells are really the driving pathogenic cells in celiac disease, so measuring these can have several roles in the context of the clinical trial.

Dr. Bob Anderson was the first to show these gluten-specific T cells are actually measurable in the bloodstream 6 days after commencing a 3-day oral gluten challenge, and more recently there have been a range of sophisticated techniques that have allowed these cells to be detected without the need for a gluten challenge.

More recently, it's been shown that an interleukin-2 cytokine signal, measurable in the bloodstream 3 to 4 hours after a person with celiac disease consumes some gluten, is also a very strong

marker for gluten-induced activation that's only seen in people with celiac disease. And interestingly, this seems to be the first biomarker that correlates closely with the onset and magnitude of the symptoms people with celiac disease may experience to gluten challenge.

Again, I'm showing this slide that Dr. Murray showed because it is an excellent study from Dr. Leonard and Dr. Silvester and colleagues, and really here, there was a comparison between 3 grams daily of gluten versus 10 grams daily of gluten over 2 weeks. One of the striking take-home messages is that at the lower dose of gluten, the interleukin-2 signal at 4 hours remains a very early and consistent readout, whereas many of the other readouts required higher doses.

I think it raises the possibility that these kinds of immune readouts can be very helpful in clinical trials, particularly when you don't want to give large doses of gluten.

At the end of the day, I think our goal is really how do we measure gluten-induced effects

reliably so that a claim can be made? I think in order to do that, a standardized and controlled approach to gluten challenge will be essential to minimize sources of heterogeneity, and we really need to lock down the optimal readouts.

Understanding the baseline healing rates I think is very important, and I think it raises a very interesting question that if there is substantial baseline damage, there probably isn't really a need to do a gluten challenge. And in some ways a better question may be, well, can this therapy improve upon standard therapy if there's already damage present?

Another aspect of baseline damage is how can that information inform stratification within the design of your clinical study?

Another point to make is that gluten challenge PROs are needed. Currently none have been designed and validated for taking into account a gluten challenge design. I think when these are developed, it's really important that we take into account the impact of a double-blind gluten

challenge and possibly even corroborating that with objective immune readouts. There are no PROs in the pediatric population, so this is clearly an important need.

Also, we need to consider that some patients with celiac disease suffer from extraintestinal symptoms, and we need to be able to capture that. I think ultimately we can optimize, validate, and incorporate some of these gluten-specific immune readouts into our clinical trials and we can substantially improve the quality of the research. Thank you.

DR. CARTEE: Thank you so much, Dr. Tye-Din, for talking about different doses that induce symptoms and immune responses in celiac disease.

Last but not least, we'll be hearing about the industry perspective on the role of gluten challenges in clinical trials. This presentation will be given by Dr. Dan Leffler, who is a gastroenterologist on faculty at Beth Israel Deaconess Medical Center and Harvard Medical School in Boston. He has published widely on clinical and

translational aspects of celiac disease, and he currently serves as the global clinical lead for celiac disease at Takeda Pharmaceuticals.

Presentation – Daniel Leffler

DR. LEFFLER: Thank you very much for the invitation, and congratulations, everyone, agency and organizing committee, on a wonderful meeting so far. Let's go on to the next slide with my disclosures.

Although I was tasked with giving the industry perspective, I actually wanted to start with a patient's perspective, and this is something that was said at a recent workshop, where a patient had been in a clinical trial said this, "Studies with gluten put more burden on patients, and investigators need to have the knowledge and resources to help with any issues. However, as much as I really didn't love having to eat gluten for a study, I don't think I would really trust the results of a study without gluten since I wouldn't know what it was treating or how much it would protect me from."

I think this really nicely encapsulates the issue. We're all here today because we want to improve the lives for patients with celiac disease and their families, and asking people to eat gluten can sometimes feel a little counterintuitive, but at the same time I think there's wide recognition that in order to make scientific progress in this field, we do need to use gluten sometimes. And really the question is, when and how can we use this most responsibly?

I just want to use this as a reminder that gluten exposure and gluten challenge is not a new thing. It's been with us since the very beginning. On top is the initial description of celiac disease by William Dickie, where you see a growth chart of a patient on and off of a gluten-free diet.

We also have these earlier guidelines on celiac disease, that Dr. Silvester showed as well, saying at least through the 1980s, gluten challenge was used in basically everyone who was diagnosed with celiac disease. As you can see here it says, basically, "the only decisive criteria for celiac

disease includes small intestinal damage, normalization on gluten withdrawal, and the reaction on reintroduction of gluten," so this is not a new phenomenon.

The upside of this is that we really have a wealth of experience, both in research and in the clinic, showing that monitored gluten exposure is generally safe. I really do want to emphasize the monitored. This is clearly not a license for everyone to go out and eat gluten. It's really saying that under the right clinical monitoring that gluten challenge and gluten exposure studies can be safely performed. That doesn't mean they won't cause symptoms, though.

This list overlaps a lot with what Dr. Murray showed. Gluten exposure in a study can cause symptoms both in gastrointestinal and extraintestinal; immune activation; elevations in celiac serologies; and small intestinal mucosal injury, as we just saw from Dr. Tye-Din.

However, I think it's also important to call out what gluten exposure in a study or in a short

gluten challenge for clinical reasons will not cause. It will not cause an increased risk of long-term complications, it does not cause permanent damage to the small intestine, and it does not cause ongoing symptoms after the study is complete. In fact, the symptoms we probably have the best data for, most patients are back to baseline within 2 or 3 days after completing a gluten challenge.

I do also want to just call out that there are cases -- and this is almost the same list as Dr. Murray presented -- when gluten challenge is not recommended, if people are pregnant or planning on pregnancy in the near future, if there's a severe celiac-related neurologic condition, or in type 2 refractory celiac disease.

So I was asked to give a couple of lessons learned from celiac disease clinical trials to date, and I think there are a lot of them. I think we've learned a great deal, which is always nice, so let me highlight a few of these; the first one being that we can actually predict protection from

gluten-induced immune activation based on known celiac disease pathophysiology and the effect in animal models.

This is something that not every disease is lucky enough to be able to say, and I think we've shown that with a really good track record of taking things from the bench and at least through gluten challenge studies showing that we can protect against gluten exposure when we understand the mechanism of action of the drug.

At the same time, I think we have to recognize that therapeutic effect in gluten challenge is going to be really difficult to reproduce when we're trying to treat active celiac disease in more treatment-type trials, phase 2B or beyond, and this is due to a couple reasons; firstly, a very large clinical trial effect, and I'm going to talk about that in a little bit.

But also, it's actually really hard to confirm when ongoing symptoms in somebody with celiac disease are due to celiac disease and due to gluten and not due to another underlying issues

such as irritable bowel syndrome. This is a big problem in clinic, it's a big problem in clinical trials, and unfortunately not one that I really see a solution for up and coming. And of course we also unfortunately still have fairly high rates of misdiagnosis of celiac disease.

I agree completely with everything Dr. Tye-Din just said about we've learned the histologic responses in both gluten dose- and duration-dependent, but there is probably diminishing returns after you get to a certain duration and a certain amount of gluten.

Small intestinal mucosal assessment is critical to understanding the effect of therapy, but as we heard in the first session, there are a lot of questions remaining about interpretation. We've also learned that histologic and symptomatic response to gluten challenge is highly variable, and this includes both the patient heterogeneity and inherent limitations of the assays. I put here histology, but it's also limitations in the PROs, which are not perfect instruments. They don't

cover all symptoms, as we know.

But importantly, it appears that it's not due to the source of gluten. We can expect about a 10 percent dropout rate due to gluten-related symptoms. This is usually, as Dr. Tye-Din said, very early within the first few days of exposure, and this tends to occur after you get to about a gram of gluten per day, but it doesn't appear to be highly dose-dependent after that.

Finally, I think all of the studies that Dr. Tye-Din just showed illustrate the last point really nicely, is that patients are engaged. This is an important disease. People are willing to participate in celiac disease research even when there's gluten and even when there are invasive procedures and multiple visits. However, on our side, or on the clinical trial side, whether you're an academic investigator or an industry sponsor, it's really our responsibility to provide appropriate support and monitoring for patients.

So with that, I want to go into two different forms and ways of using gluten in

clinical trials. The first one is the more classic one. This is almost all the data that Dr. Tye-Din just showed us on gluten challenge. This is defined as daily high-dose gluten exposure, usually 3 to 12 grams per day, with the aim of exacerbating disease activity, at least in a placebo arm.

The uses of this are to study the pathophysiology of celiac disease and help us develop new biomarkers, and in drug studies for proof of concept and sometimes dose-finding studies, just ensuring that a therapy that we're bringing to clinic can actually protect against gluten.

On the other hand, we have this relatively newer form of study, although it has been around for a while in different forms, where you actually are giving something we are now starting. It's called simulated inadvertent gluten exposure. This is defined as intermittent low-dose gluten exposure, a couple hundred milligrams of gluten a couple times a week, so an order of magnitude, at least.

The goal of this is to make it equivalent to accidental exposure in the real world. The aim of this is to help us understand if a therapy might have efficacy in real-world exposure-like settings. The uses for this, in later stage therapies, are their ability to protect against real-world, accidental gluten exposure and reducing clinical trial effects that lead to reduced gluten exposure; and again, I'll show you a little data on that in a minute.

Just to show what these look like schematically, here's a traditional gluten challenge study. These are typically small studies in patients with well-controlled celiac disease. They're given a fairly significant amount of gluten each day for 2 to 12 weeks. The primary endpoint of this is really protection from worsening of intestinal damage for a therapeutic trial, with a secondary endpoint usually of symptoms.

The reason for this is partially the nocebo effect, as was just illustrated, but also because we know, and it's sort of intuitive, that if

somebody knows they're going to get really sick, they're not going to sign up for this trial, so it actually selects for less symptomatic people. For these reasons, I think the objective endpoints like histology and biomarkers are really appropriate for gluten challenge studies.

On the other hand, you have gluten exposure studies or these simulated gluten exposure studies These are larger and longer studies using, again, much less gluten, half a gram to a gram of gluten per week in divided doses.

In this, the inputs are very different. It's not protection from worsening or even intestinal damage, but you actually are looking for improvement in signs and symptoms of celiac disease as your primary endpoint with a secondary in most cases of improvement in intestinal histology or improvement in other modalities.

These are longer studies, and I completely agree with what Dr. Lebwohl said earlier. These are 6 months to a year. I don't think we really know the perfect time for these studies, but this

seems appropriate looking for these types of changes.

I want to talk a little bit more about the rationale for these inadvertent gluten exposure type studies. As we've heard already today, most therapies under development are aimed to protect against disease activation due to accidental gluten exposure, and people are doing their best on a gluten-free diet. This is a large part of the celiac population.

But we know that major lifestyle changes, such as participating in a clinical trial -- and I would note at least anecdotally -- and living through a pandemic actually reduced gluten exposure.

This was actually illustrated really nicely by Stefanalo, et al. in a Clinical Gastro and Hepatology paper earlier this year, where the only intervention they had was to tell people to collect stool and urine so they could look at gluten. Gluten exposure was low in the beginning and rose slowly over the course of the study, suggesting

that there was this monitoring effect where people changed their behavior. I think in a more typical clinical trial, which is much more rigorous, this effect is only going to be much greater.

This risk of clinical trial-related reduced gluten exposure gives us two risks in understanding what a therapy may or may not do. The first risk is that a therapy is shown to be effective in a clinical trial but against the reduced amount of gluten that people are exposed to in the setting of the trial, but really is ineffective against higher real-world exposures. The results of this would be a drug could be approved, but later is found to be ineffective.

The second risk is just the opposite. The therapy appears to be ineffective in a trial as residual symptoms in a background of reduced gluten exposure and less likely to be gluten related, but may actually have been effective in a real-world setting where people have higher gluten exposure, then symptoms are more likely gluten related. In this case, a drug may not be approved, which may

actually have had clinical benefit. I think, obviously, in the celiac community, I think both of these outcomes are ones we would like to avoid.

There are a few operational considerations I wanted to talk about regarding the use of gluten in studies. Many of these have been mentioned, so I'll go over these in brief.

First of all, slower enrollment due to concerns with gluten exposure, I think this is a place where we need to be realistic, we need to have more education, but really, I think our best tool in the toolbox for this is close partnership with our patient advocacy groups to help us provide advice on study materials, and recruitment strategies, and overall education of the celiac community.

There's a potential for missed gluten doses confounding data analysis, and I think we need to emphasize the need to follow all study procedures, but I think we need to monitor gluten compliance similar to how we do for drugs. That's not been something that we've done in all trials in the

past. Dr. Murray already mentioned the use of objective gluten exposure tests, which we may want to consider.

We need to plan for some degree of dropout due to gluten-related symptoms. I think this could be mitigated, to some extent, through site an investigator training. But we also need to ensure adequate study power, and we need to think about the right way to handle missing data when people drop out related to gluten effects.

As Dr. Tye-Din just mentioned -- and I won't belabor it further -- we do need more standardization of gluten amount and form. However, I will note that, conversely, the source of gluten, whether the gluten's from Australia or North America, doesn't seem to make any difference. Gluten is gluten, but how you give it and how much you give can make a big difference.

To conclude, I think maybe just to start, I think the whole point of these workshops show that we really don't know what the optimal design of celiac disease trials is that will give us

confidence that the results of the trial, if positive, will translate into meaningful benefit in the real world.

So I think we do need flexibility at this stage, but I think we also need to start thinking about once drugs are approved, what else should we be setting? What postmarketing studies are appropriate to really confirm that the studies we use are actually translating? Maybe that's a topic for GREAT VIII or whatever in the future, but I do think that's a topic that the field will have to wrestle with.

I think gluten exposure is a vital tool in celiac research and therapeutic development, but when and how to use it really does require careful consideration. It can be highly valuable in assessing protection from the effects of gluten in many phase 2 and I think phase 3 studies, but it will be generally not needed or even counterproductive in phase 1 studies, or open-label studies, or postmarketing studies.

Interventions, as we've heard, can have

differential impact on histology versus other endpoints. I think histology is critical now, but as many others have said today, and I completely support, I do hope in the future we'll be able to move to less burdensome and less invasive technologies.

Finally, I think gluten challenge studies, these precipitation of damage studies, really do need to be differentiated from gluten exposure studies, which are maintenance or simulation of real-world conditions.

Gluten challenge studies remain the most efficient design for proof-of-concept studies and can assist with dose ranging, whereas gluten exposure studies I think may improve our confidence, but the results of studies, of treatment of ongoing active celiac disease, actually will translate to real-world benefit.

So again, thank you for your attention, and I look forward to participating in another engaging panel discussion.

DR. CARTEE: Thank you so much, Dr. Murray,

Dr. Tye-Din, and Dr. Leffler. I'm expecting a spirited discussion when we come back from a 10-minute break. Let's resume at 2:30, please.

(Whereupon, at 2:21 p.m., a recess was taken.)

Panel Discussion and Q&A

DR. TOMAINO: Okay. I'd like to welcome everybody back for our final panel discussion. I'd like to welcome and thank again, Dr. Murray, Dr. Tye-Din, and Dr. Leffler. In addition to myself as the moderator and Dr. Cartee, we are welcoming our additional panelists for this session. I'm going to briefly introduce myself and turn it over to Dr Cartee, and then we will ask our panelists to please briefly introduce themselves.

Again, I'm Juli Tomaino. I'm the deputy director of the Division of Gastroenterology at the FDA.

Dr. Cartee?

DR. CARTEE: Thanks, Juli.

Amanda Cartee, University of Alabama, Birmingham.

We have Irena Lavine.

DR. LAVINE: Hi. Irena Lavine, medical officer in the Division of Gastroenterology at the FDA.

DR. CARTEE: Dr. Ben Lebwohl?

DR. LEBWOHL: Ben Lebwohl, Celiac Disease Center, Columbia University.

DR. CARTEE: Dale Lee?

DR. LEE: Dale Lee, pediatric gastroenterologist, director of the celiac program at Seattle Children's Hospital, University of Washington.

DR. CARTEE: Dr. Francisco Leon?

DR. LEON: Hi. Francisco Leon. I am the chief scientific officer of ProventionBio. I am a drug developer in celiac disease, have founded Celimmune, Provention, Glutenostics, worked at Alba Therapeutics, and have conducted a few gluten challenge studies. Thank you.

DR. CARTEE: Ms. Kelsey Smith?

MS. SMITH: Hi. I'm Kelsey. I am a celiac patient. I've been diagnosed for six years. I've

participated in one study for a little while, and I live in Washington, D.C.

DR. TOMAINO: Great. Thank you again. And specifically, thank you to Kelsey for sharing your story with us.

Let's start by talking about -- we've heard various perspectives on the gluten challenge from our speakers. We've also heard through various channels, including here today, that patients are hesitant to enroll in a clinical trial that has a gluten challenge, and this is one of the reasons why we're having a workshop like this. We do hear your concerns, and it's something that we don't take lightly; so let's get into this discussion.

Really, the crux of this session is to help understand when and why would a gluten challenge be necessary, meaning that the necessary information cannot be answered by alternative means.

Maybe I'll open up to Dr. Lebwohl to take that question first.

DR. LEBWOHL: I think we learned in a difficult way that without introducing gluten and

allowing for as much of a real-world experience as possible, we run a great risk of a type 2 error; in other words, of a medication that may work against gluten-induced damage but there's no gluten around.

Even though we hear that gluten is everywhere and patients are exposed to low levels of gluten frequently, in the context of a randomized trial, people's behavior might change and they may not be exposed to enough gluten to observe a biological effect. That seemed to be the case -- at least the explanation -- for the negative result of, for example, the Latiglutenase phase 2 trial, and we don't want to repeat that same exercise.

So introducing gluten, whether in the context of a formal challenge or in what Dr. Leffler was suggesting as a sprinkling or intermittent exposure setting, seems to be our best chance of showing that an effective drug is effective.

DR. TOMAINO: Thank you.

Dr. Lee, maybe you could share the

perspective from a pediatric gastroenterologist, hearing some of the presentations and the discussion about the utility in a pediatric trial, for example.

DR. LEE: Yes, absolutely. Thank you. I very much agree with the presentations from before, and I agree completely with Dr. Lebwohl. If we're going to be concluding efficacy of a drug, we have to know what the exposure is. If there is no certainty of the gluten exposure, you cannot conclude efficacy of a medication here, so you have to be able to control the exposure.

I have to bring up a point. When I heard Dr. Fasano's discussion earlier, I really appreciate his opinion about the concern about giving a gluten exposure to a child because of concern for growth. I will have to respectively give a different perspective.

In my opinion, children and the growth concern is precisely the reason why we have to get these medications tested and approved in children so that we can prevent this complication.

As Dr. Leffler nicely demonstrated with his data, we don't have certainty that X duration of a gluten exposure will end up with a long-standing clinical complication. I think it is extremely unlikely, with a short-term gluten exposure, for the correct population chosen in pediatrics to have significant side effects. I think appropriate exclusion criteria need to be considered. But in my opinion, I think that a gluten challenge absolutely plays an important role for children, and I would advocate for it.

DR. TOMAINO: Dr. Leon, from the industry perspective do you have any other thoughts, anything additional to share, in addition to what we heard from Dr. Leffler?

DR. LEON: Thank you, Dr. Tomaino. I completely agree with my colleagues and everything that has been said. Just to bring forth a few points, celiac disease is a bit behind the other autoimmune diseases in terms of therapy, but we do have this advantage that it was the first autoimmune disease where a trigger was found. It

is a target organ that regenerates, and we know that up to 12 weeks of exposure have no long-term consequences. We know that we can use these gluten challenges to accelerate research, especially in early development, so I agree that we just need to continue to standardize the studies and make them safe for patients.

There are ways to prevent undue burden. If a patient has excessive symptoms, the patient can drop out, and that gets appropriately quantified as a treatment failure, statistically. I think they provide extremely helpful go/no-go decision-making tools for our clinical trial development.

MS. SMITH: Just from a patient perspective -- obviously, I'm not a doctor and I don't understand that side of it -- I get the hesitancy from patients to undergo gluten challenges. But if I'm being presented a drug, and the manufacturer is saying, "Oh, this will make you feel better if you ingest gluten," I would trust that more if they had studies that showed this is the ingestion of gluten and this is the impact on

either your symptoms or the histology and the effects on your actual intestines.

DR. CARTEE: Thank you so much for that insight, Ms. Smith. Just to follow up on that, are there certain amounts or durations of gluten exposure during a clinical trial that might sway you to participate or not to participate?

MS. SMITH: I think the most important thing to underline here is the education of what's happening during the study and the impact. For me personally, when I was diagnosed, my gastroenterologist told me to go Google celiac disease and I would soon know more than him, and my initial response was absolutely no gluten ever for any reason because I will get cancer, because that's what I read when I Googled it. That's what you see on the forums and that's what you see on Facebook, not from people who study the disease and who understand the actual impact.

So honestly, it's been through this research that I've had through the Celiac Disease Foundation, or from listening to studies from some

of the researchers and medical professionals here, that I've understood that there's a difference between the long-term ingestion of gluten and a shorter-term monitored ingestion of gluten.

So having an actual medical professional walk me through what that would look like and having a trial that would allow me to better accommodate having these symptoms in my day-to-day life would definitely motivate me more to participate in something that had a gluten challenge.

Additionally, speaking with people who've gone through it in the past and who talked about their motivations and the reasons why have also swayed my hard stance of I will never participate to, okay, that's something that I would be willing to investigate, because knowing that you are making a difference for the people that come after you, people like Beckett and future children, is way more motivational when I have a medical professional saying here's how I'm going to guide you through it.

Then just that flexibility and understanding that these symptoms, they come on quickly, and they can impact you even beyond the 2 to 3 days that you're seeing in some of these studies, and understanding that might not be something that everybody is capable of, but there are people who can do that, and there are lifestyles that can accommodate that if the study is able to have that level of flexibility and understanding of where they're coming from.

DR. LEE: If I might add to what Ms. Smith mentioned, I think that's such a poignant description of the patient perspective. One thing that stood out to me, you mentioned for the generations to come.

Our celiac patient community is really unique in that they are invested in supporting each other because this is something that greatly impacts their future children, their future generations, as well as a huge community and families around them. So the desire to come together and try to do something for the better of

the whole, I've been so impressed by that, I think, clearly from an adult perspective, different, but from a child's perspective as well, too.

I think to discount children as being able to make some of these decisions and wanting to enroll, I don't want to speak for them. I'd like to give them the opportunity. My hope would be that in the design of future trials, it would be thought that either adult data would extrapolate to pediatric approval, either that or, a priori, there would be pediatric inclusion in the study design.

For example, I think age 12 to 17, which is adolescent, is very different than the younger children. So being able to at least involve that age group would be hugely impactful because such a large majority of onset of celiac disease is in this pediatric age range.

DR. CARTEE: Great.

Maybe we can hear a little bit more from industry or some of the other providers who have enrolled in prior clinical trials about what kind of discussions you have with patients.

Francisco, you were just getting ready to speak, so I'm sorry for interrupting you.

DR. LEON: No, no, no. I was actually thinking that, indeed, industry can adapt these studies, and should adapt these studies, to the mechanism of action of the drug and to the patient population to be studied in consultation with regulators. It's very different to use a short, high-dose, pure gluten challenge, than a much milder gluten baked-in-food, longer-term challenge that just increases symptoms gradually over a period of many weeks.

Obviously, we need to explain very carefully the expected effects to volunteers so that they can determine if that's the right study for them. They may prefer a short study that might knock them out for a couple days versus a 10-week much milder gluten challenge.

But I need to emphasize that regardless of the type of study, all of these studies offer answers because we've learned enough. We have all of these tools that we're presented, from

experimental assessments to the validated patient-reported outcomes, to understand if a drug has an effect or not and if it is safe or not when provided with gluten.

That may help us discard early drugs that should not be developed and avoid exposing many more patients in much longer studies to drugs that perhaps are not as promising.

I do think that there is a big role for these studies. They are done in other areas as well. As you all know, there are allergy challenges and allergy infectious disease challenges to test vaccines or stress tests for heart disease. So it's not uncommon to come up with a design that will advance the field while prioritizing patient safety, which is paramount.

DR. MURRAY: If I could make a comment -- if that's okay -- about the issue of persuading patients or discussing with participants, potential participants, about gluten exposures or gluten challenges, I think it's different.

If you're talking to a patient who is doing

well and you're talking about a deliberate gluten challenge, I have a lot of willingness among the participants who really want to engage to help others.

On the other hand, when I meet a participant who has been enrolled into a trial for symptomatic individuals, and I talk to them about deliberately being exposed to gluten, I see a lot more hesitancy and concern about that because they already have symptoms.

I'm also thinking about it in a way of does this help us, these gluten exposures, identify the symptoms that are related to gluten as opposed to symptoms that are not related to gluten in a trial, and is that a way, perhaps, of persuading -- I don't want to say persuading but maybe engaging with participants who have symptoms.

But that group of symptomatic participants I think are quite different. They're looking for relief, and they accept they might get placebo drug. But the idea that they might get gluten, I think, causes a lot of concern among at least some

of them.

DR. TOMAINO: Dr. Murray, you actually set us up perfectly for a question that was coming to mind. And maybe we could continue the discussion that we're having to hear the perspectives of how you've each handled or addressed enrolling patients in trials or in research that has a gluten challenge.

But also your thoughts of the concern that Dr. Murray just mentioned, that the more symptomatic patients might not be willing to participate in such a trial. So that could lead to ascertainment bias, for example, and what can be done to address that.

DR. LEFFLER: So I'll take a stab at that. I think these are critical questions and I think there is a lot we can do. I think one thing that we should always do, whether this is a clinical trial or whether this is a gluten challenge for a clinical reason, is to explain to patients what monitoring will be done. What is a recourse if they get sicker; if they get severe symptoms? How

will they be able to stop the medication? Are there rescue medications we can use? Those discussion really do help, I think, explain and reduce the risk of ascertainment bias.

I also think there's temporal trends in people's willingness to do these trials. What I mean by that is there are things external to their symptoms that make people more less likely to participate in a trial, especially where it includes gluten.

A 20-year-old about to go into their exams in college, probably not a great time. I had somebody in clinic who had an equivocal diagnosis of celiac disease and was going to do a gluten challenge, but then was, "Oh, by the way, I'm getting married in two weeks," probably not a great time to do a gluten challenge.

So I think if you're really talking to patients about what the concerns are, whether it's things external to their disease process or just their symptoms, I think a lot of that can be mitigated. But again, I don't know that we've

always done the best job of giving, as sponsors giving investigators the tools to do that well.

DR. LEON: I still think that bias is definitely there. When we think about it in the context of early development, it is just an additional risk. It adds uncertainty to translate the results of the phase 1 or phase 2 into future phase 3 results. It's a risk for the companies, really.

But still, the trial as long as it controls the amount of gluten, compliance with the challenge, and uses the right instruments, it will be able to provide a mechanistic answer. Does this drug address the disease pathophysiology or not? Can it address inflammation? Can it address symptoms?

Then the big question is that the other types of design that Dr. Leffler spoke about, the simulated inadvertent gluten exposure that might be used in late-stage development potentially as a confirmatory study, for example, in that case, ascertainment bias might be much more of a

challenge where it might limit the patient population that is being studied. It might limit the label.

So I think what this means is that we cannot rely entirely or solely on these type of trials. We need to combine gluten challenge studies, gluten exposure trials, natural course of the disease studies, and natural exposure studies to provide the totality of the data on whether a drug is having a benefit and what the risks are.

DR. TYE-DIN: Could I just add a quick comment to echo Dr. Leffler's remarks about having a great discussion with the participant? I think that's so crucial.

If you advertise for a trial and say that there will be a gluten challenge involved, that can alienate people up front and put them off. So I think if you can actually have that sit-down with them and provide relevant information about the potential short-term symptoms they may experience, how any of those symptoms will be managed, and any of the long-term effects, I think that goes a long

way to mitigating the risk of ascertainment bias, and you can get a lot more people in that way.

What I've found as a very interesting observation is that many people who believe they are highly sensitive to gluten exposure, when they end up participating in studies, and often are given a purified form of gluten that is low in FODMAPs, for example, they may actually be minimally symptomatic. And they're actually really surprised that their expected symptoms are very different to what they actually do experience.

MS. SMITH: I think the other thing I would add to this is, again, it's not necessarily something you can control for in a trial setting, but just the understanding that patients would be more willing to participate in this if they had more education from the very beginning.

The hesitancy and the not wanting to participate is because of what we've learned about what gluten does to our bodies and not necessarily because we don't want to participate in a clinical trial. That just speaks to the overarching

misunderstanding about celiac outside of the celiac community; so if you're diagnosed by a gastroenterologist who doesn't necessarily understand celiac or who only sees one or two patients a year.

DR. TOMAINO: Thank you for that.

I'm hearing, obviously, that communication with the patients is really important, and education particularly upon enrollment into the clinical trial, explaining what's going to happen in the trial. Why are we doing this? Why is this necessary? How are we going to keep you safe? That's all very critical.

One question that came up was the concern that patients are going to become symptomatic and will drop out from the trials that have the gluten challenge. Dr. Tye-Din had a really nice summary table that showed, overall, a low number of dropouts. It was a descriptive summary, so I don't know the specific numbers. Then Dr. Leffler shared that there's about 10 percent based on the industry experience.

Of course some patients experience symptoms very quickly and more severe. Is there some thought that maybe that isn't fully due to celiac; maybe there's an allergic component? And what are your thoughts on the ways that trials could be designed to enroll the appropriate patient population, and then also have appropriate safety monitoring to try to prevent that from happening?

DR. LEFFLER: Let me actually -- oh, sorry, Jason. Go ahead.

DR. TYE-DIN: No --

DR. LEFFLER: Alright.

One interesting thing we've learned, which we didn't know 10-15 years ago is that symptoms change over the course of a challenge, and within the first day or two, people can get severe nausea and vomiting, and I think Dr. [indiscernible] and Dr. Anderson's work shows this really nicely. Then if they continue on, they make it past that, their symptoms actually change to more lower GI, abdominal discomfort and diarrhea type symptoms, and I think those are easier symptoms for people to

persist with, even if they're unpleasant.

I think this is why we see early dropouts and not late dropouts. It's not because it's allergic or a different disease pathophysiology, but I think the progression of symptoms with acute exposures changes over time as those exposures become chronic.

Maybe I'll let Dr. Tye-Din answer the second part of that question.

DR. TYE-DIN: One of my comments was just going to be that, typically, we might see, after an acute gluten challenge study with a single dose, symptoms occurring at the earliest around 30 minutes, but typically around the 2 to 3-hour mark; that would be really reaching the peak in the most symptomatic patients.

But if we're talking about symptoms within minutes of exposure, that would be atypical for gluten and that would raise the possibility of an alternative cause, like an allergy. But certainly in the single-dose gluten challenge studies, the rise of symptoms were very nicely paralleled by the

increase in circulating interleukin-2. So there was a very good correlation between the magnitude of the interleukin-2 rise and the severity of symptoms such as nausea or vomiting.

So I think that that would confirm that these symptoms are likely to be gluten specific and relevant to the celiac disease.

DR. LEBWOHL: I would say that the observation in the Nexvax data, that nausea and vomiting was so prominent, really speaks to the quantity of gluten at the outset being an important determinant of what kind of symptoms the subjects, patients, get.

I was wondering if maybe a ramp-up in gluten content would attenuate these acute symptoms and allow for a longer or more sustained challenge and fewer dropouts. It's not something that I've seen in gluten challenge studies. In clinical practice, we do it. I learned that from Joe Murray. He taught me like 10 years ago to start with a corner of a slice of bread. I'm wondering why we're not doing more of that in our gluten challenge studies.

DR. LEON: Yes. An alternative as well along those lines is to do a run-in period with placebo gluten. For example, if you provide gluten in cookies -- and this is what we do with our friend, Marco Mackey -- you bake the cookies first without gluten, provide them to patients for 1 or 2 weeks, and then introduce the gluten-containing cookies. That initial run-in period takes care of non-specific effects of the gluten challenge and a lot of psychological effects.

On the first few days, patients report symptoms of celiac disease that are obviously not related to gluten because there's no gluten in the cookies, but you see a dramatic change. Once the real gluten is introduced, those symptoms now increase substantially and keep peaking for up to 6 to 8 weeks, as has been described in the slides presented by Jason.

So there are several ways to make sure that the symptoms are really due to gluten. You measure gluten consumption and excretion to make sure the patients are actually taking the gluten and not

discarding it, and you keep a very low bar for the patient withdrawing from the study. We don't want anybody to go beyond a reasonable amount of suffering, obviously.

We know that all patients volunteering for a gluten challenge study are taking a huge burden to help science and to help the next generation, but there is so much that we can ask them to do. We can take care of the dropouts statistically with an exit visit to understand what was the level of immune activation, et cetera, and then count them as treatment failures so that their effort actually counts in the analysis.

DR. MURRAY: I'd like to come to the question of patient selection, the appropriate patient selection. We know some patients will select themselves out of a study because they don't want to be exposed.

In the past what we've done is take symptomatic patients, and we've tried things like the traditional measures we use clinically: positive serology, maybe detectable serology, and

histology showing substantial injury as potentially requirements to get into a study for symptomatic disease.

I think, certainly with the Celiac Action trial, we scoped a lot of people who had symptoms, substantial symptoms, and two-thirds of them had no significant damage. Maybe they had some. They were in the well-treated celiac category with a VHCD above 2, but they didn't have substantial objective measures of what we think of as active disease, but they had a lot of symptoms.

Are we going to consign those patients' symptoms to IBS -- some of our colleagues in other areas of GI do that -- or have they got symptoms that are due to celiac disease but perhaps not due to gluten? I certainly believe with my patients -- and I've got patients who get symptoms when they expose to gluten, and I've got patients who've got symptoms due to their underlying celiac disease, or their inflammatory condition, or even their microinflammatory condition that may be different. The mechanism of the drugs used may

target both of those circumstances.

DR. TOMAINO: So you've once again raised a good point that leads directly into another question that we were thinking to raise for this discussion, and I'm going to turn it over to Dr. Cartee to open that up.

But this is something that is important for us to think about and something that we did want to touch on here is, how do we know that the symptoms are related to celiac disease? Then again, are those symptoms related to gluten? So it's sort of a linked, two-fold question.

DR. CARTEE: So several questions here. We've heard from Dr. Tye-Din that there has been pretty much a dose effect for the amount of gluten and for the duration of gluten exposure on adaptive immune response.

A couple questions kind of stemming from this that relate to what Dr. Murray raised would be, are there patients who have different levels of sensitivity to gluten? And if that's the case, is there a way to really capture how many of those

symptoms are actually related to gluten exposure? I think we'll start with that.

DR. LEON: I think our way of limit [indiscernible] may not be the only way that works, but I think providing a solid matrix that contains FODMAPs, contains ATIs, and all the other sources of immune activation and symptoms, except for gluten, and then adding gluten to it.

I'll ask you to contrast and compare those two periods, and if you measure gluten at the same time, and you look at serology, which is highly specific as well -- as Joe Murray mentioned, if you have detectable antibodies, that is a good indication. If you have anti-DGP antibodies, for example, deamidated gluten peptide antibodies, it's a good indication that there is an immune activation due to gluten because that's the only thing that brings those antibodies up.

So when you combine all of that and perhaps add some T-cell measures -- they're difficult to do, but antigen-specific T cells, interleukins produced by T cells like interleukin-2 -- you end

up getting a pretty good idea of whether the symptoms you're measuring are really correlating with gluten-driven immune activation.

DR. TYE-DIN: I think it can be a very challenging thing to differentiate gluten-driven symptoms from other causes such as irritable bowel syndrome and FODMAP-containing foods because the symptoms can be identical. So I don't think there's a very easy way to do it, apart from controlling for FODMAP content or trying to link the gluten exposure to, for example, and immune readout, and I think that's quite a reliable way to do it.

I do think that a lot of people with celiac disease, at least from my clinical practice, do experience some irritable bowel, and sometimes their persistent symptomatology could be driven by non-gluten-containing foods, and that type of symptomatology may be sometimes interpreted as being due to active celiac disease or gluten.

I suppose at a clinical level, the only way that we might distinguish that would be by looking

at our patients, and if they have negative celiac serology and they've got well-healed small intestinal histology, we say, well, if it's celiac disease, it's well treated. It implies they're on a good gluten-free diet, therefore their persistent symptomatology is probably not related to ongoing gluten exposure. Now we have the tool of gluten immunogenic peptide monitoring that may be added in to provide additional objective measurement of actual gluten exposure.

So I think those are some clinical ways that might help corroborate whether you've got a gluten-driven symptomatology, network of symptoms, or another cause for that.

DR. LEBWOHL: Similar to what Joe pointed out, celiac disease, and not gluten, can cause symptoms by means of ongoing intestinal damage. If someone has total villous atrophy, they're going to have insufficient brush border lactase, so they're going to have symptoms from other foods due to gluten-induced intestinal damage.

Just as an alternative to a method Francisco

described, which I think is a perfectly sound method, another way to think about it is instead of exposing people to a complex delivery device, including FODMAP, ATIs, et cetera, expose people during a run-in period to purified, encapsulated gluten versus sham as a crossover.

Among those who have more symptoms during gluten period than during sham, you just subtract symptoms during one period from the other, and that's your population that you want to study because that's a more well-defined population with purely gluten-induced symptoms.

DR. TYE-DIN: I think that comes back to the idea of a screening challenge at the study entry; that way you might be able to define symptomatology. Ideally you do that in a double-blind fashion, although, I think at a practical level that can make the trial quite complicated, but I think that's a really good point you make.

DR. CARTEE: Maybe we could hear from Ms. Smith about the patient's perspective.

Do you ever have times when you have symptoms that you think might not be from gluten, and are you able to differentiate symptoms from gluten versus some other cause?

MS. SMITH: Yes. And I want to be clear this is super anecdotal. I'm one patient, and each celiac patient has such different experiences. But during the pandemic, I did go on a low FODMAP diet. I was eating entirely pre-prepared meals that were low FODMAP and gluten-free for a period of 6 months. That really allowed me to level-set my own digestive system and not everyone's able to do that.

During that time, I also towards the end would eat out periodically to see my reactions and how I was feeling at places that I would consider safe, that I'd eaten at before the pandemic and before all these different prepared meals that I was eating. I can say that before looking at the symptoms I was having and comparing them to the symptoms I had later, there for me was a difference.

Now I was experiencing a lot of pretty severe gastroenterological issues. I wasn't eating. I was losing a lot of weight. I had a lot of diarrhea. But being able to measure that with the low FODMAP diet, I was able to see different symptoms that came around such as having additional headaches and brain fog that was extensive, sleep disruption, and things that I wasn't necessarily seeing with my IBS or other symptoms.

I think, anecdotally, in talking to a lot of other celiacs, they feel the same way. They can notice, I went out to eat at this restaurant, and within a few hours I have X symptoms, and I know that means I had cross-contamination versus I ate a crouton, or something along those lines that would have gluten in it versus a lower amount.

So I think that there are certainly ways that you can measure that and there are certainly different methods that celiac patients use for our own personal ways of measuring if we got gluten, so to say, or if it was just an accidental exposure or a light cross-contamination.

DR. TOMAINO: I have one follow-up question for --

DR. LEFFLER: Just to reiterate in summary -- oh, sorry. Go ahead.

DR. TOMAINO: I was just going to ask Kelsey one follow-up, and I do apologize if you mentioned this earlier.

Are your symptoms the same each time you get exposed to gluten?

MS. SMITH: Yes. If I can attribute it to a meal that I didn't prepare myself that could possibly have had some kind of issues, I do have very similar symptoms versus the other gastroenterological symptoms that I was managing and dealing with in the past.

I think specifically they're outside of the things like diarrhea. It would be like severe nausea, headaches, brain fogginess, and sleep disruption. And those are things that I wasn't experiencing necessarily with some of my other symptoms.

DR. TOMAINO: Thank you.

Please go ahead, Dr. Leffler. Sorry about that.

DR. LEFFLER: That was actually perfect because actually I was going to say I think with gluten exposures, especially if they're timed and placebo-controlled, people do tend to have very syndromic responses that don't change over time for a specific person. It can be very different between people, but they'll always be the same for that person over time. So I think with those, you can usually say pretty clearly, okay, these are the gluten-related symptoms for Kelsey. These are the gluten-related symptoms for someone else.

It's very different if you're taking somebody with chronic symptoms that are ongoing and waxing and waning. I don't know that we have any good way, in the clinic or in research, to say this person has symptoms due to celiac disease and this person has symptoms due to FODMAPs, or IBS, or a dozen other conditions.

This is what we see in our non-response to celiac disease studies. Gluten exposure is one of

the major causes, but it's about 30-35 percent. The rest are due to other issues. As Ben said earlier, I think this is one of the issues with the results of the Latiglutenase study, and I think it is a problem that I'm not sure we have a solution for outside of careful -- I don't think patient selection alone can fix that problem, personally.

DR. TOMAINO: Dr. Lee, what about from the pediatric patient perspective? What have you observed in your patients and what do they tell you?

DR. LEE: I think the adult discussion thus far, there's been a lot of discussion about irritable bowel syndrome symptomatology, and we absolutely see that in pediatrics as well, too. I haven't seen a study, but I feel like perhaps it's a little bit less prominent in our pediatric celiac population; again, just completely anecdotal. I don't know the exact data.

I think the discussion highlights the importance of patient-reported outcomes; very important, yes, but at the end of the day, we have

to be cautious with those just in isolation. They're part of the clinical picture of response to therapy, so looking at the harder endpoints of serologies.

In pediatrics, we also have the additional vital sign of growth trajectory as well, too, and of course mucosal healing as well, so a little bit of a similar perspective from pediatrics, but I think a few twists.

DR. TOMAINO: Thank you.

We have about five minutes left. I want to switch gears a little bit to talk about something that has been mentioned several times throughout the presentations and even in this panel discussion. We've heard that there are several methods, although they're not FDA approved, to measure gluten in urine and stool, and we've also heard about IL-12.

So I'm interested to hear a little bit more. Dr. Tye-Din touched on this in his earlier comment. But are you all routinely using these methods in clinical practice? And if so, how have you been

using them?

DR. MURRAY: Maybe I can kick off. When patients report to me that they get severe symptoms intermittently often associated with eating out, I suggest to them to use one of the stool detection or urine detection kits to confirm that there was actually gluten exposure.

So I will do that for patients who report that type of event, a temporally distinct event that they suspect has a particular exposure as a way of confirming that. I've also had patients use the foods detection device to test food, especially in patients who travel a lot or eat out a lot.

So that's what I do clinically. Does it have some utility? My patients, some of my patients, tell me it does. It's a little clunky to do that, but that's certainly what I've seen from clinical use.

DR. TYE-DIN: I agree. Clinically I've been using with my patients the at-home gluten detect kit so that patients can test their own stool. I usually give them free, so they use one every

couple of days and do that for about a month, and that gives them a sense for whether there is some inadvertent gluten sneaking in or not. And that I think can sometimes help inform management.

DR. LEBWOHL: There are clinical scenarios where it does seem to be very useful, someone with intermittent symptoms, low-level antibody elevation, so it can be helpful. I still think it's a technology. It's still sort of finding its way in terms of best utility.

I do think that these are going to be very helpful in randomized trials, though, to detect gluten ingestion, so to ensure adherence to a gluten challenge and/or to see if someone's subject to the so-called trial effect where they're suddenly becoming much more strictly gluten avoidant.

DR. LEE: In my clinical practice, I don't oftentimes use a gluten detection kit in the urine or stool, but it is a valuable tool to have. Like Dr. Murray stated, we do have patients who use gluten detection devices, but clearly they have

some limitations here.

If I have a concern, my first step will always be to ask my patient and family to meet with one of our knowledgeable celiac dietitians to have a discussion about potential exposures.

DR. TOMAINO: Thank you.

Just in the last couple minutes, we've heard a lot about IL-2 levels. I misspoke. I said IL-12; IL-2. What are your thoughts or what data are available on IL-2 spikes after a repeated gluten challenge, and is there any indication that repetitive IL-2 measurements may predict histologic damage?

DR. TYE-DIN: I think they're really good questions. I think in my presentation I put a reference in where we reported some data looking at gluten challenges performed five months apart, same amount of gluten given each time; the second challenge being a double-blind, placebo-controlled, challenge.

Interestingly, the first time around, I think about 8 participants vomited, and coming back

to Dr. Leffler's point about consistency, these seemed to show quite a lot of consistency. The second time around, 7 out of the 8 vomited again. But there were additional people, so a total of 16 people vomited on this occasion, and interleukin-2 was twice as high overall. The median level was twice as high, although within each individual, the interleukin-2 level was similar to what it was the first time around.

So I think that there's certainly evidence that recurrent gluten exposure may lead to potentially more notable symptoms the second time around, although we really need more data on that, but it does seem to be reflected in the interleukin-2 level

Again, I think I mentioned that the baseline level of damage did seem to impact the rising interleukin-2, so I think it's a great question to determine if we can correlate those two things, which needs to be done.

DR. LEBWOHL: If time permits, I'd be interested in the sensitization that you're

observing. That's potentially a problem for the so-called gluten exposure studies that Dan Leffler's been describing; is that a potential concern?

Sensitization is not something I observe in clinical practice except among those who are newly diagnosed and go strictly gluten-free, and then they become more sensitive.

DR. TYE-DIN: Yes. I think that's an important question. I don't think we have the answers yet, but I think these were very high doses of gluten that we used, so maybe that's a relevant factor as opposed to smaller doses that might not have these kind of boosting effects.

DR. LEE: I think --

DR. TOMAINO: Great. Thank you.

DR. LEE: Can I offer one perspective?

Go ahead, Dr. Lee. One last point, please.

DR. LEE: I think from the pediatric perspective, these short-dose gluten introduction trials and the rise in IL-2, for example, 4 hours after exposure, I think it's a unique opportunity

in pediatrics if we are concerned about duration of exposures.

I think it's an exciting new way to approach looking at this, in particular, in populations where we are worried about longer-standing exposures.

DR. TYE-DIN: Yes, I agree. I think it's got a lot of potential in this space.

DR. TOMAINO: Thank you so much.

It's time to wrap up. It's amazing how quickly the 45 minutes goes. I think we could have a whole workshop on this topic.

I also want to acknowledge the very high volume of questions that have been coming in through the Q&A. Unfortunately, we haven't been able to address all of them directly, but I think we did touch on many of them through our discussion. We are seeing all of them and we're saving them.

So thank you for submitting your questions and your feedback, and thank you to the wonderful panelists for this session, and to Kelsey Smith for

sharing your valuable patient perspective.

With that, I'll conclude our Session 3, and I'll turn it over to Irena Lavine for some closing remarks.

Closing Remarks – Irena Lavine

DR. LAVINE: Good afternoon. Before officially closing the workshop today, I would like to say a few closing remarks.

This has been a very productive workshop with lively panel discussions. We had the pleasure to hear from a variety of stakeholders to achieve our goal of having a collaborative discussion on the important and challenging issues in drug development in celiac disease.

In summary, during Session 1, Dr. Lebwohl discussed an approach to monitoring disease through histologic assessment, including when clinicians conduct endoscopy to monitor response and how clinicians defined well-controlled or quiescent disease.

Dr. Silvester discussed unique considerations for using histologic assessments to

monitor response in pediatric patients. We then heard from Dr. Robert regarding the pros and cons of the various histologic scoring systems and which scoring system is most often used in clinical practice. The session was followed by an excellent discussion by the experts and patients on the panel.

During Session 2, we focused on similarities and differences in the natural history of celiac disease between adult and pediatric patients. Dr. Khurana discussed regulatory considerations for extrapolation of efficacy from adult to pediatric patients. Mr. Friedman shared his perspective as a patient living with celiac disease and what he would consider to be an ideal treatment if there were a drug that could treat celiac disease.

Dr. Leonard described the clinical manifestations, natural history, and unmet needs of pediatrics celiac disease. Finally, Dr. St. Clair presented the FDA perspective on the approach to defining clinical benefit in pediatric clinical trials. We then had another vibrant discussion

with our panel.

During Session 3, Dr Murray discussed the current approach for evaluating and monitoring patients after gluten challenges, unintentional gluten exposure, and clinical practice.

Dr. Tye-Din discussed the available data and literature on the dose and duration of gluten exposure that elicits clinical signs and symptoms and changes in histology and patients.

Finally, we heard from Dr. Leffler on operationalizing a gluten challenge and simulated inadvertent gluten exposure in clinical trials and lessons learned from industry representatives. The session was followed by an animative panel discussion.

Hearing the different perspectives today from clinicians, industry, patients, and FDA representatives will help advance drug development in celiac disease. We had a scientific discussion on what we currently know and where knowledge gaps exist regarding the histologic assessment, pediatric celiac disease, and gluten challenges.

The discussions today will help inform our regulatory thinking. Frequent communications and collaborations among the FDA, industry sponsors, clinicians, and patients will likely result in successful development of celiac disease treatment.

On behalf of my division director, Dr. Jessica Lee, deputy director, Dr. Juli Tomaino, deputy director for safety, Dr. Joyce Korvick, and the entire Division of Gastroenterology, I would like to thank you all for attending the GREAT VI Workshop on Celiac Disease.

Thank you to our co-sponsors from ACG, AGA, and NASPGHAN. I especially would like to thank our speakers, moderators, and panelists for their time and effort preparing for this workshop and participating today, and a special thank you to all of our patient representatives for sharing their stories, and all of the patient advocacy groups and patients living with celiac disease.

I really appreciate the steering committee members who helped shape the agenda and provided ongoing feedback. I also would like to thank the

public meeting support staff and AV team who helped facilitate this workshop today.

Adjournment

DR. LAVINE: I will now conclude the workshop, and thank you all for joining today.

(Whereupon, at 3:21 p.m., the workshop was adjourned.)