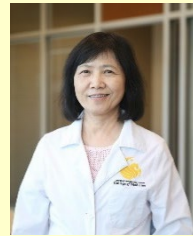


Impact of a Gluten Free Diet on Celiac Disease as Measured by the NIH PROs



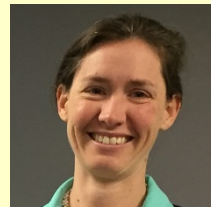
UCF Health GI Research Group

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Celiac Disease¹

- Celiac disease is an autoimmune disorder which affects the digestive process of the small intestine.
- Celiac disease is estimated to affect at least 1% of the population, or approximately nearly 3 million people in the United States.
- When a person with celiac disease consumes gluten, a protein found in wheat, rye and barley, the individual's immune system attacks the small intestine which reduces the absorption of nutrients into the body.
- Celiac disease results in significant GI distress, but it has been associated with cognitive decline and a variety of psychological symptoms and cognitive deficits such as “brain fog.”

¹ Rubio-Tapia, A., Hill, I. D., Kelly, C. P., Calderwood, A. H., & Murray, J. A. (2013). ACG clinical guidelines: diagnosis and management of celiac disease. *The American Journal Of Gastroenterology*, 108(5), 656–676. <https://doi-org.ezproxy.net.ucf.edu/10.1038/ajg.2013.79>

Behavioral Integration in the GI Clinic

- During the 2017 – 2018 academic year we integrated behavior specialists into the UCF GI Clinic to provide comprehensive assessment using various NIH Health Measures (Patient-Reported Outcome Measurement Information System (PROMIS), NIH Toolbox, and Neuro-QoL) using an iPad while the patient was waiting to see the specialist.^{3,4}



³ <http://www.healthmeasures.net/>

⁴ Patients signed informed consent to participate

Our Treatment Protocol

- Once diagnostic test results are collected and there is confidence the diagnosis of Celiac Disease (through serology, biopsy, and phenotypic analysis), the primary treatment is to place patients on a Gluten Free Diet (GFD)⁵.
- This is accomplished through by referral to Registered Dieticians and supplementary psychoeducation with Behavior Specialists during a clinic appointment (baseline).
- The goal of a GFD is to eliminate the toxic ingredients that cause the autoimmune reaction and include nutrient-rich alternatives:
 - Safe:** Meats, poultry, fish, fruits, vegetables, legumes, dairy products, rice, corn, potato, oats, yucca, buckwheat, quinoa, millet, and teff.
 - Unsafe:** Wheat, some oats, rye, and barley.
- Cookbooks, apps (such as the “Gluten Free Barcode Scanner”) and other online resources are provided to the patient.
- The UCF Health GI clinic routinely follows patients at 3-month intervals with clinic appointments and repeated lab work (follow-up).

⁵ Case, S. (2005). The gluten-free diet: how to provide effective education and resources. *Gastroenterology*, 128(4 Suppl 1), S128–S134.

Outline

- We will be presenting our treatment protocol as applied to two new cases of Celiac Disease in the UCF Health GI Clinic
- They were started on a GFD in the 2017-2018 academic year.
- This will include description of
 - Patient Characteristics
 - Clinical/Lab Measures
 - Measures of Patient Reported Outcomes (GI-PROMIS, NIH Toolbox, and Neuro-QoL)

Case 1

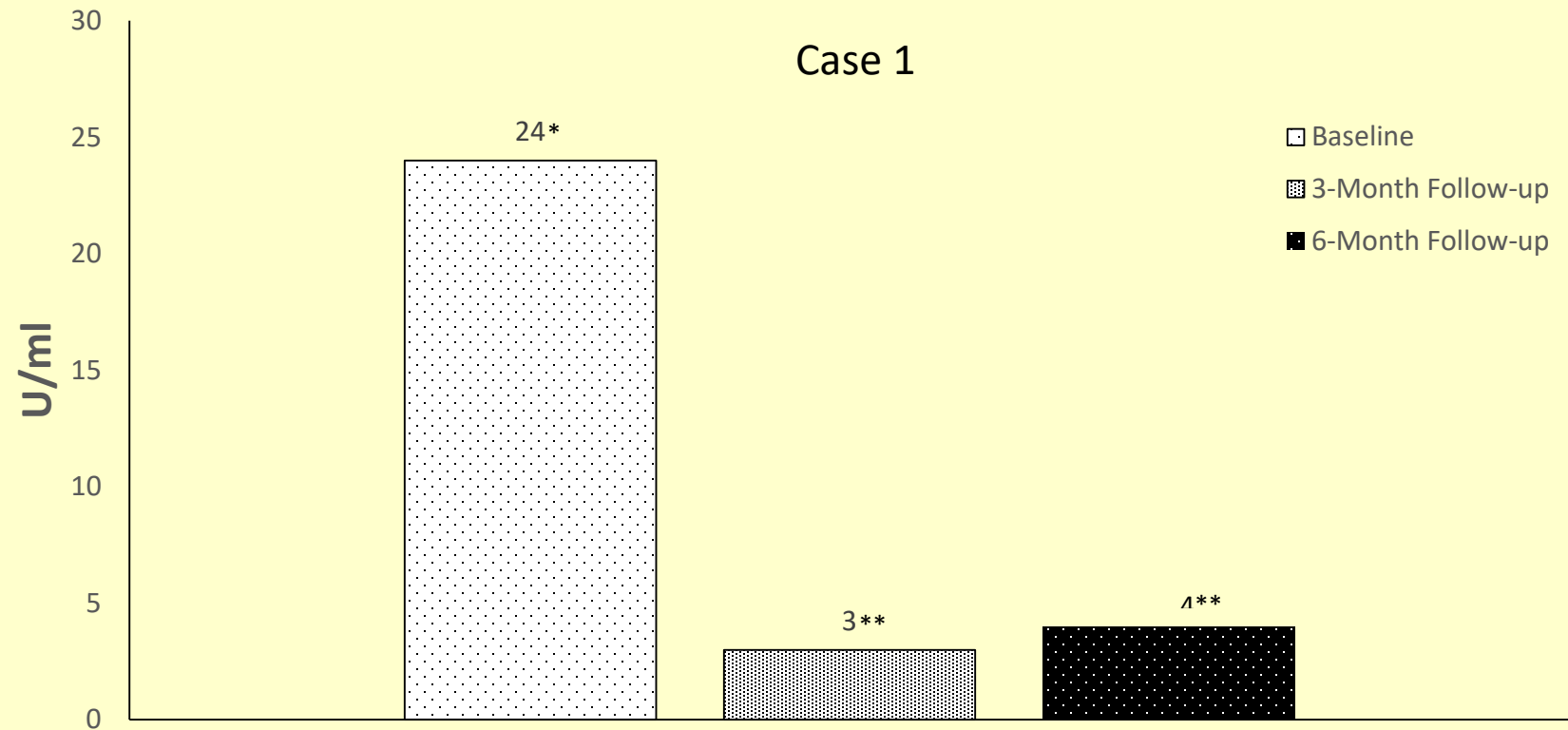
Table 1

Case 1: Summary of Patient Characteristics at Baseline

Measure	
Age	20
Sex	Female
Race	White
Marital Status	Single
Education	H.S. degree, College Student
BMI	27.2
Presenting Symptoms on Intake Forms	Bloating, Constipation, Rash, Fatigue, & Headache
Other Reported Symptoms on Intake Forms	Brain Fog, Bruising, and Lightheadedness

Table 2
Case 1: Summary of Medical & Lab Measures at Baseline

Measure	
Total IgA (serology)	Normal
Endomysial (EMA) IgA (serology)	Positive
Marsh Score (biopsy)	3C
HLA DQ2 (phenotypic marker)	Positive
HLA DQ8 (phenotypic marker)	Negative



*Positive compared to laboratory reference interval
**Negative compared to laboratory reference interval

Figure 1. Tissue Transglutaminase (tTG) Antibody, IgA, at Baseline and Follow-up

Case 1: Interpretation of Medical & Lab Results

- Normal Total IgA indicates the immune system is not suppressed (serology).
- Tissue Transglutaminase (tTG) Antibody indicates gluten sensitivity (serology).
- Positive EMA has a high specificity with Celiac Disease (serology).
- A Marsh Score of 3C is consistent with Celiac Disease (biopsy).
- 85% of Individuals with Celiac Disease are HLA DQ2 Positive (phenotypic marker).

Tissue Transglutaminase (tTG) Antibody levels at the follow-up sessions indicate patient is compliant with GFD.

Interpretation of Significant Change in Case Studies

Reliable Change Index⁶

- The reliable change index is used to determine if there has been improvement or deterioration in functioning that exceeds the probable range of measurement error.
- Thus, all baseline – retest difference scores are interpreted after adjusting for measurement error.
- Specifically, the standard error of the difference (SE_{diff}) is used to create a Confidence Interval (CI) around the baseline-retest difference score.
- Difference scores are considered reliable when they exceed the $p < .05$ level.

⁶ Iverson, G. L. (2018). Reliable Change Index. In J. S. Kreutzer et al. (eds.), *Encyclopedia of Clinical Neuropsychology*, pp. 2984 – 2987. Springer International Publishing AG, <https://doi.org/10.1007/978-3-319-57111-9>.

Case 1: Psychometric Assessment of GI Health (Description of GI-PROMIS Scales)

- We used a subset of 4 GI-PROMIS Scales (v1.0)
 - Belly Pain (5 items)
 - Constipation (9 items)
 - Diarrhea (6 items)
 - Gas & Bloating (13 items)
- Questions were patient self-administered after brief instructions
- Items were uploaded to www.healthmeasures.net free scoring service (without PHI) and it returns summary scores, T-scores, and other psychometric information
- All interpretation of GI-PROMIS Measures are based on T-scores

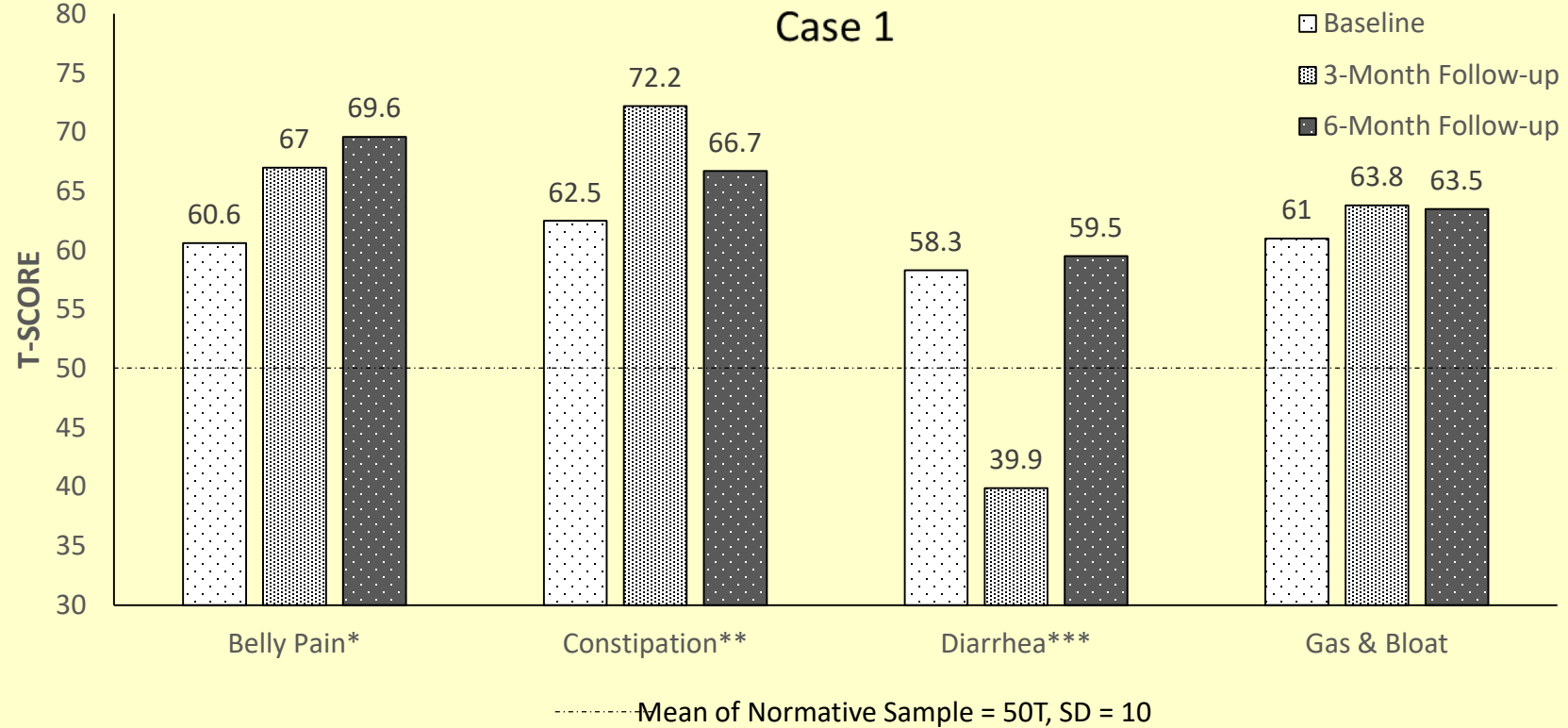
Example GI-PROMIS Items as Presented on Touch Screen

Q22 How much did belly pain bother you?

- Not at all (1)
 - A little bit (2)
 - Somewhat (3)
 - Quite a bit (4)
 - Very much (5)
-

Q23 How often did you have discomfort in your belly?

- Never (1)
- Rarely (2)
- Sometimes (3)
- Often (4)
- Always (5)



*Belly Pain - Reliable Change Index, Time 3 worse than Time 1, $p < .05$.

**Constipation - Reliable Change Index, Time 2 worse than Time 1, $p < .05$.

***Diarrhea - Reliable Change Index, Time 2 better than Time 1, $p < .05$.

**Figure 2: Gastrointestinal Symptoms (GI-PROMIS) at Baseline and Follow-up
(Lower scores indicate lower (desirable) self-reported symptoms)**

Case 1: Interpretation of Psychometric Assessment of GI Health (GI-PROMIS)

- GI-PROMIS measures indicate that at the 3 time points most areas are symptomatic and moderately to severely elevated (at least 1 SD above the population mean).
- GI-PROMIS measures do not indicate reliable symptom reduction at 6-month follow-up. In fact, Belly pain is worse at 6-months
- There appears to be an inverse relationship between Constipation and Diarrhea at the 3-month follow-up, with Constipation increasing and diarrhea decreasing
- Patient is experiencing moderately severe GI symptoms most likely associated with Celiac Disease

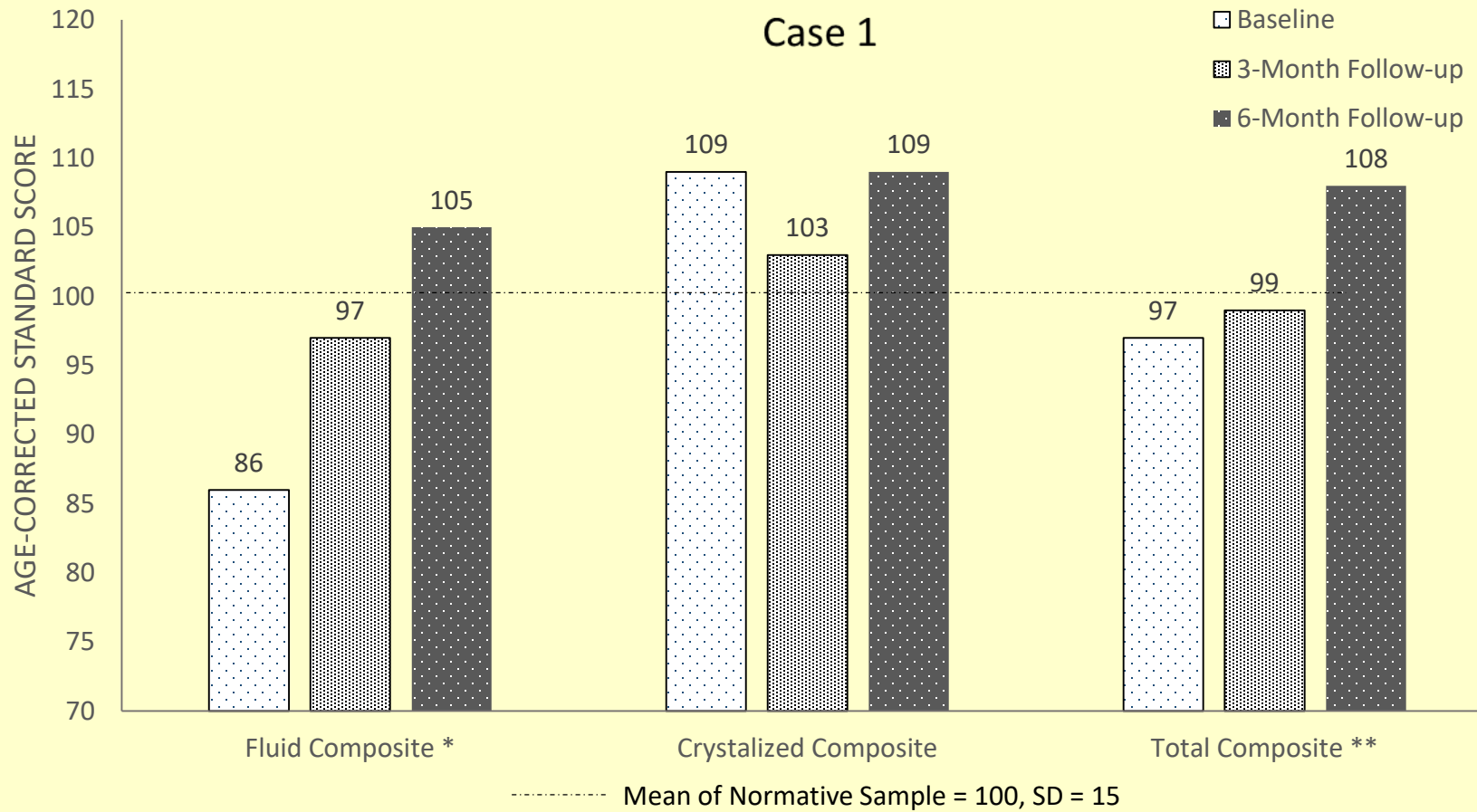
Assessment of Cognitive Functioning with the NIH Toolbox

- The NIH Toolbox assesses Cognition, Emotion, Motor, and Sensation Functions.
- We used the Cognition Battery: This assesses the mental processes involved in gaining knowledge and comprehension, such as thinking, knowing, remembering, judging, and problem-solving. These higher-level functions of the brain encompass language, imagination, perceptions, and the planning and execution of complex behaviors.
- This series of Toolbox tests provide performance-based estimates of function (also known as "objective measures").



NIH Toolbox Cognition Composite Scores

- Fluid Cognition Composite
 - Dimensional Change Card Sort – Set shifting (EF)
 - Flanker Inhibitory Control and Attention Test (EF)
 - List Sorting Working Memory Test
 - Picture Sequence Memory Test
 - Pattern Comparison Processing Speed Test
- Crystallized Cognition Composite
 - Picture Vocabulary Test
 - Oral Reading Recognition Test
- Cognitive Function (Total) Composite



*Fluid Composite - Reliable Change Index, Time 3 better than Time 1, $p < .05$.

**Total Composite - Reliable Change Index, Time 3 better than Time 1, $p < .05$.

Figure 3: NIH Toolbox Cognition Battery at Baseline and Follow-up (Higher scores indicate better (desirable) performance)

Case 1: Interpretation of Results of NIH Toolbox Cognition Battery

- Patient demonstrates average general cognitive ability at all 3 time points, with the Fluid Composite score being a weakness at baseline.
- Fluid Composite score is higher at 6-month follow-up indicating improved cognitive flexibility and reasoning.
- This improvement is above what is expected from practice effects which have been found to contribute only a 2-3 point improvement on the NIH Toolbox composite scales.⁵
- The improvement in the Total Composite score is probably due to the increase in the Fluid performance.

⁵ Heaton, R. K., Akshoomoff, N., Tulsky, D., Mungas, D., Weintraub, S., Dikmen, S., ... Gershon, R. (2014). Reliability and validity of composite scores from the NIH Toolbox Cognition Battery in adults. *Journal Of The International Neuropsychological Society: JINS*, 20(6), 588–598. <https://doi-org.ezproxy.net.ucf.edu/10.1017/S1355617714000241>

Assessment of Quality of Life (Description of Neuro-QoL Tests used)

- Neuro-QoL (Quality of Life in Neurological Disorders) is a measurement system that evaluates and monitors the physical, mental, and social effects experienced by adults and children living with neurological conditions.
- Similar to the GI-PROMIS measures in administration and scoring

The logo for NeuroQoL features the text "NeuroQoL" in a black, sans-serif font. A stylized green neuron with a blue nucleus and several green dendrites is positioned between the "o" and "Q".

NeuroQoL



Assessment of Quality of Life (Description of Neuro-QoL Domains)

Physical Health

Fatigue

Mental Health

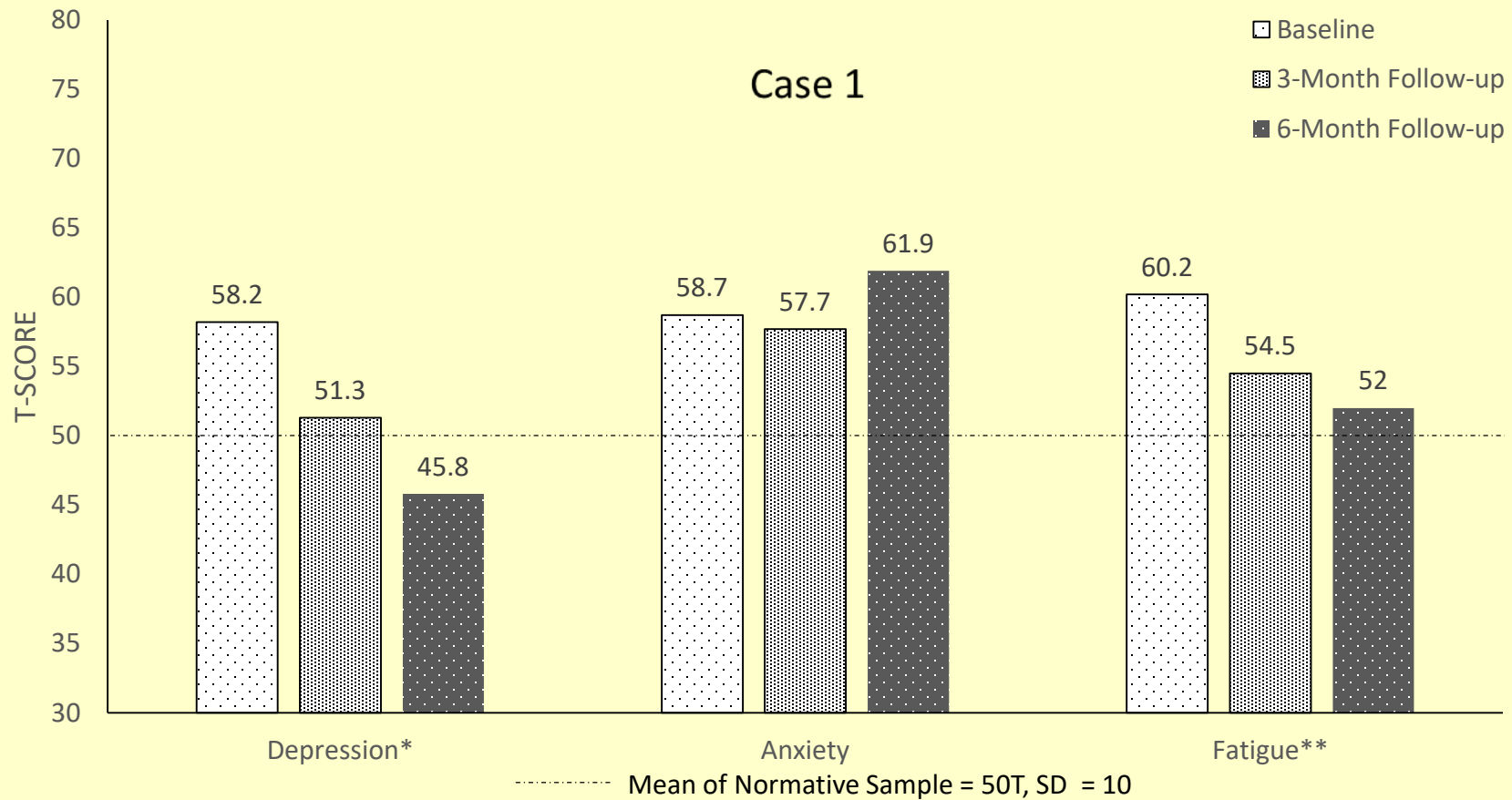
Anxiety

Depression

Social Health

Ability to
Participate in Social
Roles & Activities

Satisfaction with
Social Roles &
Activities



*Depression - Reliable Change Index, Time 3 better than Time 1, $p < .05$.

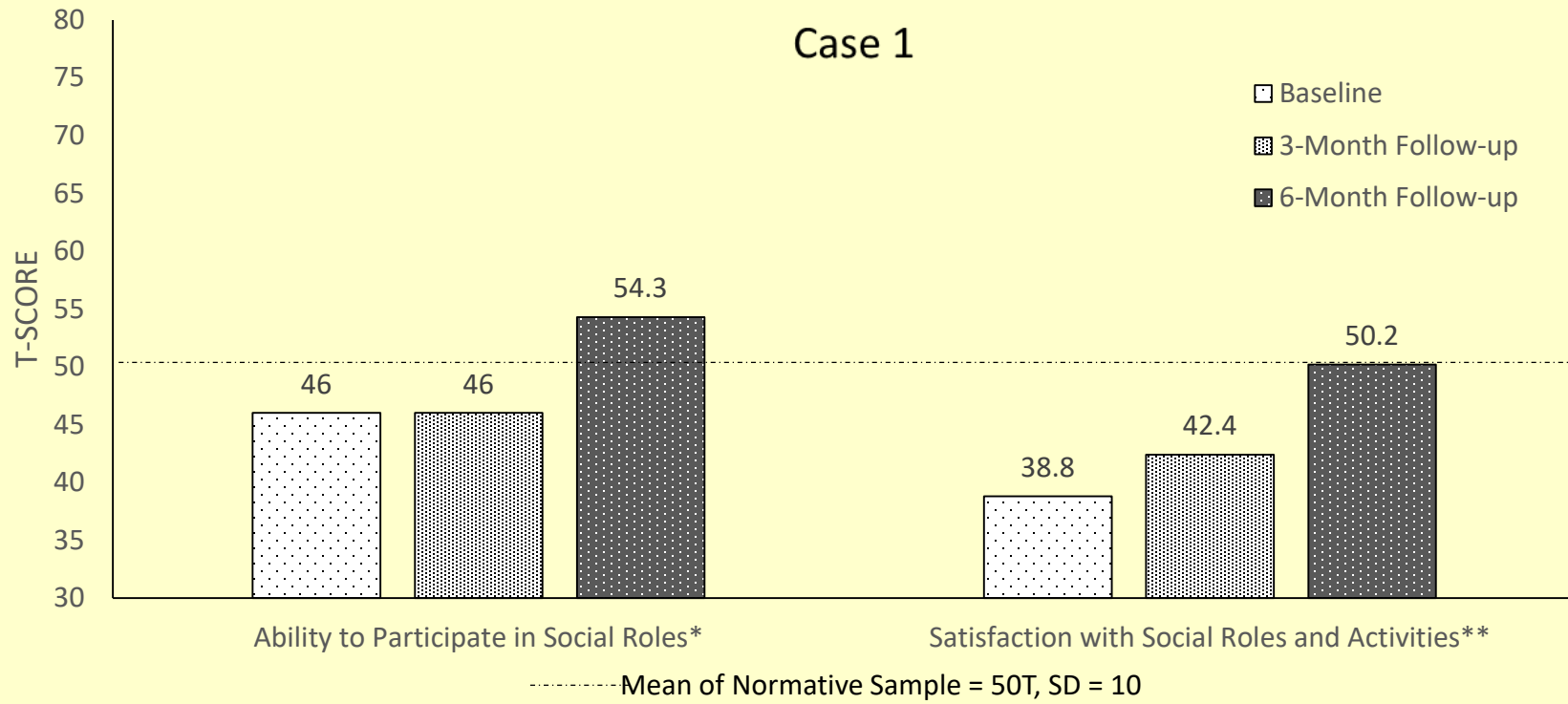
**Fatigue – Reliable Change Index, Time 3 better than Time 1, $p < .05$.

Figure 4: Self-Report of Emotional Distress as measured by the Neuro-QoL (Lower scores indicate better (desirable) self-reported symptoms)

Case 1: Interpretation of Neuro-QoL Results

Mental and Physical QoL

- The patient is exhibiting moderate levels of Depression, Anxiety, and Fatigue at Baseline.
- At the 6-month follow-up Depression and Fatigue have reduced to normative levels.



*Ability to Participate in Social Roles - Reliable Change Index, Time 3 better than Time 1, $p < .05$.

**Satisfaction with Social Roles – Reliable Change Index, Time 3 better than Time 1, $p < .05$.

Figure 5: Self-Report of Social Functioning as measured by the Neuro-QOL (Higher scores indicate better (desirable) self-reported symptoms)

Case 1: Interpretation of Neuro-QoL Results for Social Health

- At the 6-month follow-up the patient is reporting greater ability to participate in social roles.
Item Example: Ability to socialize with friends.
- At the 6-month follow-up the patient is reporting greater satisfaction with social roles.
Item Example: Less disappointment with ability to participate in family activities.

Case 1: Conclusions

- Patient has moderate to severe GI symptoms in every area measured
- GI symptoms are unchanged on the GI-PROMIS for the observation period (perhaps longer history of adherence to a GFD is necessary for healing, i.e. 12-months)
- Patient appears to have good adherence to the GFD
- Cognitive functioning is improved
- Depression and Fatigue are improved
- Social functioning is improved
- Comprehensive assessment indicates that the patient experienced significant improvement in many areas of functioning despite no change in the specific GI symptoms
- Cannot attribute improvements to the GFD, decrease in Depression may result in general cognitive and social benefits.
- GFD may have generalized effects improving patients self-efficacy and sense of control

Case 2

Table 3

Case 2: Patient Characteristics at Baseline

Measure	
Age	67
Sex	Female
Race	White
Marital Status	Widow
Education	H.S. Degree, Some College
BMI	19.5
Presenting Symptoms on Intake Forms	Weight loss, Irregularity, Gas, and Bloating
Other Reported Symptoms on Intake Forms	Anxiety, and Osteoporosis

Table 4

Case 2: Clinical Measures at Baseline

Measure	
Duration of Diagnosis	12 months
Marsh Score	3
HLA DQ2	Positive
HLA DQ8	Negative

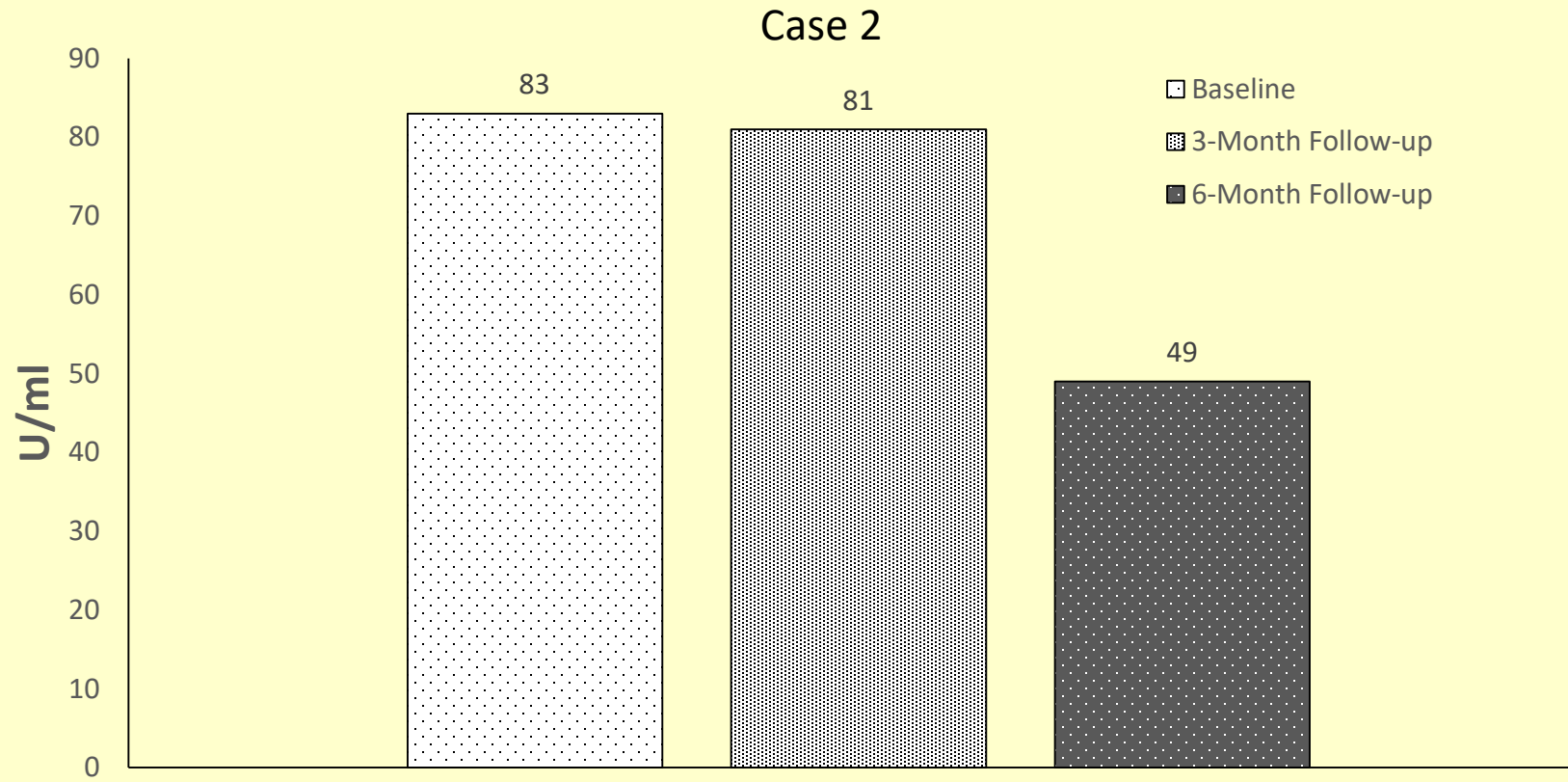


Figure 6. Tissue Transglutaminase (tTG) Antibody, IgG

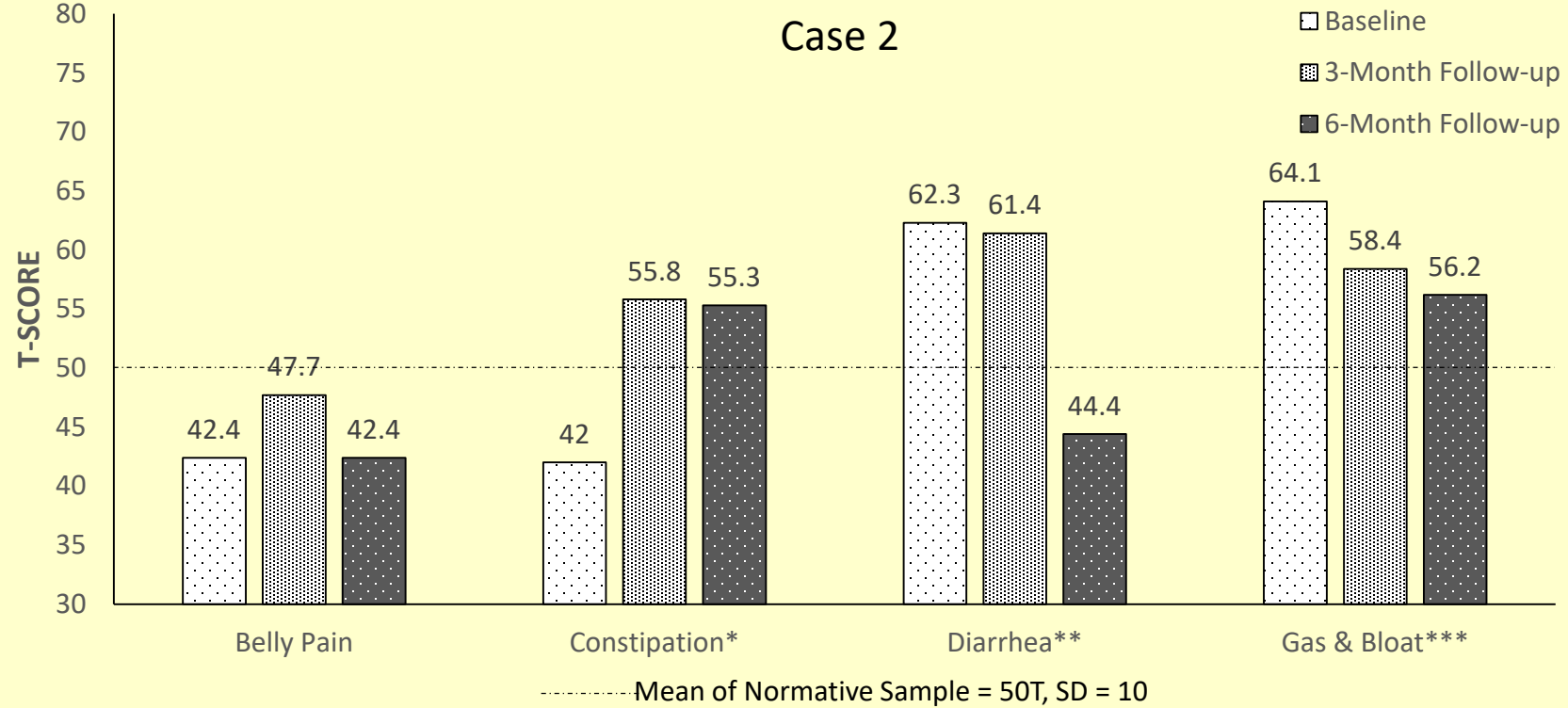
Case 2: Interpretation of Medical & Lab Results

Medical & Lab Results at Baseline

- Tissue Transglutaminase (tTG) Antibody indicates gluten sensitivity (serology).
- Lower Marsh Score is suggestive of Celiac Disease (biopsy).
- HLA DQ2 Positive (is a phenotypic marker).

Tissue Transglutaminase (tTG) Antibody levels at the follow-up sessions indicate patient has lowered their exposure to gluten.

Case 2: Assessment of GI Health
GI-PROMIS Measures



*Constipation - Reliable Change Index, Time 3 worse than Time 1, $p < .05$.

**Diarrhea - Reliable Change Index, Time 3 better than Time 1, $p < .05$.

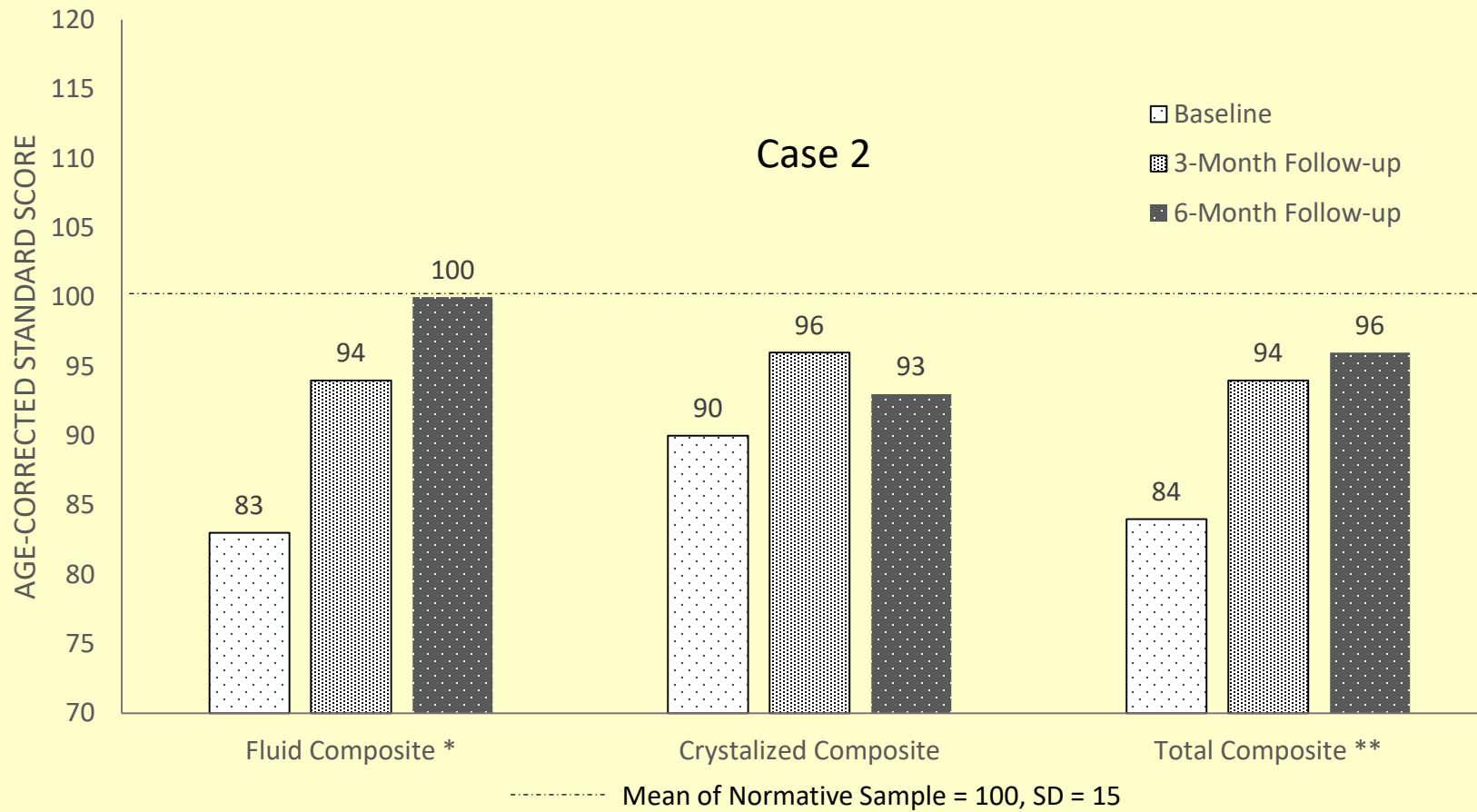
***Gas & Bloat - Reliable Change Index, Time 3 better than Time 1, $p < .05$

Figure 7: Gastrointestinal Patient Reported Outcome Measurement Information System (GI-PROMIS) at Baseline and Follow-up (Lower scores indicate better (desirable) self-reported symptoms)

Case 2: Interpretation of PROMIS-GI Results

- GI-PROMIS measures indicate that at baseline the patient's prominent GI symptoms are moderate to severe elevations in Diarrhea, and Gas and Bloating (at least 1 SD above the population mean).
- GI-PROMIS measures indicate measured symptom reduction at 6-month follow-up in Diarrhea, and Gas and Bloating.
- Again, there appears to be an inverse relationship between Constipation and Diarrhea at follow-ups, with Constipation increasing and diarrhea decreasing

Case 2: NIH Toolbox Cognition Assessment



*Fluid Composite - Reliable Change Index, Time 3 better than Time 1, $p < .05$.

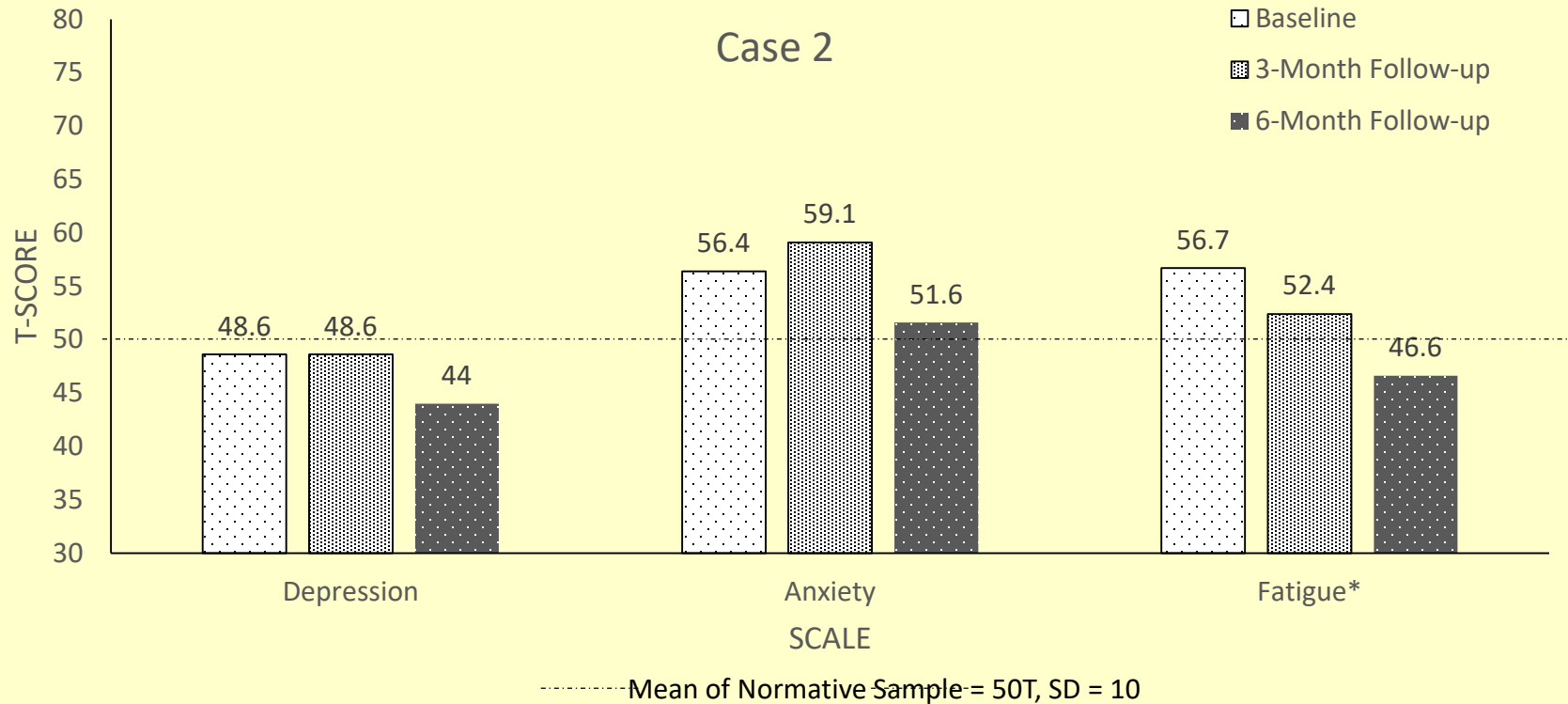
**Total Composite - Reliable Change Index, Time 3 better than Time 1, $p < .05$.

Figure 8: NIH Toolbox Cognition Battery at Baseline and Follow-up (Higher scores indicate better (desirable) performance)

Case 2: Interpretation of Cognitive Assessment

- Patient demonstrates low average general cognitive ability at baseline
- Fluid Composite score is higher at 6-month follow-up indicating improved cognitive flexibility and reasoning.
- Patient demonstrates average cognitive general cognitive ability at follow-up.
- This improvement is above what is expected from practice effects.
- The improvement in the Total Composite score is probably due to the increase in the Fluid performance.

**Case 2: Results and Interpretation of Neuro-QoL
Findings: Mental, Physical, and Social QoL Scales**



*Fatigue – Reliable Change Index, Time 3 better than Time 1, $p < .05$.

Figure 9: Neuro-QoL Emotional Health Self-Report at Baseline and Follow-up (Lower scores indicate better (desirable) performance)

Neuro-QoL Emotional & Physical Functioning Results

- Case 2 was exhibiting elevated levels of Anxiety, and Fatigue at Baseline.
- At the 6-month follow-up Fatigue has been reduced to normative levels.

Neuro-QoL Social Functioning Results

- Case 2 was exhibiting normative levels of social ability and satisfaction throughout the observation period with no changes.

Case 2: Conclusions

- Confidence in diagnosis of Celiac Disease is lower in this case because of fewer test results.
- At baseline, the patient had moderate to severe GI symptoms in the specific areas of Diarrhea, and Gas and Bloating.
- Diarrhea, and Gas and Bloating were reduced at 6-month follow-up.
- Patient appears to have reduced their exposure to gluten with the GFD by the 6-month follow-up.
- Cognitive functioning is improved at the 6-month follow-up.
- Fatigue is improved at the 6-month follow-up.
- Comprehensive assessment indicates that the patient experienced significant improvement in across areas of functioning including specific GI symptoms.
- Improvements in GI symptoms, Cognition, and Fatigue may be due to the direct or indirect effects of the GFD.

Overall Discussion

- The NIH PRO Measures used here demonstrate that we can assess both specific GI and systemic symptoms with great detail in the outpatient setting without disrupting clinic flow.
- Careful assessment of symptoms demonstrate that lifestyle changes (implementing a GFD) has benefits on general functioning (both cases) and specific GI symptoms (second case).
- Especially exciting is that in both cases, cognitive functioning improved within 6-months of implementation of the GFD. This suggests that any cognitive decline associated with the disorder is reversible with the GFD.
- The change in cognitive flexibility occurred in both a young and elderly patient.

Overall Discussion

- Causality cannot be determined with Case Studies or Clinical Series, but they can suggest areas for future research.
- Many mechanisms of action for the GFD are possible:
 1. Decrease in immune response and recovery of the gut epithelium in the small intestine improve both nutrient absorption and availability to the CNS (direct effect).
 2. Improved nutrient absorption may reduce fatigue which in turn increases cognitive, emotional, and social functioning (fatigue as a mediator).
 3. Implementation of a GFD may increase a patient's sense of self-control and efficacy which in turn decreases depression and interference with cognitive and social functioning (self-efficacy and depression as mediators).