The Role of **Patient Advocacy** in Clinical Trials

Marilyn G. Geller
Chief Executive
Celiac Disease Foundation

About the Celiac Disease Foundation

Since our founding in 1990, the Celiac Disease Foundation has played a key role in achieving federal recognition of celiac disease, improving diagnostic tools, and accelerating research for better treatments and a cure.

Research

- iCureCeliac® Patient Registry
- Patient Recruitment Services
- iQualifyCeliac Patient Recruitment Platform
- Patient Recruitment Funds Research Prizes and Grants

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Education

- Patients, families, healthcare providers, industry, and the public
- Partnerships for educational programs and provider training with Celiac Disease Centers, AGA, NASPGHAN, Academy of Nutrition and Dietetics, SSCD
- Industry Partnership in Patient Education & Advocacy Summit

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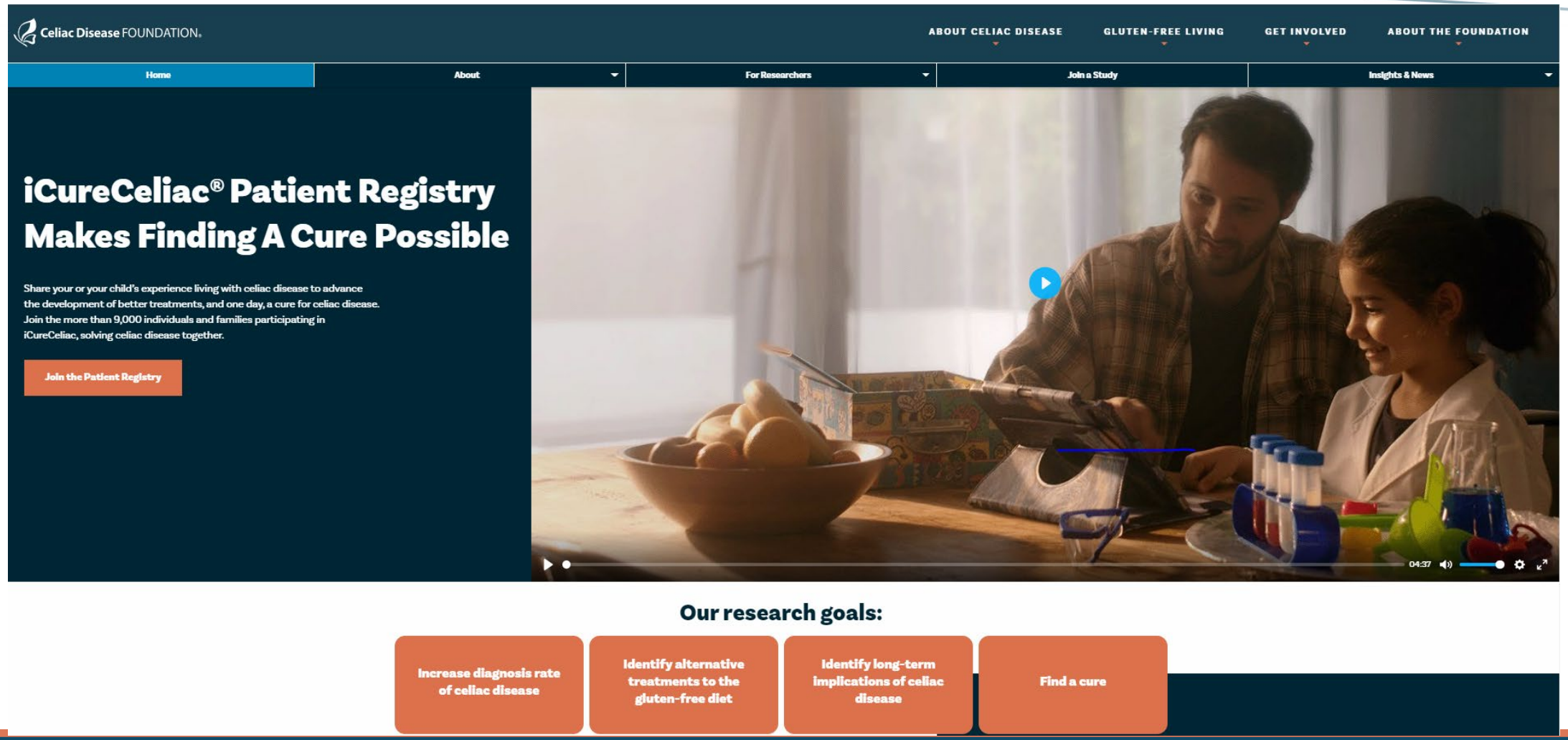
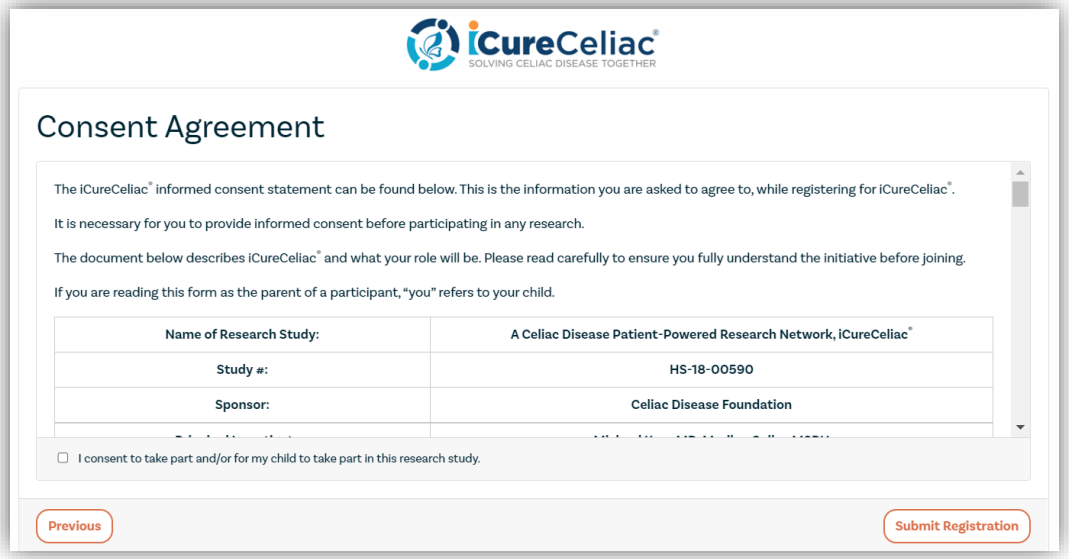
Advocacy

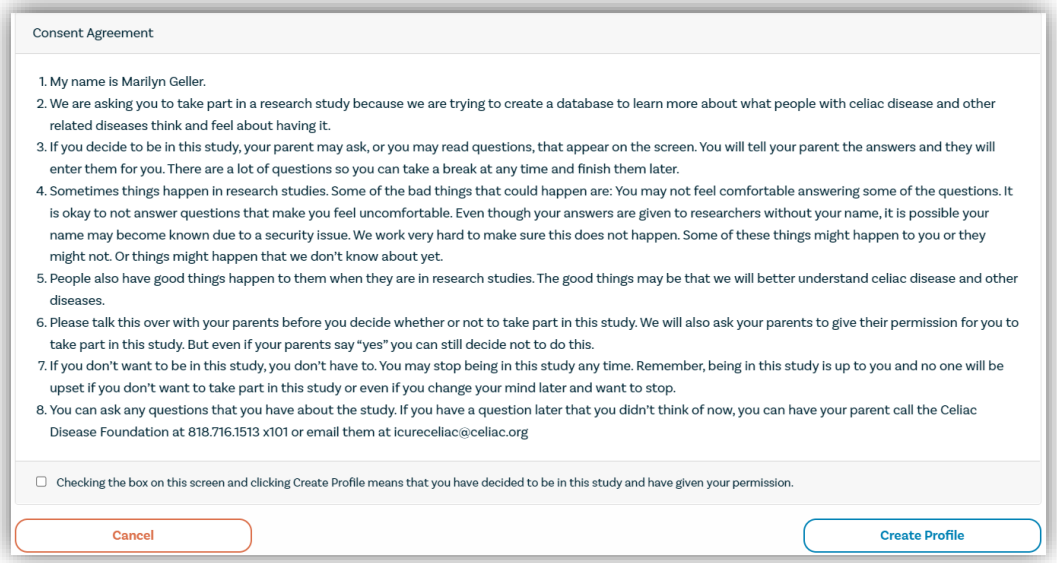
- Celiac Disease Caucus, NIH, FDA, CDC, HHS, CDMRP
- Patient Education & Advocacy Summit, State Advocacy Ambassador Training Program
- AOECS (Association of European Coeliac Societies)

iCureCeliac® Patient Registry

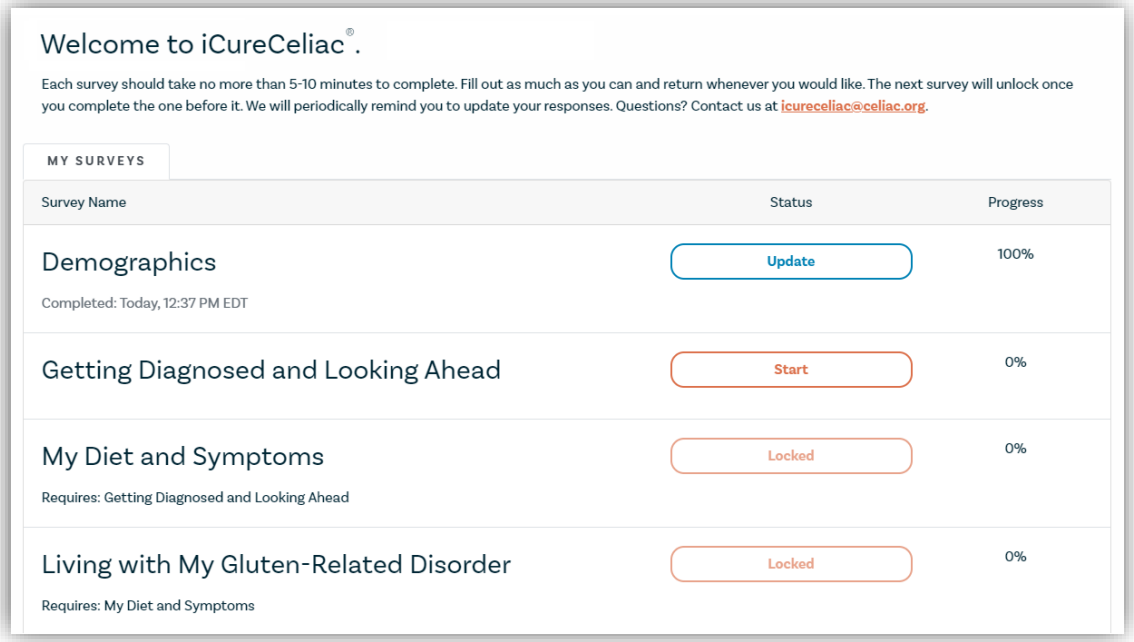


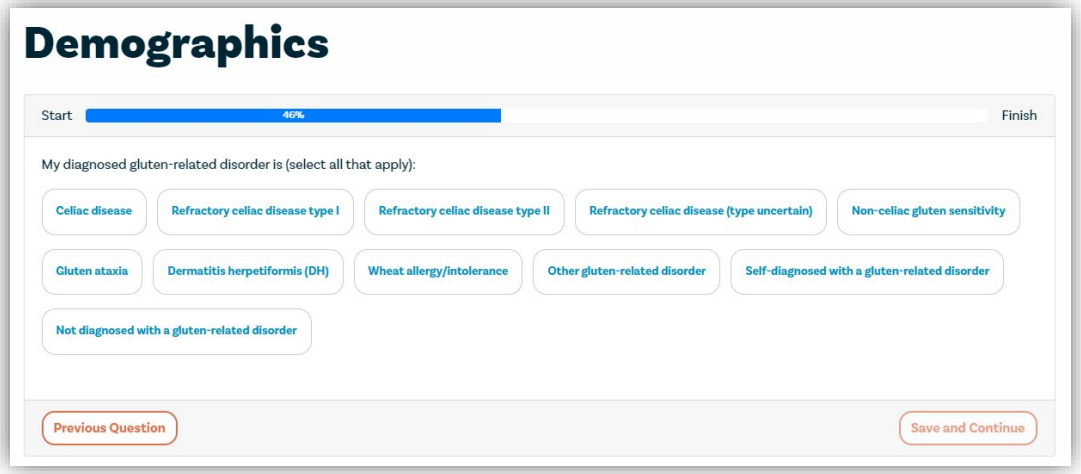
iCureCeliac® Patient Registry



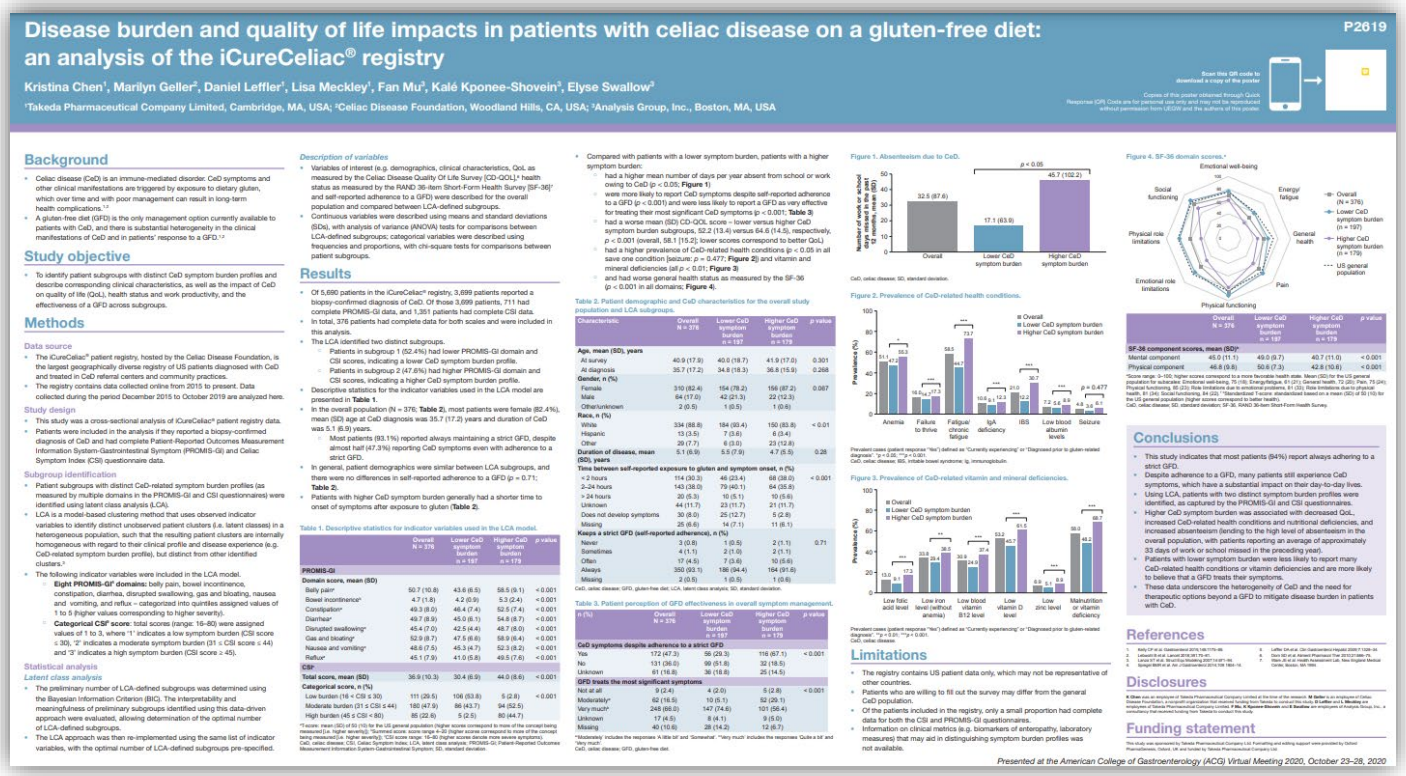


iCureCeliac® Patient Registry





Posters, Abstracts, and Publications



Disease burden and quality of life impacts in patients with celiac disease on a gluten-free diet: an analysis of the iCureCeliac® registry

P2619

Kristina Chen[1], Marilyn Geller[2], Daniel Leffler[1], Lisa Meckley[1], Fan Mu[3], Kalé Kponee-Shovein[3], Elyse Swallow[3]

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Background

- Celiac disease (CeD) is an immune-mediated disorder. CeD symptoms and other clinical manifestations are triggered by exposure to dietary gluten, which over time and with poor management can result in long-term health complications.[1,2]
- A gluten-free diet (GFD) is the only management option currently available to patients with CeD, and there is substantial heterogeneity in the clinical manifestations of CeD and in patients' response to a GFD.[1,3]

Study objective

- To identify patient subgroups with distinct CeD symptom burden profiles and describe corresponding clinical characteristics, as well as the impact of CeD on quality of life (QoL), health status and work productivity, and the effectiveness of a GFD across subgroups.

Methods

Data source

- The iCureCeliac® patient registry, hosted by the Celiac Disease Foundation, is the largest geographically diverse registry of US patients diagnosed with CeD and treated in CeD referral centers and community practices.
- The registry contains data collected online from 2015 to present. Data collected during the period December 2015 to October 2019 are analyzed here.

Study design

- This study was a cross-sectional analysis of iCureCeliac® patient registry data.
- Patients were included in the analysis if they reported a biopsy-confirmed diagnosis of CeD and had complete Patient-Reported Outcomes Measurement Information System-Gastrointestinal Symptom (PROMIS-GI) and Celiac Symptom Index (CSI) questionnaire data.

Subgroup identification

- Patient subgroups with distinct CeD-related symptom burden profiles (as measured by multiple domains in the PROMIS-GI and CSI questionnaires) were identified using latent class analysis (LCA).
- LCA is a model-based clustering method that uses observed indicator variables to identify distinct unobserved patient clusters (i.e. latent classes) in a heterogeneous population, such that the resulting patient clusters are internally homogeneous with regard to their clinical profile and disease experience (e.g. CeD-related symptom burden profile), but distinct from other identified clusters.[4]
- The following indicator variables were included in the LCA model.
  - **Eight PROMIS-GI[a] domains:** belly pain, bowel incontinence, constipation, diarrhea, disrupted swallowing, gas and bloating, nausea and vomiting, and reflux – categorized into quintiles assigned values of 1 to 5 (higher values corresponding to higher severity).
  - **Categorical CSI[b] score**: total scores (range: 16–80) were assigned values of 1 to 3, where '1' indicates a low symptom burden (CSI score ≤ 30), '2' indicates a moderate symptom burden (31 ≤ CSI score ≤ 44) and '3' indicates a high symptom burden (CSI score ≥ 45).

Statistical analysis

Latent class analysis

- The preliminary number of LCA-defined subgroups was determined using the Bayesian Information Criterion (BIC). The interpretability and meaningfulness of preliminary subgroups identified using this data-driven approach were evaluated, allowing determination of the optimal number of LCA-defined subgroups.
- The LCA approach was then re-implemented using the same list of indicator variables, with the optimal number of LCA-defined subgroups pre-specified.

Description of variables

- Variables of interest (e.g. demographics, clinical characteristics, QoL as measured by the Celiac Disease Quality Of Life Survey [CD-QOL][a] health status as measured by the RAND 36-item Short-Form Health Survey [SF-36][c] and self-reported adherence to a GFD) were described for the overall population and compared between LCA-defined subgroups.
- Continuous variables were described using means and standard deviations (SDs), with analysis of variance (ANOVA) tests for comparisons between LCA-defined subgroups; categorical variables were described using frequencies and proportions, with chi-square tests for comparisons between patient subgroups.

Results

- Of 5,690 patients in the iCureCeliac® registry, 3,699 patients reported a biopsy-confirmed diagnosis of CeD. Of those 3,699 patients, 711 had complete PROMIS-GI data, and 1,351 patients had complete CSI data.
- In total, 376 patients had complete data for both scales and were included in this analysis.
- The LCA identified two distinct subgroups.
  - Patients in subgroup 1 (52.4%) had lower PROMIS-GI domain and CSI scores, indicating a lower CeD symptom burden profile.
  - Patients in subgroup 2 (47.6%) had higher PROMIS-GI domain and CSI scores, indicating a higher CeD symptom burden profile.
- Descriptive statistics for the indicator variables used in the LCA model are presented in **Table 1**.
- In the overall population (N = 376; **Table 2**), most patients were female (82.4%), mean (SD) age at CeD diagnosis was 35.7 (17.2) years and duration of CeD was 5.1 (6.9) years.
  - Most patients (93.1%) reported always maintaining a strict GFD, despite almost half (47.3%) reporting CeD symptoms even with adherence to a strict GFD.
- In general, patient demographics were similar between LCA subgroups, and there were no differences in self-reported adherence to a GFD (*p* = 0.71; **Table 2**).
- Patients with higher CeD symptom burden generally had a shorter time to onset of symptoms after exposure to gluten (**Table 2**).
- Compared with patients with a lower symptom burden, patients with a higher symptom burden:
  - had a higher mean number of days per year absent from school or work owing to CeD (*p* < 0.05; **Figure 1**)
  - were more likely to report CeD symptoms despite self-reported adherence to a GFD (*p* < 0.001) and were less likely to report a GFD as very effective for treating their most significant CeD symptoms (*p* < 0.001; **Table 3**)
  - had a worse mean (SD) CD-QOL score – lower versus higher CeD symptom burden subgroups, 52.2 (13.4) versus 64.6 (14.5), respectively, *p* < 0.001 (overall, 58.1 [15.2]; lower scores correspond to better QoL)
  - had a higher prevalence of CeD-related health conditions (*p* < 0.05 in all save one condition [seizure: *p* = 0.477; **Figure 2**]) and vitamin and mineral deficiencies (all *p* < 0.01; **Figure 3**)
  - and had worse general health status as measured by the SF-36 (*p* < 0.001 in all domains; **Figure 4**).

Table 1. Descriptive statistics for indicator variables used in the LCA model.

	Overall N = 376	Lower CeD symptom burden n = 197	Higher CeD symptom burden n = 179	*p* value
PROMIS-GI				
Domain score, mean (SD)				
Belly pain[a]	50.7 (10.8)	43.6 (6.5)	58.5 (9.1)	< 0.001
Bowel incontinence[a]	4.7 (1.8)	4.2 (0.9)	5.3 (2.4)	< 0.001
Constipation[a]	49.3 (8.0)	46.4 (7.4)	52.5 (7.4)	< 0.001
Diarrhea[a]	49.7 (8.9)	45.0 (6.1)	54.8 (8.7)	< 0.001
Disrupted swallowing[a]	45.4 (7.0)	42.5 (4.4)	48.7 (8.0)	< 0.001
Gas and bloating[a]	52.9 (8.7)	47.5 (6.6)	58.9 (6.4)	< 0.001
Nausea and vomiting[a]	48.6 (7.5)	45.3 (4.7)	52.3 (8.2)	< 0.001
Reflux[a]	45.1 (7.9)	41.0 (5.8)	49.5 (7.6)	< 0.001
CSI[b]				
Total score, mean (SD)	36.9 (10.3)	30.4 (6.9)	44.0 (8.6)	< 0.001
Categorical score, n (%)				
Low burden (16 < CSI ≤ 30)	111 (29.5)	106 (53.8)	5 (2.8)	< 0.001
Moderate burden (31 ≤ CSI ≤ 44)	180 (47.9)	86 (43.7)	94 (52.5)	
High burden (45 ≤ CSI < 80)	85 (22.6)	5 (2.5)	80 (44.7)	

[a]Score: mean (SD) of 50 (10) for the US general population (higher scores correspond to more of the concept being measured [i.e. higher severity]). [b]Summed score, score range 4–32 (higher score correspond to more of the concept being measured [i.e. higher severity]); CSI score range: 16–80 (higher scores denote more severe symptoms).
CeD, celiac disease; CSI, Celiac Symptom Index; LCA, latent class analysis; PROMIS-GI, Patient-Reported Outcomes Measurement Information System Gastrointestinal Symptom; SD, standard deviation.

Table 2. Patient demographic and CeD characteristics for the overall study population and LCA subgroups.

Characteristic	Overall N = 376	Lower CeD symptom burden n = 197	Higher CeD symptom burden n = 179	*p* value
Age, mean (SD), years				
At survey	40.9 (17.9)	40.9 (18.7)	41.9 (17.0)	0.301
At diagnosis	35.7 (17.2)	34.8 (18.3)	36.8 (15.9)	0.268
Gender, n (%)				
Female	310 (82.4)	154 (78.2)	156 (87.2)	0.087
Male	64 (17.0)	42 (21.3)	22 (12.3)	
Other/unknown	2 (0.5)	1 (0.5)	1 (0.6)	
Race, n (%)				
White	334 (88.8)	184 (93.4)	150 (83.8)	< 0.01
Hispanic	13 (3.5)	7 (3.6)	6 (3.4)	
Other	29 (7.7)	6 (3.0)	23 (12.8)	
Duration of disease, mean (SD), years	5.1 (6.9)	5.5 (7.9)	4.7 (5.5)	0.28
Time between self-reported exposure to gluten and symptom onset, n (%)				
< 2 hours	114 (30.3)	46 (23.4)	68 (38.0)	< 0.001
2–24 hours	143 (38.0)	79 (40.1)	64 (35.8)	
> 24 hours	20 (5.3)	10 (5.1)	10 (5.6)	
Unknown	44 (11.7)	23 (11.7)	21 (11.7)	
Does not develop symptoms	30 (8.0)	25 (12.7)	5 (2.8)	
Missing	25 (6.6)	14 (7.1)	11 (6.1)	
Keeps a strict GFD (self-reported adherence), n (%)				
Never	3 (0.8)	1 (0.5)	2 (1.1)	0.71
Sometimes	4 (1.1)	2 (1.0)	2 (1.1)	
Often	17 (4.5)	7 (3.6)	10 (5.6)	
Always	350 (93.1)	186 (94.4)	164 (91.6)	
Missing	2 (0.5)	1 (0.5)	1 (0.6)	

CeD, celiac disease; GFD, gluten-free diet; LCA, latent class analysis; SD, standard deviation.

Table 3. Patient perception of GFD effectiveness in overall symptom management.

n (%)	Overall N = 376	Lower CeD symptoms burden n = 197	Higher CeD symptom burden n = 179	*p* value
CeD symptoms despite adherence to a strict GFD				
Yes	172 (47.3)	56 (29.3)	116 (67.1)	< 0.001
No	131 (36.0)	99 (51.8)	32 (18.5)	
Unknown	61 (16.8)	36 (18.8)	25 (14.5)	
GFD treats the most significant symptoms				
Not at all	9 (2.4)	4 (2.0)	5 (2.8)	< 0.001
Moderately[a]	62 (16.5)	10 (5.1)	52 (29.1)	
Very much[a]	248 (66.0)	147 (74.6)	101 (56.4)	
Unknown	17 (4.5)	8 (4.1)	9 (5.0)	
Missing	40 (10.6)	28 (14.2)	12 (6.7)	

[a]Moderately' includes the responses 'A little bit' and 'Somewhat'; 'Very much' includes the responses 'Quite a bit' and 'Very much'.
CeD, celiac disease; GFD, gluten-free diet.

Figure 1. Absenteeism due to CeD.

CeD, celiac disease; SD, standard deviation.

Figure 2. Prevalence of CeD-related health conditions.

Prevalent cases (patient response "Yes") defined as "Currently experiencing" or "Diagnosed prior to gluten-related diagnosis". *p < 0.05, **p < 0.01, ***p < 0.001.
CeD, celiac disease; IBS, irritable bowel syndrome; Ig, immunoglobulin.

Figure 3. Prevalence of CeD-related vitamin and mineral deficiencies.

Prevalent cases (patient response "Yes") defined as "Currently experiencing" or "Diagnosed prior to gluten-related diagnosis". *p < 0.01, **p < 0.001.
CeD, celiac disease.

Limitations

- The registry contains US patient data only, which may not be representative of other countries.
- Patients who are willing to fill out the survey may differ from the general CeD population.
- Of the patients included in the registry, only a small proportion had complete data for both the CSI and PROMIS-GI questionnaires.
- Information on clinical metrics (e.g. biomarkers of enteropathy, laboratory measures) that may aid in distinguishing symptom burden profiles was not available.

Figure 4. SF-36 domain scores.[a]

	Overall N = 376	Lower CeD symptom burden n = 197	Higher CeD symptom burden n = 179	*p* value
SF-36 component scores, mean (SD)[a]				
Mental component	45.0 (11.1)	49.0 (9.7)	40.7 (11.0)	< 0.001
Physical component	46.8 (9.8)	50.6 (7.3)	42.8 (10.6)	< 0.001

[a]Score range: 0–100; higher scores correspond to a more favorable health state. Mean (SD) for the US general population (to achieve this, the emotional well-being, 75 (18); Energy/fatigue, 61 (21); General health, 72 (20); Pain, 74 (pain); Physical functioning, 86 (23); Role limitations due to emotional problems, 81 (32); Role limitations due to physical health, 81 (34); Social functioning, 84 (22). [b]Standardized T score: standardized based on a mean (SD) of 50 (10) for the US general population (higher scores correspond to better health).
CeD, celiac disease; SD, standard deviation; SF-36, RAND 36-Item Short-Form Health Survey.

Conclusions

- This study indicates that most patients (94%) report always adhering to a strict GFD.
- Despite adherence to a GFD, many patients still experience CeD symptoms, which have a substantial impact on their day-to-day lives.
- Using LCA, patients with two distinct symptom burden profiles were identified, as captured by the PROMIS-GI and CSI questionnaires.
- Higher CeD symptom burden was associated with decreased QoL, increased CeD-related health conditions and nutritional deficiencies, and increased absenteeism (tending to the high level of absenteeism in the overall population, with patients reporting an average of approximately 33 days of work or school missed in the preceding year).
- Patients with lower symptom burden were less likely to report many CeD-related health conditions or vitamin deficiencies and are more likely to believe that a GFD treats their symptoms.
- These data underscore the heterogeneity of CeD and the need for therapeutic options beyond a GFD to mitigate disease burden in patients with CeD.

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Disclosures

K Chen was an employee of Takeda Pharmaceutical Company Limited at the time of the research. **M Geller** is an employee of Celiac Disease Foundation, a nonprofit organization that received funding from Takeda to conduct this study. **D Leffler** and **L Meckley** are employees of Takeda Pharmaceutical Company Limited. **F Mu**, **K Kponee-Shovein** and **E Swallow** are employees of Analysis Group, Inc., a consultancy that received funding from Takeda to conduct this study.

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Presented at the American College of Gastroenterology (ACG) Virtual Meeting 2020, October 23–28, 2020

Patient Recruitment Services

STUDY DESIGN CONSULTATION

Offering guidance on the design of research questions, approach, and strategy from early stages of development through study implementation, we help you define measures and outcomes that are clinically significant and meaningful to patients, address bottlenecks in the enrollment process, and create solutions for common barriers to study participation.

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Solicit feedback and gather valuable insights from patients to improve your study feasibility, recruitment, and retention. We offer board strategy development, member selection, and meeting coordination and facilitation.

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The right messaging is key to a successful patient recruitment campaign. We provide proven strategies that resonate with the celiac disease community, including in-house design of your study logo, a customized hosted microsite, and creative assets for your multiplatform marketing campaign.

MULTIPLATFORM MARKETING CAMPAIGN

Utilizing our robust website reach at celiac.org, social media channels, and Eat! Gluten-Free app, we broadcast your study opportunity to those who care about it most. Targeted recruitment to iCureCeliac® and iQualifyCeliac participants who meet your subject profile further reduces your cost by identifying the right patients, accelerating enrollment, and improving trial retention and satisfaction.

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Branded with your marketing design, our proprietary iQualifyCeliac platform screens patients based upon your study parameters. This, combined with our in-house call center of skilled patient services representatives, produces the highest quality geotargeted-to-site referrals in days–not months.

STUDY SITE ENGAGEMENT

We work in tandem with your study site coordinators to ensure a seamless enrollment process. Site coordinators receive virtual training and a secure login to our iQualifyCeliac platform to access pre-screened referrals assigned to their sites. All from their portal, site coordinators can log contact attempts, receive reminders to follow up, schedule first visits, and capture enrollment or randomization status. The sponsor portal allows you to view real-time recruitment statistics and monitor study site contact and enrollment progress.

PATIENT COMPENSATION

Through our partnership with Greenphire, we offer Virtual ClinCard management integrated with our iQualifyCeliac platform for seamless patient compensation.

PATIENT DATA CAPTURE

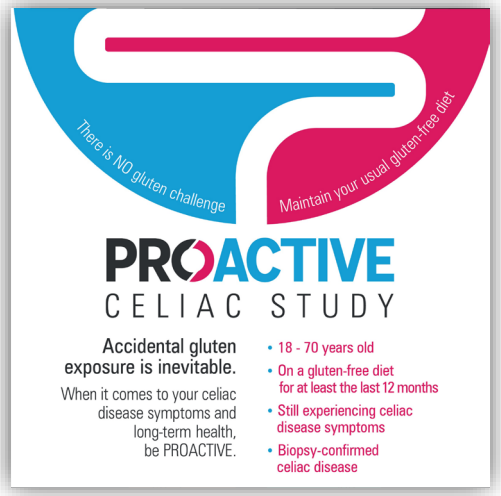
Empower patients to capture and submit data on their smart phone or tablet with our user-friendly secure and HIPAA-compliant cloud-based clinical platform. Capture eConsent, eCOA, ePRO, eDiary, symptom and wearable device data, customized to your study or trial.

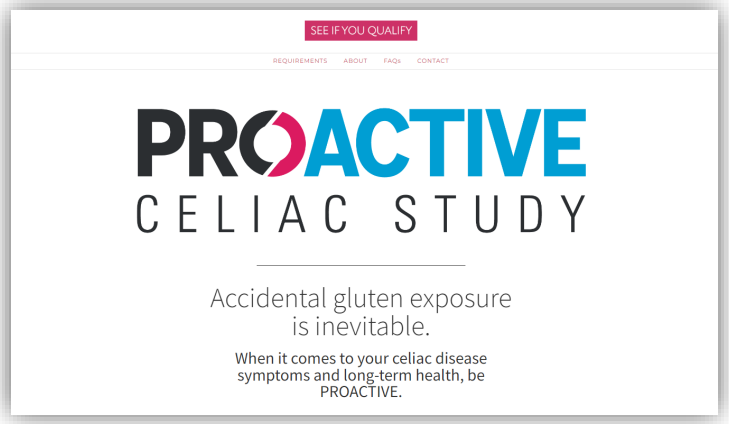
ICURECELIAC® PATIENT REGISTRY DATA LICENSE

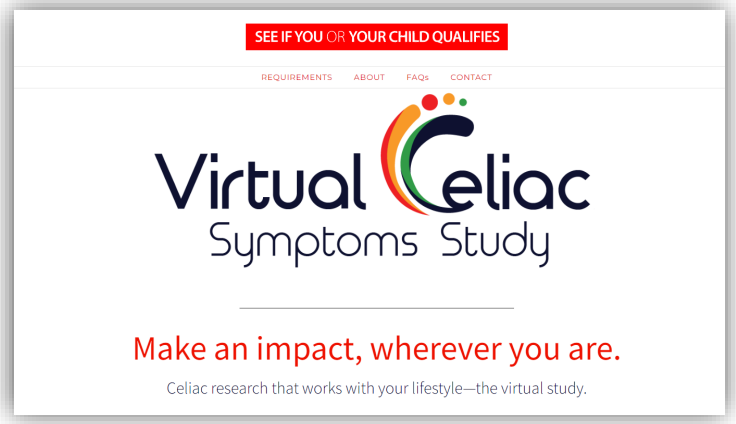
Our online patient-powered research network, iCureCeliac®, allows patients to share their health data and insights to accelerate research investigating topics important to people with celiac disease. Anonymized data contributed under informed consent are available to assist you with your study or trial aims.

Survey questions span topics including treatment preferences, quality of life, biomarkers of celiac disease, and many others. Validated instruments include the Celiac Symptoms Index (CSI), Celiac Dietary Adherence Test (CDAT), Celiac Disease Quality of Life Measure (CD-QOL), SF-36, PROMIS Gastrointestinal, PROMIS 29 Profile, and PROMIS Pediatric 25 Profile.

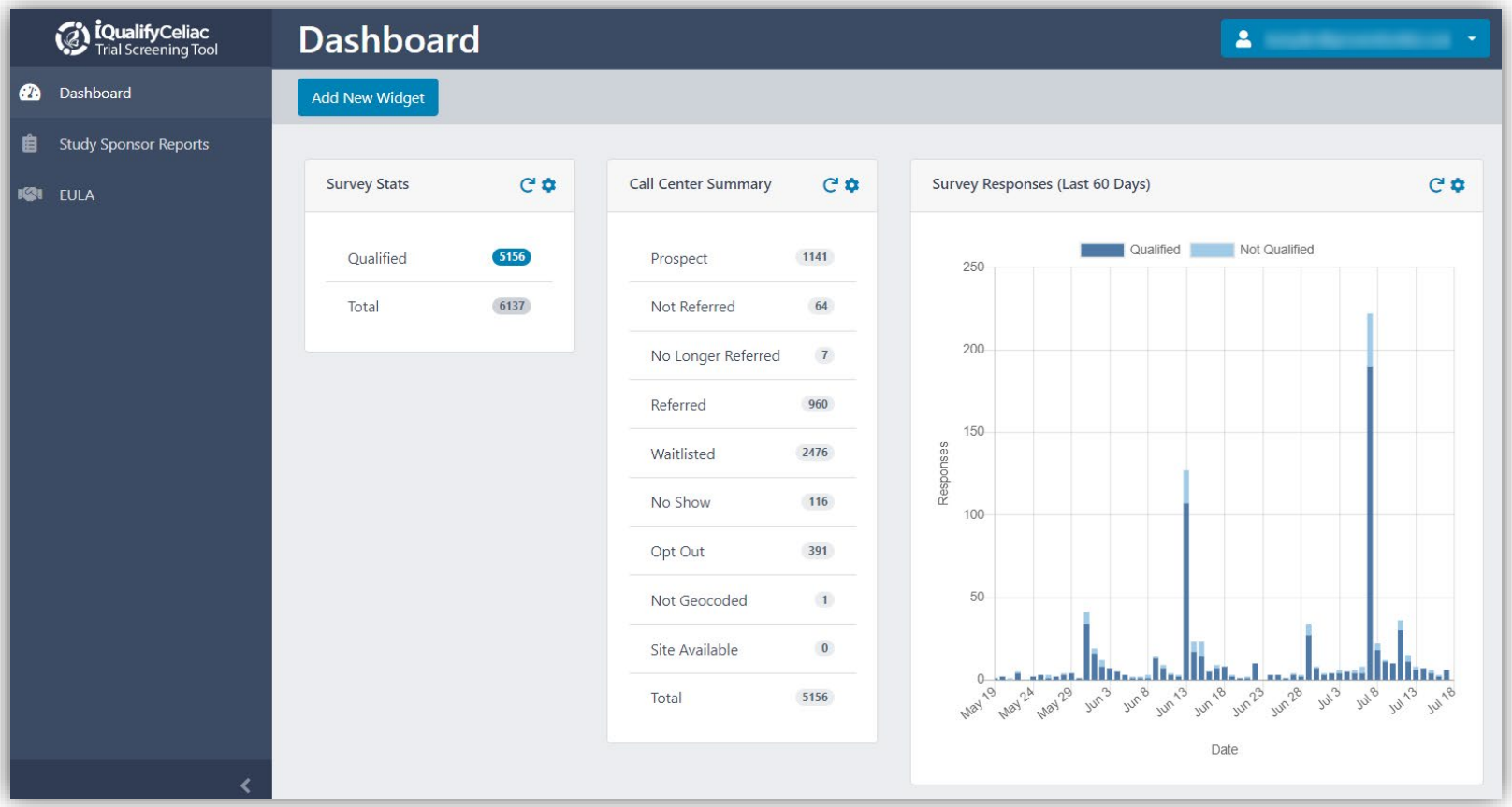
Multiplatform Marketing Campaign



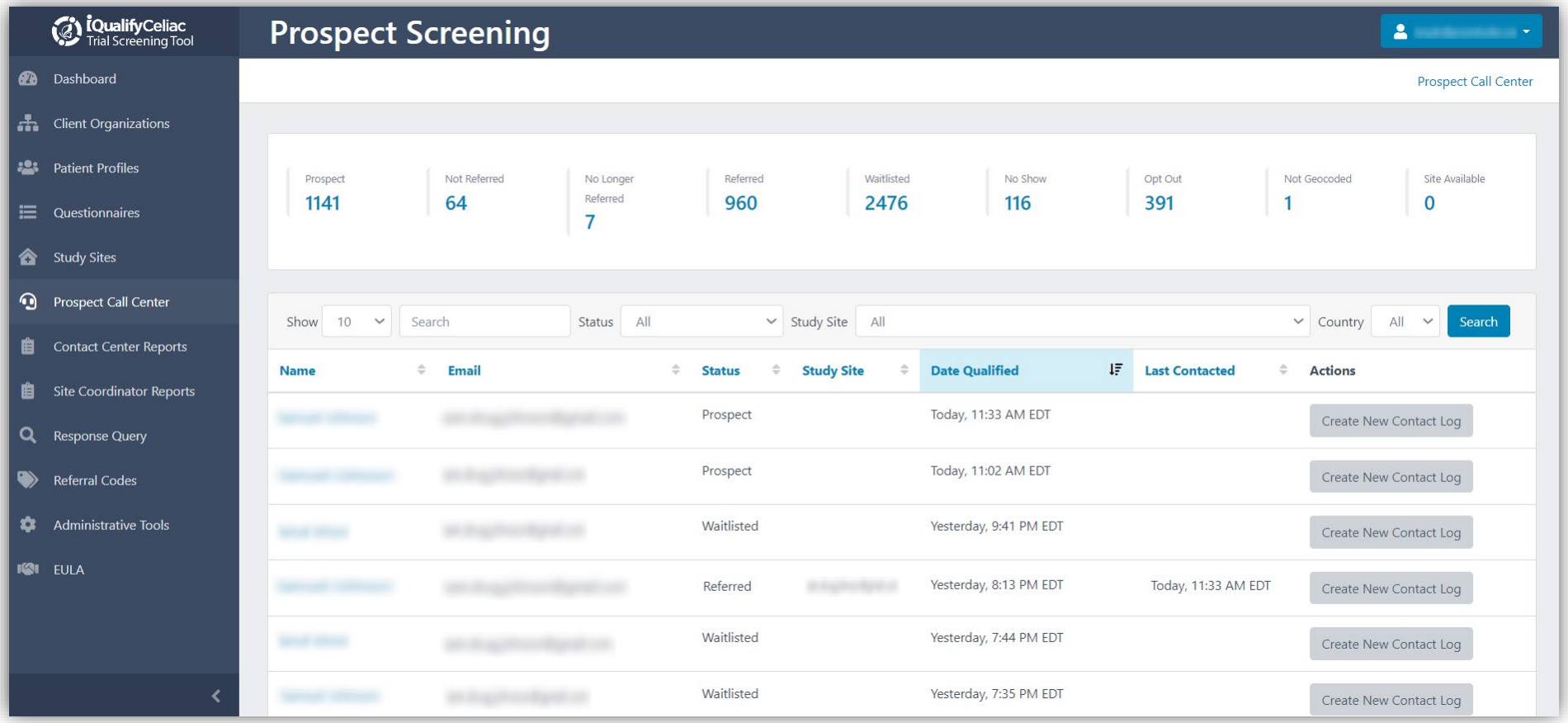




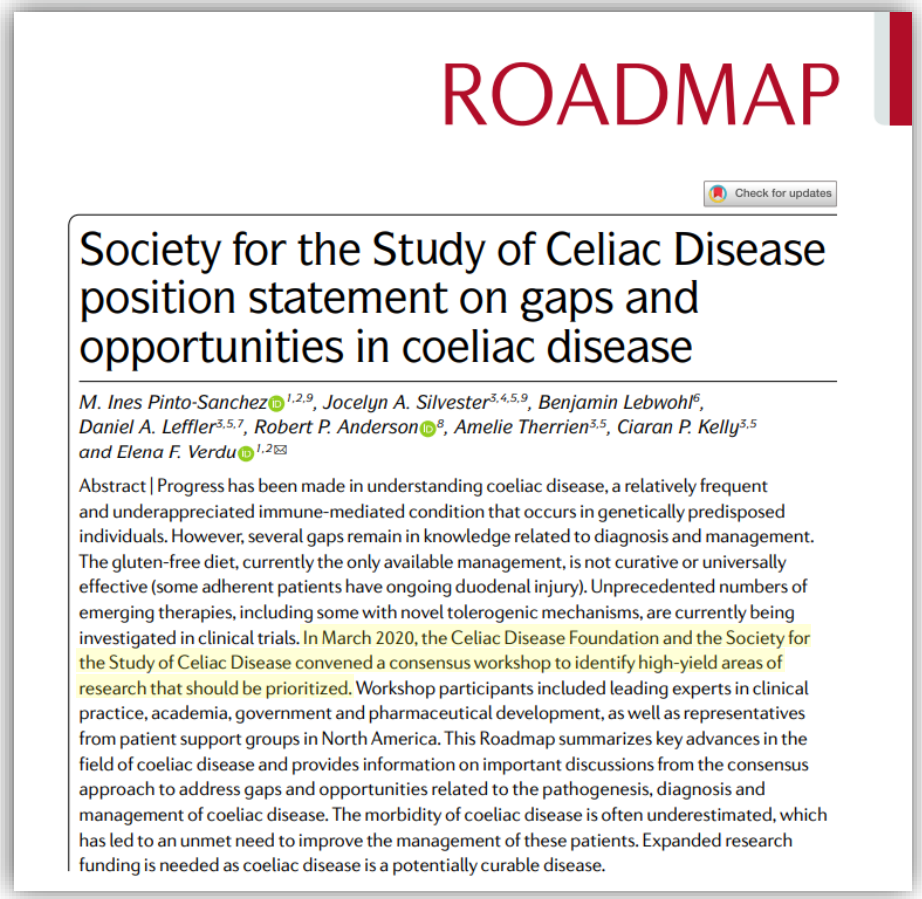
iQualifyCeliac Study Screening



iQualifyCeliac Study Screening



SSCD and CDF Collaborations: Consensus Workshop



ROADMAP

Check for updates

Society for the Study of Celiac Disease position statement on gaps and opportunities in coeliac disease

M. Ines Pinto-Sanchez[1,2,9], Jocelyn A. Silvester[3,4,5,9], Benjamin Lebwohl[6], Daniel A. Leffler[3,5,7], Robert P. Anderson[8], Amelie Therrien[3,5], Ciaran P. Kelly[3,5] and Elena F. Verdu[1,2]✉

Abstract | Progress has been made in understanding coeliac disease, a relatively frequent and underappreciated immune-mediated condition that occurs in genetically predisposed individuals. However, several gaps remain in knowledge related to diagnosis and management. The gluten-free diet, currently the only available management, is not curative or universally effective (some adherent patients have ongoing duodenal injury). Unprecedented numbers of emerging therapies, including some with novel tolerogenic mechanisms, are currently being investigated in clinical trials. In March 2020, the Celiac Disease Foundation and the Society for the Study of Celiac Disease convened a consensus workshop to identify high-yield areas of research that should be prioritized. Workshop participants included leading experts in clinical practice, academia, government and pharmaceutical development, as well as representatives from patient support groups in North America. This Roadmap summarizes key advances in the field of coeliac disease and provides information on important discussions from the consensus approach to address gaps and opportunities related to the pathogenesis, diagnosis and management of coeliac disease. The morbidity of coeliac disease is often underestimated, which has led to an unmet need to improve the management of these patients. Expanded research funding is needed as coeliac disease is a potentially curable disease.

NIH ADCC Meeting and Accelerating Progress Workshop

Celiac Disease-Focused Autoimmune Disease Coordinating Committee (ADCC) Meeting Agenda

Teleconference/Videoconference
May 29, 2020

1:00 PM – 1:10 PM **Welcome and Introductions**
Ellen Goldmuntz, M.D., Ph.D.
Annette Rothermel, Ph.D.,
Division of Allergy Immunology and Transplantation, NIAID

1:10 PM – 1:25 PM **Updates from Federal Agencies, Private Organizations and Foundations**

1:25 PM – 1:40 PM **Unmet Need in Celiac Disease - Patients' Views**
Marilyn Geller, CEO, Celiac Disease Foundation

1:40 PM – 2:05 PM **Basic Research, Unmet Needs and Opportunities**
Bana Jabri, M.D, Ph.D., Professor of Pediatrics, The University of Chicago

2:05 PM – 2:30 PM **Clinical-Translational Research: Gaps and Opportunities in Prevention and Diagnosis**
Joseph A. Murray, M.D., Professor of Medicine, The Mayo Clinic

2:30 PM – 2:55 PM **Non-dietary treatments for celiac disease: Why? Who? What?**
Ciarán P. Kelly, M.D., Professor of Medicine, Harvard Medical School

2:55 PM - 3:00 PM **Wrap up and Discussion of Future Meetings**
Ellen Goldmuntz, M.D., Ph.D.

Accelerating Progress in Celiac Disease Research Workshop

Agenda and Faculty List

Day 1: Thursday, March 18, 2021		
9:00 am – 10:00am – Speaker Check-in (Check Slides, Audio, Power points)		
10:00 - 10:05 **(all times in EST)**	Welcome	Dr. Charles Hackett, Deputy Director, Division of Allergy, Immunology, and Transplantation, NIAID
	Meeting Announcements and Logistics	NIH Workshop Organizers
	NIH Workshop Organizers Dr. Annette Rothermel *(NIAID)* Dr. Terez Shea-Donohue *(NIDDK)* Dr. Patricia Greenwel *(NIDDK)*	**Workshop Co-Organizers:** Dr. Joseph Murray *(Mayo Clinic Rochester)* Dr. Alessio Fasano *(MGH)* Dr. Andrei Ivanov (*Cleveland Clinic)*
Session I: Celiac Disease Overview **Session Moderator**: Dr. Edwin Liu (*Children's Hospital Colorado)* Q&A Monitor – Dr. Annette Rothermel *(NIAID)* 3-minute reminder from Timekeeper		
10:05 -10:30 *25 mins*	Celiac Disease: The Spectrum of Disease and its Outcomes	Dr. Benjamin Lebwohl *(Columbia, NYC)*
10:30 - 10:45 *15 mins*	Patient Advocate	Ms. Marilyn Geller *(Celiac Disease Foundation)*
10:45 - 11:05 *20 mins*	How Does Celiac Disease Fit into the Spectrum of Autoimmune Diseases	Dr. Mark Anderson *(UCSF)*
11:05 - 11:25 *20 mins*	The Genetics of Celiac Disease: From GWAS to Single Cell RNAseq to Celiac Disease-On Chip	Dr. Iris Jonkers *(University of Groningen, NL)*

NIH Notice of Special Interest in Celiac Disease and RCDC

Apply for Research Funds To Accelerate Progress of Celiac Disease Research

Funding News Edition: **December 15, 2021**

See more articles in this edition

If you are a researcher who can advance our understanding of the etiology and pathogenesis of celiac disease research, apply for funds through the Notice of Special Interest (NOSI): Accelerating Progress in Celiac Disease Research. NIAID participates in this NOSI alongside three other NIH institutes and centers (ICs): National Center for Complementary and Integrative Health (NCCIH), National Cancer Institute (NCI), and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Research Objectives

Clinical manifestations of celiac disease are multifaceted, and its pathogenesis can involve a combination of predisposing genes, gluten, and environmental factors. While many aspects of the underlying mechanism are well understood, there remains an unmet need in understanding celiac disease pathogenesis, including a limited understanding of pathways of disease and tissue destruction, and the cause of tolerance loss to a component of food.

This NOSI encourages research applications that include the following NIAID-relevant research topics:

- Underlying mechanisms of loss of oral tolerance
- Autoimmune triggers in celiac disease
- Strategies that can eliminate and revert the pathogenic memory gluten-specific CD4 memory T cells
- Cellular circuits and mechanisms involved in tissue destruction
- The role of microbiota in the loss of oral tolerance and tissue destruction
- The discovery of immune modulating interventions and strategies to prevent celiac disease and/or restore tolerance
- Biomarkers that predict tissue destruction in celiac disease

Research/Disease Areas (Dollars in millions and rounded)	2014	2015	2016	2017	2018	2019	2020	2021	2022 Estimated	2023 Estimated	2019 US Mortality [19]	2019 US Prevalence SE [19]
Caregiving Research	+	+	$74	$87	$121	$151	$217	$244	$253	$255	-	-
Celiac Disease	+	+	+	+	+	+	+	$9	$9	$9	-	-
Cerebral Palsy	$21	$20	$26	$26	$26	$28	$35	$30	$32	$34	3,822	-
Cerebrovascular	+	+	$520	$610	$718	$759	$888	$999	$1,034	$1,019	256,352	-
Cervical Cancer	$116	$99	$99	$114	$112	$106	$113	$120	$126	$124	4,687	1.1% (0.09%)
Charcot-Marie-Tooth Disease	$14	$14	$11	$10	$12	$13	$15	$17	$18	$17	-	-
Child Abuse and Neglect Research	$30	$27	$29	$29	$41	$43	$50	$40	$43	$41	-	-

FDA CDER and Patient Advocacy in Drug Development

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI (GREAT VI) Workshop on Celiac Disease

Virtual meeting
July 22, 2021

AGENDA

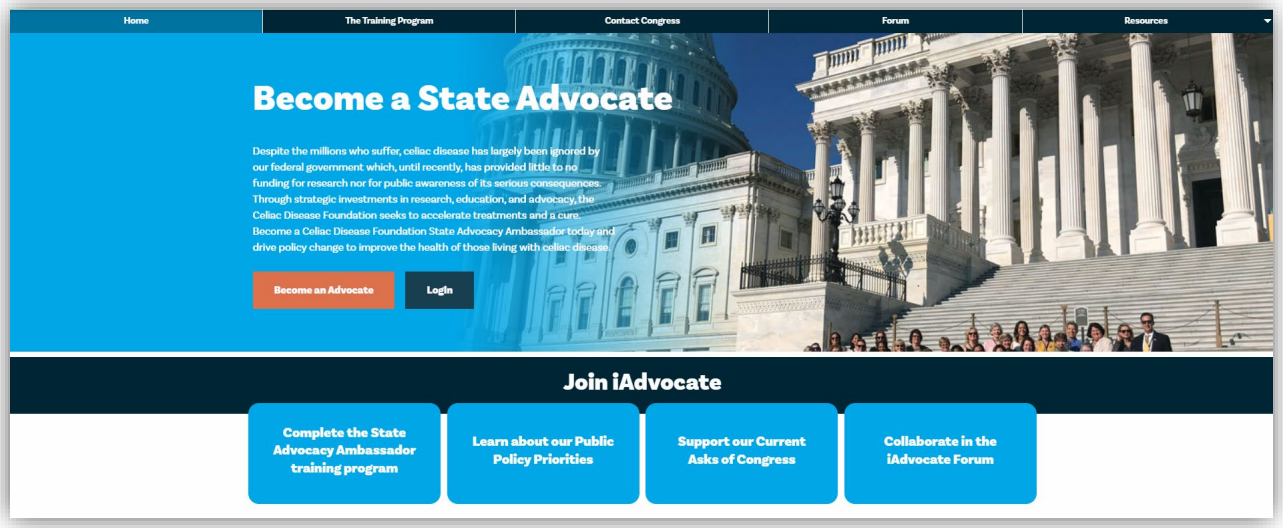
The goal of today's workshop is to discuss the overall approach to drug development in celiac disease that includes an assessment of both clinical symptoms and histology. The workshop will focus the discussion on the histologic endpoints to assess treatment benefit in patients with celiac disease; regulatory framework for pediatric drug development in celiac disease; and the role of gluten challenge in clinical trials to provide a forum for open discussion between stakeholders to facilitate drug development.

10:05 a.m. Panel discussion and Q & A* *(40 min)*

Panelists: Prista Charuworn, Stephen Lagana, Irena Lavine, Benjamin Lebwohl, Edwin Liu, Marie Robert, Jocelyn Silvester, Kelsey Smith

11:50 a.m. Panel discussion and Q & A* *(40 min)*

Panelists: Prista Charuworn, Alessio Fasano, Tyler Friedman, Kathy and Beckett Hardin, Mona Khurana, Maureen Leonard, Suna Seo, Christopher St. Clair, Marisa Stahl



FDA Draft Guidance Public Submissions

SSCD
SOCIETY FOR THE STUDY OF CELIAC DISEASE

June 8, 2022

The Society for the Study of Celiac Disease (SSCD) is an organization of medical, scientific and allied health professionals, formed to advance research in celiac disease and gluten-related disorders and to improve clinical care, including diagnosis and treatment. The SSCD thanks the FDA for providing expectations for the development of therapies for adjunctive treatment to a gluten-free diet.

We support the development of such guidance as facilitating the therapies for celiac disease, for which the unmet need is substant symptoms and/or enteropathy, the inevitability of gluten exposu nature of the gluten-free diet are key issues that the scientific an and will continue to emphasize.

We recognize the difference between guidance for drug develop patient population for the drug after its testing and approval; ind enteropathy together with symptoms represent a relatively small celiac disease who are looking for, and would benefit from, non-

Here, we summarize some specific concerns related to the draft g

- While the term "gluten-free diet" is commonly invoked as disease, it is important to note that removal of all gluten i treatment in celiac disease.[1] Rather, the goal of clinical ca disease control with minimizing the burden and quality of diet. [2] The largest clinical unmet need for treatments in ce of symptoms in patients who are truly not exposed to glut control in spite of ongoing efforts at gluten avoidance.
- The requirement for improvement or resolution of histolo weeks may preclude the development of therapies that in symptoms in the face of stable enteropathy. Villus archite heal slowly, and in some cases may persist for years, even gluten avoidance. This is particularly a concern in older ad some flexibility in expectation of the magnitude of expect variables such as patient's age and duration of disease. As presentations to the FDA,[3] markers of immunologic respo 2, may be an alternative measure of biologic disease modi is more responsive than histology. [4]
- The draft guidance recommends using a clinically accepted histologic scale such as the Marsh-Oberhuber classification (lines 94-98). This scale is occasionally used in clinical practice for the diagnosis of celiac disease (with "villus atrophy" or "villus blunting" without a classification more commonly used), but has less reproducibility than the villus height/crypt depth ratio (VH:CD), a tool that is increasingly used by investigators due to its responsiveness to change, fine scaling, and utility as a continuous variable. [5] Further, the Marsh-Oberhuber classification collapses two parameters, intraepithelial lymphocyte count and villus architecture, whose responsiveness are not highly correlated and have both different biologic mechanisms and clinical importance.
- The draft guidance includes the recommendation for dietitian involvement during the treatment period of a candidate drug. Assessment by an expert dietitian is not standardized, nor is availability widespread. A more broadly defined dietary counseling session (as opposed to involvement of a registered dietitian with specialized expertise in the gluten-free diet) directed at gluten avoidance may be more practical. We believe that *intensive* dietitian involvement throughout a trial may raise the likelihood of type 2 error in trials, but involvement to a more modest extent is appropriate.
- There is a substantial unmet need for children and adolescents with celiac disease, groups for whom unique considerations for diagnosis and monitoring are at play. This was a prominent component of the Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics conference hosted by the FDA in July, 2021; we hope and expect that this draft guidance will be adapted for pediatric and adolescent populations.[3]

We look forward to partnering with the FDA as the development of non-dietary therapies for celiac disease proceeds.

SSCD Executive Council
Benjamin Lebwohl, MD, MS, President
Ritu Verma, MD, President-Elect
Ciaran Kelly, MD, Past President
Daniel Leffler, MD, MS, Secretary
Vanessa Weisbrod, Treasurer
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Maureen Leonard, MD, MMSc, Councilor
Amelie Therrien, MD, MSc, Councilor

SSCD Writing Committee
Daniel Adelman, MD
Marilyn Geller
Joseph Murray, MD

Celiac Disease FOUNDATION
celiac.org

June 8, 2022

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Submitted via www.regulations.gov

Re: Docket Number FDA-2021-D-1238 for "Celiac Disease: Developing Drugs for Adjunctive Treatment to a Gluten-Free Diet"

Dear Sir or Madam:

The Celiac Disease Foundation (CDF) is the nation's leading nonprofit organization dedicated to improving the lives of the more than three million Americans affected by this chronic, immune-mediated disease by accelerating the development of treatments, and ultimately a cure for celiac disease.

CDF was pleased to see the Food and Drug Administration's (FDA) draft Guidance to Industry, titled "Celiac Disease: Developing Drugs for Adjunctive Treatment to a Gluten-Free Diet." CDF thanks FDA for hearing recognizing that the only current "treatment" which is, for the vast majority not achievabl that are adjunctive to the gluten-free diet. Wit and despite patients' best efforts to adhere to ongoing symptoms. The publication of the dr alleviating the suffering of celiac patients sponsors as they strive to develop safe and eff

CDF is proud to have supported the FDA G appreciates that FDA gave a forum for patie monotherapy that would allow them to regul for treatments targeting the serious need to mit can arise from accidental exposures to gluten from cross-contamination in food, where the impact patients' ability to attend work or sch living. FDA also allowed the patients and c hardship brought on by the hypervigilance re and the guilt and fear experienced by patients, their medically required diet creates for all wit

We thank FDA for hearing the patients' concerns and desires, and it is our hope that this Guidance will provide clarity in the development of treatments that benefit patients with celiac disease.

CDF appreciates that in order to develop safe and effective treatments, rigorous enrollment criteria are needed in order to assure clear and unequivocal evidence of the safety and efficacy of future treatments. We further understand that to generate clear and interpretable data from properly conducted and well controlled clinical trials, any potential therapeutic must be tested in a population that has objectively measurable disease. CDF is committed to educating its constituency on the importance of participating in clinical trials and will work with industry sponsors to enroll studies of therapies being conducted under an Investigational New Drug Application. We hope that the enrollment criteria outlined in the draft Guidance will not restrict either access or enrollment in these studies.

Lastly, CDF understands that in a perfect world where gluten avoidance is easily achievable a therapeutic treatment would not be necessary, but in the real world, very few can truly achieve the necessary level of gluten avoidance to heal an injured gut or alleviate associated symptoms. Therefore, development of therapeutically beneficial treatments is imperative, and we urge FDA to monitor the progress of sponsored studies to enroll sufficient numbers of participants to achieve the objectives of the Guidance and if needed, adjust those enrollment criteria that appear to impede the timely development of novel treatments for patients with celiac disease.

Sincerely,

Marilyn G. Geller
Chief Executive Officer
Celiac Disease Foundation

Thank you to the SSCD
For more information visit celiac.org/iqualifyceliac

Marilyn G. Geller
Chief Executive
Celiac Disease Foundation