



# Moving away from a 'one size fits all' clinical model in celiac disease: Can we and should we?

Daniel Leffler MD, MS, AGAF

Beth Israel Deaconess Medical Center

Associate Professor of Medicine



CELIAC RESEARCH  
PROGRAM  
HARVARD MEDICAL SCHOOL

Harvard Medical School

Senior Medical Director Takeda Pharmaceuticals



## Disclosures

- Employee Takeda Pharmaceuticals
- Executive Committee Foundation for Celiac Disease Outcome Measures
- Statements and opinions in this presentation are mine and do not represent the views Takeda or any other organizations



# Segmenting the Celiac Disease Population

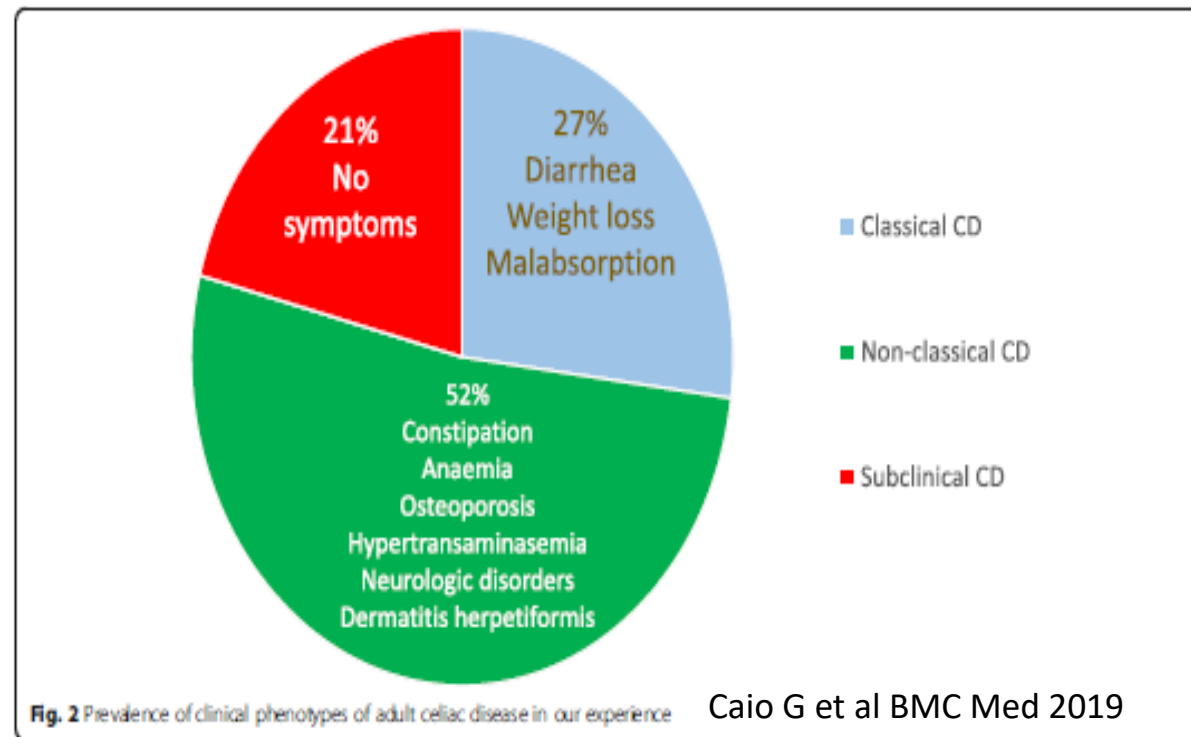
1. What we do currently
2. Should we do more
3. Possibilities for patient segmentation

# Segmenting the Celiac Disease Population

1. What we do currently
2. Should we do more
3. Possibilities for patient segmentation

# Current ways of stratifying the celiac disease population

- At Diagnosis
  - By Presentation
    - Classic vs other
  - By Serology
    - Seropositive vs. seronegative
  - By Age of diagnosis
    - Pediatric vs. adult
  - By Genetics
    - DQ2 vs. DQ8
  - By Degree of intestinal injury
    - Marsh...

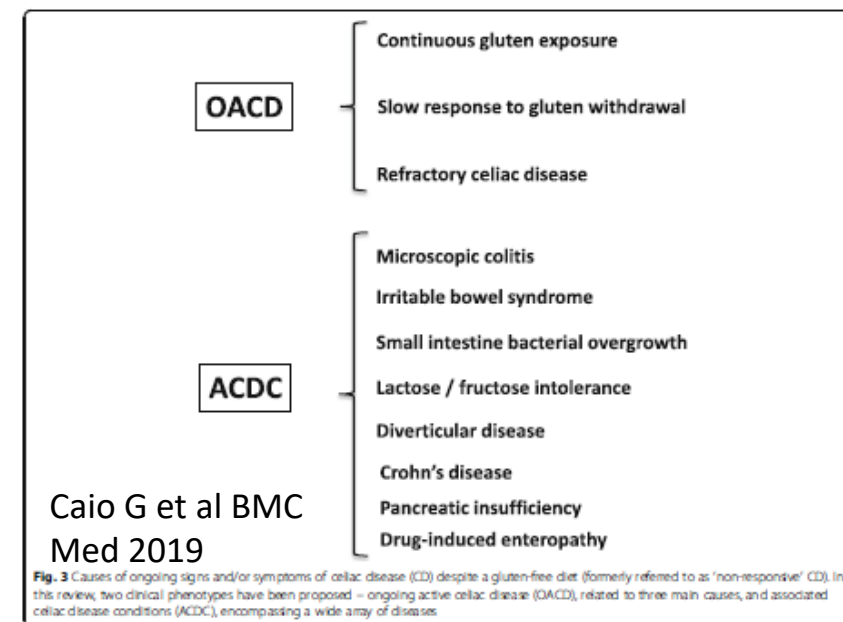
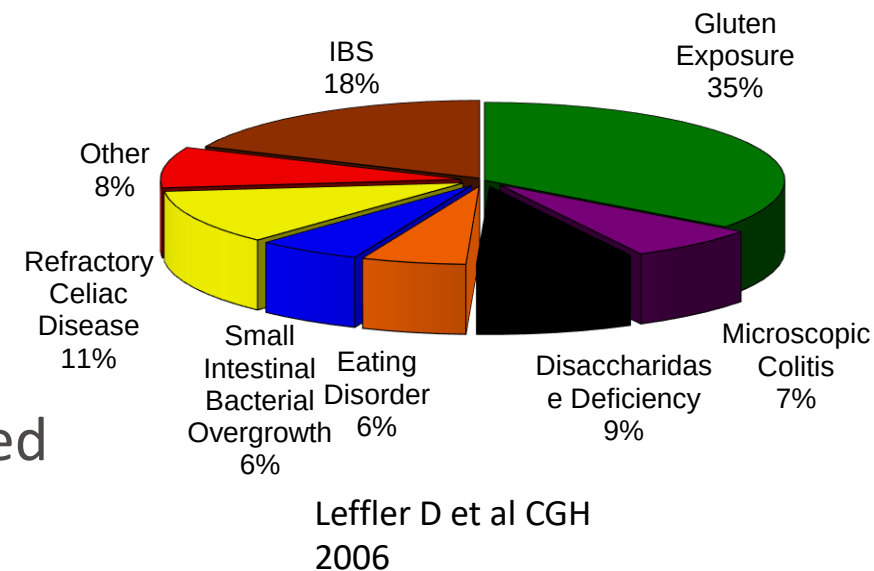


Helpful for screening studies and publications allowing for comparison across populations but not for clinical care

# Current ways of stratifying the celiac disease population

- After Diagnosis
  - By response to the gluten free diet
    - Responsive vs. non-responsive
    - Ongoing active celiac disease (OACD) vs. Associated CD conditions (ACDC)
    - ‘Diet controllable’ vs. refractory
    - Type 1 vs. Type 2 refractory celiac disease

Helpful for initial clinical assessment but less so for treatment (outside of RCD subtyping)



# Segmenting the Celiac Disease Population

1. What we do currently
2. **Should we do more**
3. Possibilities for patient segmentation

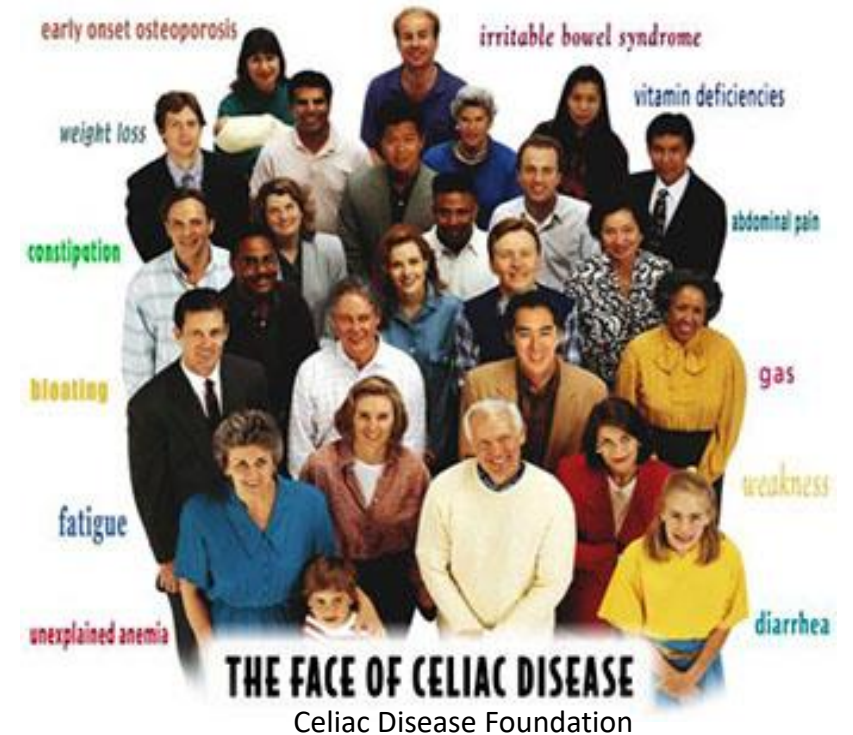
# Why might we want to stratify the celiac population

- Its what all the 'mature' immune diseases do

Can we move from this:

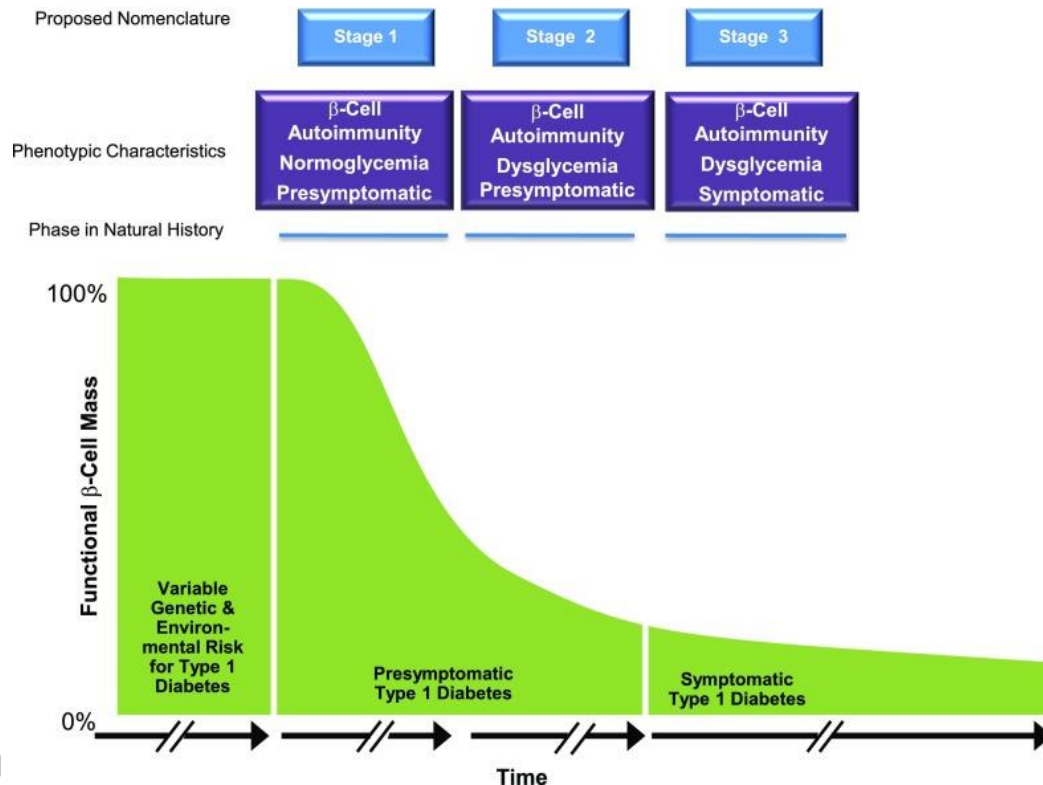


To this?



# Type 1 Diabetes

- “Adoption of [a] staging classification provides a standardized taxonomy for type 1 diabetes and will aid the development of therapies and the design of clinical trials to prevent symptomatic disease, promote precision medicine, and provide a framework for an optimized benefit/risk ratio...to prevent symptomatic disease”



Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association

*Diabetes Care* 2015;38:1964–1974 | DOI: 10.2337/dc15-1419

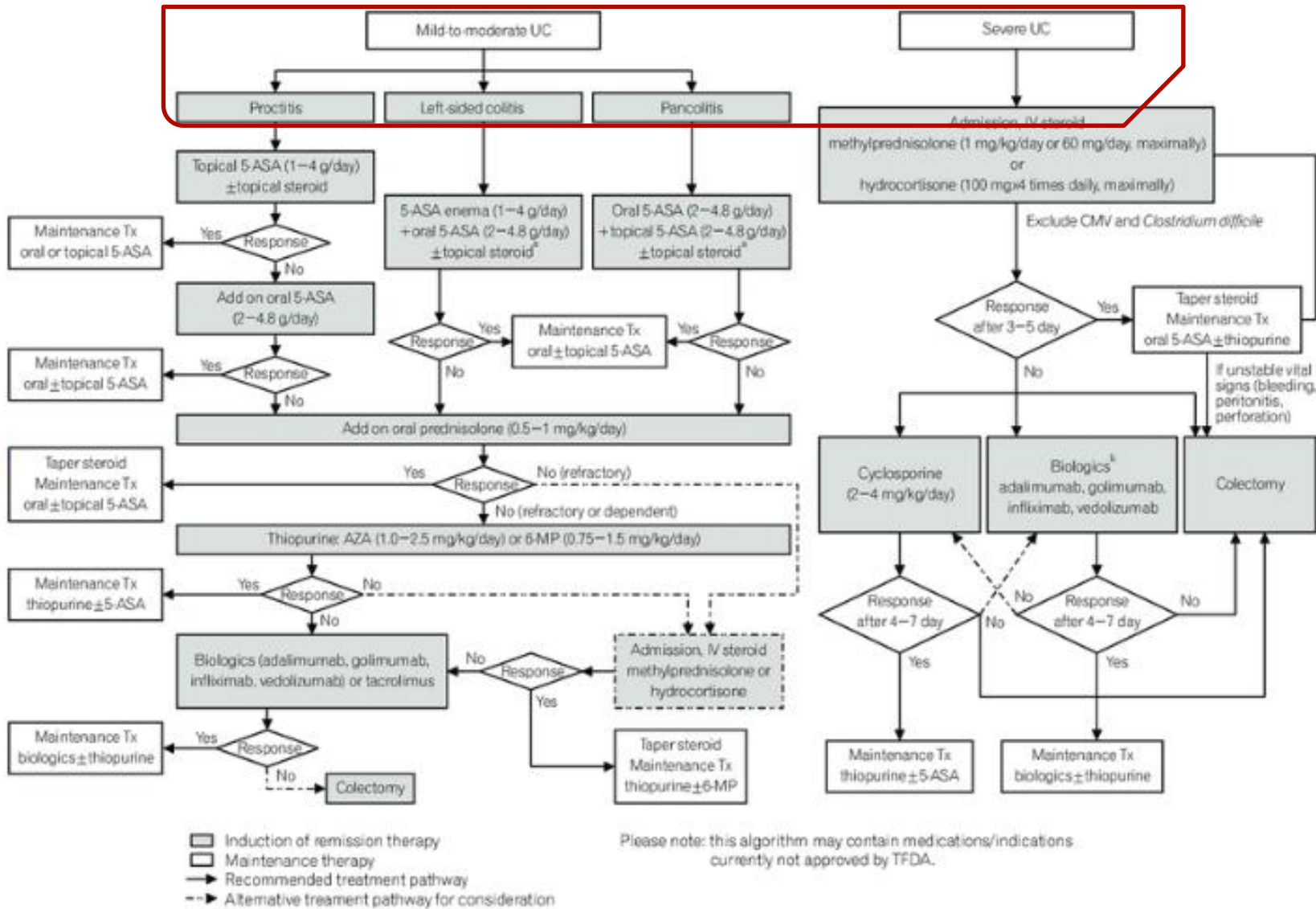
Richard A. Insel,<sup>1</sup> Jessica L. Dunne,<sup>1</sup>  
Mark A. Atkinson,<sup>2</sup> Jane L. Chiang,<sup>3</sup>  
Dana Dabelea,<sup>4</sup> Peter A. Gottlieb,<sup>5</sup>  
Carla J. Greenbaum,<sup>6</sup> Kevan C. Herold,<sup>7</sup>  
Jeffrey P. Krischer,<sup>8</sup> Åke Lernmark,<sup>9</sup>  
Robert E. Ratner,<sup>3</sup> Marian J. Rewers,<sup>5</sup>  
Desmond A. Schatz,<sup>2</sup> Jay S. Skyler,<sup>10</sup>  
Jay M. Sosenko,<sup>10</sup> and Anette-G. Ziegler<sup>11</sup>

# Ulcerative Colitis

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# Segmenting the Celiac Disease Population

1. What we do currently
2. Should we do more
3. Possibilities for patient segmentation in celiac disease

# Segmenting the Celiac Disease Population

1. What we do currently
2. Should we do more
3. Possibilities for patient segmentation
  - Biology
  - Clinical phenotype
  - Patient preference

# Potential ways to stratify patients

- **Biology**
- Clinical phenotype
- Patient preference

# Gluten Response in Patients with Celiac Disease

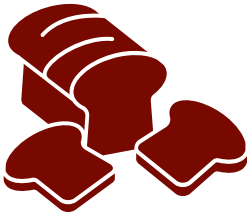
HLA DQ2/8 Positive

**START**  
**Gluten**  
**Challenge**

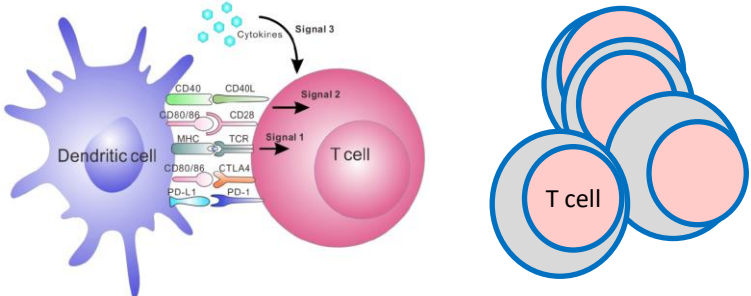


**Predisposition**

**TIME**  
**0**



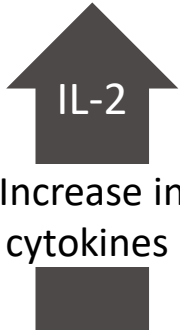
Increase in Gut Homing and Gluten-specific T cells



**Adaptive Immune Response to Gluten**

**4**  
**HRS**

**Acute Response**

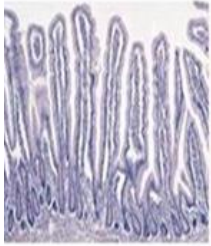


Nausea

**6**  
**DAYS**

**>15**  
**DAYS**

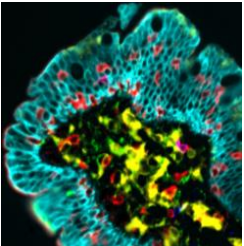
**Intestinal Damage**



Morphometry  
Vh:Cd



Video capsule  
endoscopy

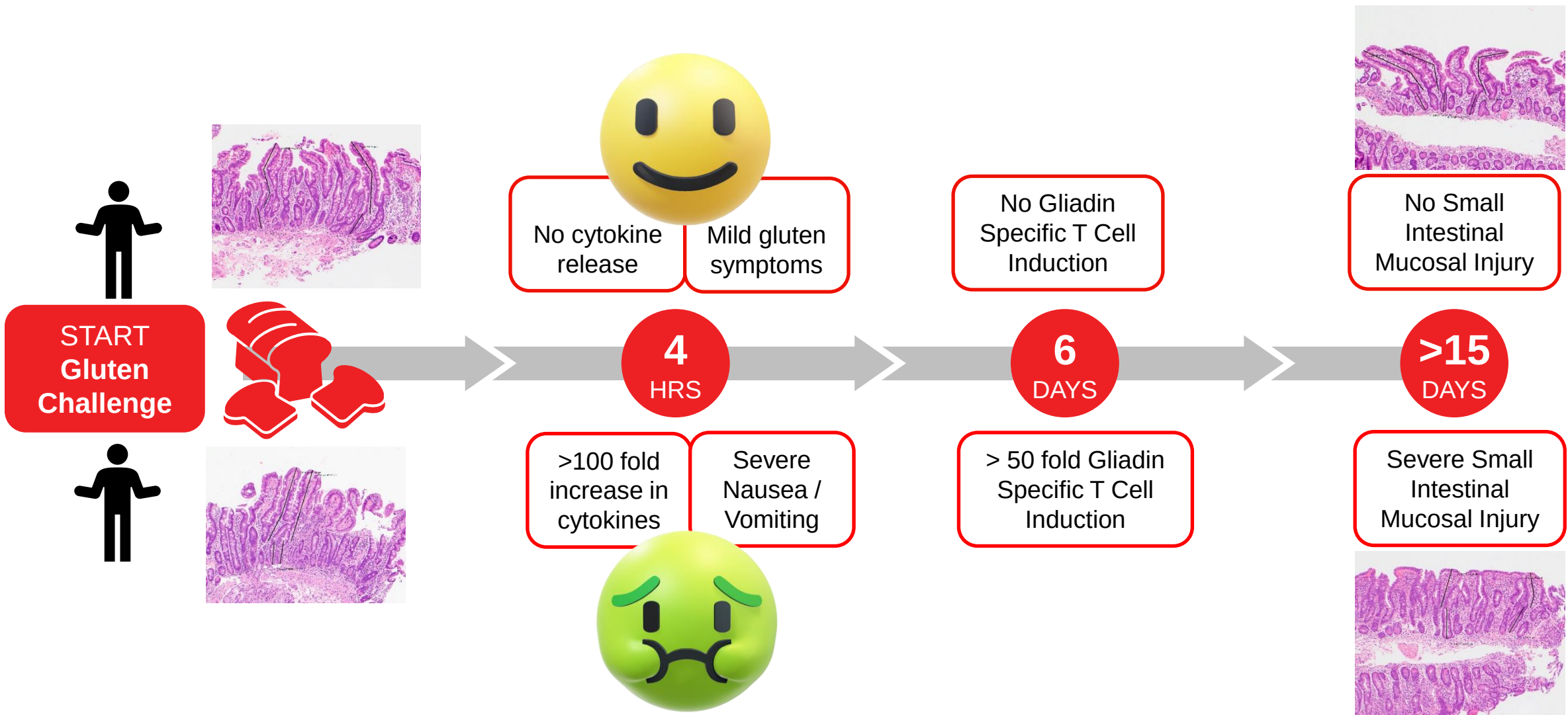


Immunohisto-  
chemistry

Evaluating Responses to Gluten Challenge: A Randomized, Double-Blind, 2-Dose Gluten Challenge Trial

Maureen M. Leonard,<sup>1,2</sup> Jocelyn A. Silvester,<sup>2,3,4</sup> Daniel Leffler,<sup>2,5</sup> Alessio Fasano,<sup>1,2</sup> Ciarán P. Kelly,<sup>2,4</sup> Suzanne K. Lewis,<sup>6</sup> Jeffrey D. Goldsmith,<sup>2,7</sup> Elliot Greenblatt,<sup>8</sup> William W. Kwok,<sup>9</sup> William J. McAuliffe,<sup>5</sup> Kevin Galinsky,<sup>5</sup> Jenifer Siegelman,<sup>5</sup> I-Ting Chow,<sup>9</sup> John A. Wagner,<sup>5</sup> Anna Sapone,<sup>5</sup> and Glenda Smithson<sup>5</sup>

# Different Patients Can Have Highly Variable Gluten Sensitivity



# Mucosal markers on a GFD are associated with threshold for inducing villus damage

## COMMUNICATION

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SCIENCE  
Open Access

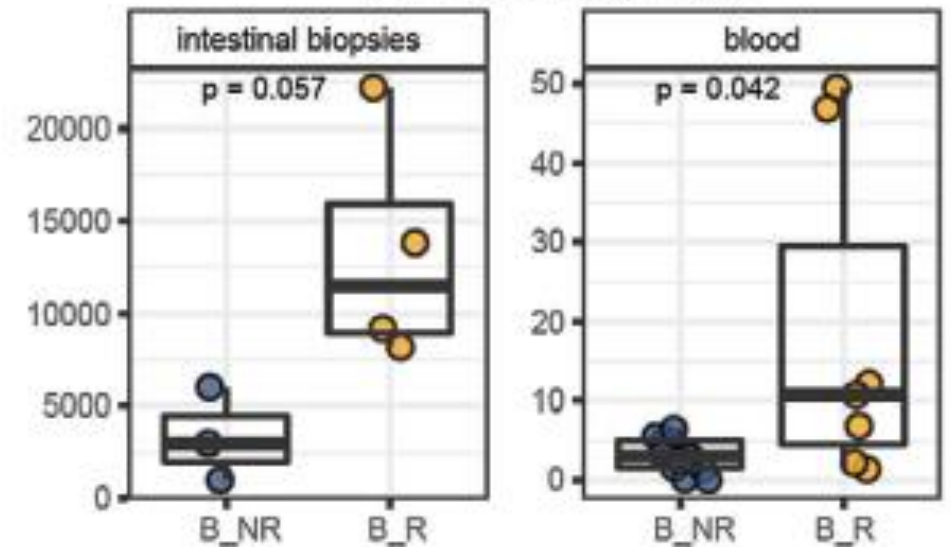
www.advancedscience.com

### In Well-Treated Celiac Patients Low-Level Mucosal Inflammation Predicts Response to 14-day Gluten Challenge

Jorunn Stamnaes,\* Daniel Stray, Maria Stensland, Vikas K. Sarna, Tuula A. Nyman, Knut E. A. Lundin, and Ludvig M. Sollid\*

- Deep remission is associated with resistance to gluten induced mucosal injury
- Is deep remission a phenotype or simply a result of less chronic gluten exposure?

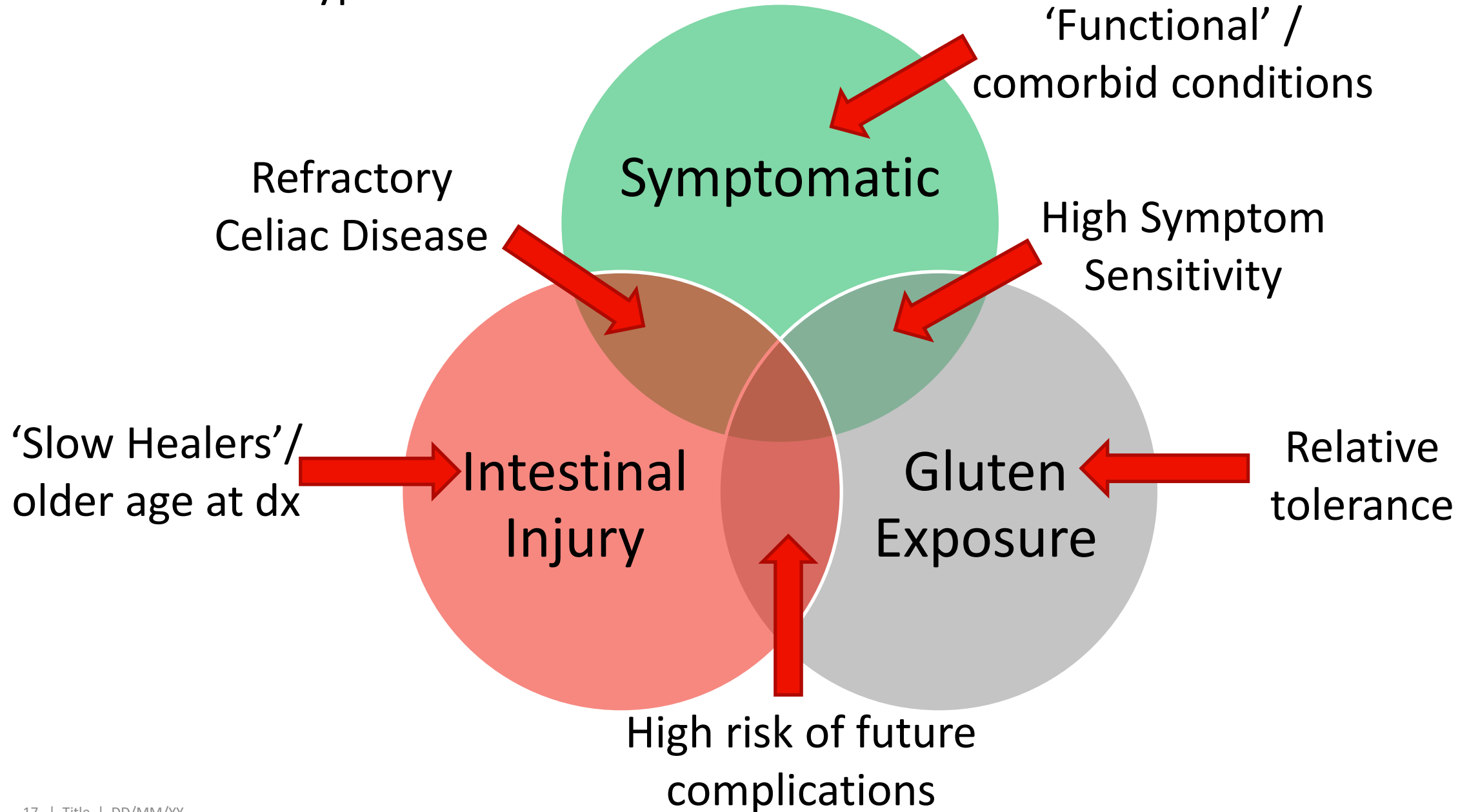
#### Gluten specific CD4+ T-cell frequency before challenge



# Potential ways to stratify patients

- Biology
- **Clinical phenotype**
- Patient preference

# Clinical Phenotype on a GFD



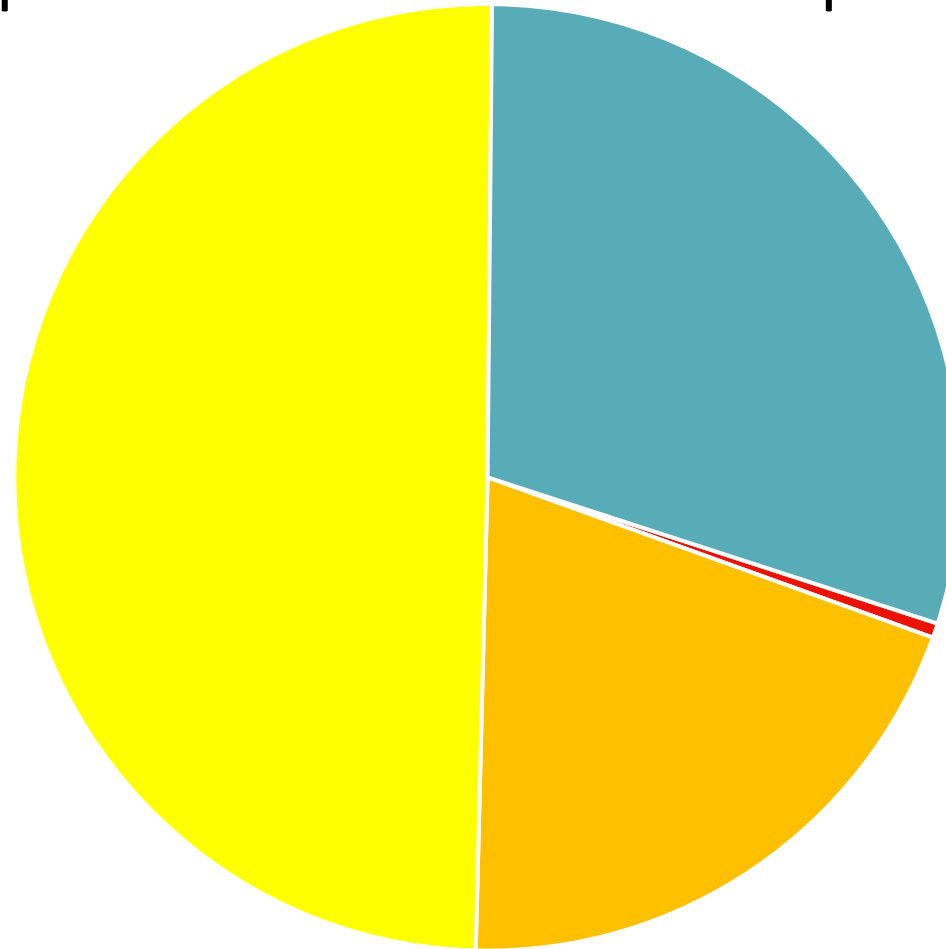
# Potential ways to stratify patients

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Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity: WHO

Proportion of Overall Celiac Population

- Refractory celiac disease
- Active disease due to imbalance between sensitivity and exposure
- Controlled but unsatisfied
- GFD is enough



## Conclusions

- In most other diseases, segmentation of the patient population allows individualized treatment approaches and can guide impactful research
- The celiac disease population is highly heterogeneous and there are multiple potential opportunities to define different celiac disease populations
- While a pragmatic structure for patient segmentation in celiac disease remains to be defined, a combination of biologic and patient centered factors may be most appropriate