The Challenges of Biomarkers and Structured Care for Rheumatic Disease
TRADITIONAL CLINICAL ASSESSMENT

- Patient report
- Physical Exam
- Procedural Based Diagnostics
APPLIED TO RHEUMATOID ARTHRITIS (RA)

Morning stiffness and symmetric joint pain

Tender and swollen joint count

Anti-CCP, RF and erosive radiographs
**STRUCTURED CARE APPLIED TO RA**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Remission</th>
<th>Low activity</th>
<th>Moderate activity</th>
<th>High activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Activity Scale (PAS) or PASII (range 0–10)</td>
<td>0–0.25</td>
<td>&gt;0.25–3.7</td>
<td>&gt;3.7 to &lt;8.0</td>
<td>≥8.0</td>
</tr>
<tr>
<td>Routine Assessment of Patient Index Data 3 (RAPID3)</td>
<td>0–1.0</td>
<td>&gt;1.0–2.0</td>
<td>&gt;2.0–4.0</td>
<td>&gt;4.0–10</td>
</tr>
<tr>
<td>Clinical Disease Activity Index (CDAI) (range 0–76.0)</td>
<td>≤2.8</td>
<td>&gt;2.8–10.0</td>
<td>&gt;10.0–22.0</td>
<td>&gt;22</td>
</tr>
<tr>
<td>Disease Activity Score (DAS) 28 (range 0–9.4)</td>
<td>&lt;2.6</td>
<td>≥2.6 to &lt;3.2</td>
<td>≥3.2 to ≤5.1</td>
<td>&gt;5.1</td>
</tr>
<tr>
<td>Simplified Disease Activity Index (SDAI) (range 0–86.0)</td>
<td>≤3.3</td>
<td>&gt;3.3 to ≤11.0</td>
<td>&gt;11.0 to ≤26</td>
<td>&gt;26</td>
</tr>
</tbody>
</table>
OPPORTUNITIES FOR RA CARE AND DISCOVERY

Veterans Outreach

Drug Development

Biomarker Development

Rheumatoid Arthritis at the University of Utah
TRADITIONAL CLINICAL ASSESSMENT APPLIED TO SYSTEMIC SCLEROSIS (SSc)

- Raynaud’s Phenomenon, telangiectasia, and skin thickening
- Capillaroscopy and skin assessment
- SSc-antibodies
CHALLENGE #1: DIFFERENTIAL RATE AND SEVERITY ORGAN INVOLVEMENT IN SSc

VASCULAR CHANGES → FIBROSIS

Skin thickness

Joint contractures, GI, lungs, heart, kidneys

Intermediate

Early

Late

Disease duration (years)

5 10 20

Diffuse cutaneous
Limited cutaneous

Pulmonary hypertension, malabsorption
CHALLENGE #2: SSc is a progressive disease of the microvasculature.

- Vascular dysfunction
- Swelling
- Decreased oxygen and nutrient delivery to tissues
- Tissue death
- Immune dysregulation
- Scarring

Typically when SSc patients get diagnosed.

Frech T, et al. Rheumatol Int. 2014
The mission of the investigators is to build a well phenotyped data and biospecimen repository of patients with early diffuse scleroderma and to facilitate translational research into scleroderma pathogenesis.

# The UCLA SITC GIT 2.0 Questionnaire

The following questions ask about your gastrointestinal (GI) symptoms and how they affected your life over the last 7 days. Answer every question by selecting the answer as indicated. Most questions have 4 choices: "No Days", "1-2 Days", "3-4 Days", or "5-7 Days". Questions 15 and 31 have 2 choices only: "Yes" or "No". If you are unsure about how to answer a question, please give the best answer you can.

In order to score the instrument, all questions must be answered.

## Reflux

<table>
<thead>
<tr>
<th>Question</th>
<th>No Days</th>
<th>1-2 Days</th>
<th>3-4 Days</th>
<th>5-7 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In the past one week, how often did you have difficulty swallowing solid food?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. In the past one week, how often did you have an unpleasant stinging or burning sensation in your chest (heartburn)?</td>
<td></td>
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</tr>
<tr>
<td>3. In the past one week, how often did you have a sensation of bitter or sour fluid coming up from your stomach into your mouth (acid reflux)?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4. In the past one week, how often did you have heartburn on eating 'acidic' foods such as Tomatoes &amp; Oranges?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>5. In the past one week, how often did you regurgitate (throw up or bring up small amounts of previously eaten food)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. In the past one week, how often did you sleep in a &quot;raised&quot; or an &quot;L shaped&quot; position?</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>7. In the past one week, how often did you feel like vomiting or throwing up?</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>8. In the past one week, how often did you vomit or throw up?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Distension / Bloating

<table>
<thead>
<tr>
<th>Question</th>
<th>No Days</th>
<th>1-2 Days</th>
<th>3-4 Days</th>
<th>5-7 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. In the past one week, how often did you feel bloated (a sensation of gas or air in the stomach)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. In the past one week, how often did you notice an increase in your belly, sometimes requiring you to open your belt, pants or shirt?</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>11. In the past one week, how often did you feel full after eating a small meal?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. In the past one week, how often did you pass excessive gas or flatulence?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Soilage

<table>
<thead>
<tr>
<th>Question</th>
<th>No Days</th>
<th>1-2 Days</th>
<th>3-4 Days</th>
<th>5-7 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. In the past one week, how often did you accidentally soil (dirty) your underwear before being able to get to a bathroom?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Diarrhea

<table>
<thead>
<tr>
<th>Question</th>
<th>No Days</th>
<th>1-2 Days</th>
<th>3-4 Days</th>
<th>5-7 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>14. In the past one week, how often did you have loose stools (diarrhea)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Constipation

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>15. In the past one week, have you noticed your stools becoming watery?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. In the past one week, have you noticed your stools becoming harder?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. In the past one week, how often were you constipated or unable to empty your bowels?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. In the past one week, how often did you have hard stools?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. In the past one week, how often did you have pain while passing your stools?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Social Function

<table>
<thead>
<tr>
<th>Question</th>
<th>0</th>
<th>1-2 Days</th>
<th>3-4 Days</th>
<th>5-7 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the past one week, how often did nausea interfere with social activities such as visiting friends or relatives?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past one week, how often did vomiting interfere with social activities such as visiting friends or relatives?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past one week, how often did stomach aches or pain interfere with social activities such as visiting friends or relatives?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past one week, how often did diarrhea interfere with social activities such as visiting friends or relatives?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past one week, how often did the fear of accidentally soiling your underwear interfere with social activities such as visiting friends or relatives?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past one week, how often did bloated sensations interfere with social activities such as visiting friends or relatives?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Emotional Well-Being

<table>
<thead>
<tr>
<th>Question</th>
<th>0</th>
<th>1-2 Days</th>
<th>3-4 Days</th>
<th>5-7 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the past one week, how often did you feel worried or anxious about your bowel problems?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past one week, how often did you feel embarrassed because of your bowel symptoms?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past one week, how often did you have problems with sexual relations because of your bowel symptoms?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past one week, how often did you fear not being able to find a bathroom?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past one week, how often did you feel depressed or discouraged due to your bowel symptoms?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past one week, how often did you avoid or delay traveling because of your bowel symptoms?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past one week, how often did you feel angry or frustrated as a result of your bowel symptoms?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past one week, how often did you have problems with your sleep as a result of your bowel symptoms?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past one week, how often did you feel 'stress' or an upset mood worsen your bowel symptoms?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The UCLA SCTC GIT 2.0 Questionnaire

Your total GIT score is **1.008**. Your individual section scores are detailed in the table below and after each section in the questionnaire.

Click here for a printable version of your results.

<table>
<thead>
<tr>
<th>Category</th>
<th>Your Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux</td>
<td>1.5</td>
</tr>
<tr>
<td>Distension/Bloating</td>
<td>1</td>
</tr>
<tr>
<td>Sooting</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
</tr>
<tr>
<td>Social Function</td>
<td>1</td>
</tr>
<tr>
<td>Emotional Well-Being</td>
<td>0.56</td>
</tr>
<tr>
<td>GIT Score</td>
<td>1.91</td>
</tr>
</tbody>
</table>

GIT Score: **1.008**  
Severity of GIT Involvement: **Severe-to-Very Severe**

Reflex Score: **1.5**  
Severity of GIT Involvement: **Severe-to-Very Severe**

Distension/Bloating Score: **1**  
Severity of GIT Involvement: **None-to-Low**

Sooting Score: **1**  
Severity of GIT Involvement: **None-to-Low**

Diarrhea Score: **1**  
Severity of GIT Involvement: **None-to-Low**

Constipation Score: **1**  
Severity of GIT Involvement: **Moderate**

Social Function Score: **1**  
Severity of GIT Involvement: **Moderate**

Emotional Well-Being Score: **0.56**  
Severity of GIT Involvement: **Moderate**
No PRESS patients reported a complete absence of GIT symptoms. GIT symptoms are not associated with immunosuppressant choice.

A multicenter incident cohort study of early diffuse cutaneous systemic sclerosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (n=83)</th>
<th>Year 1 (n=37)</th>
<th>Year 2 (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total GIT 2.0</td>
<td>0.32 0.45</td>
<td>0.19 0.33</td>
<td>0.26 0.34</td>
</tr>
<tr>
<td>Reflux</td>
<td>0.38 0.75</td>
<td>0.63 0.75</td>
<td>0.5 0.56</td>
</tr>
<tr>
<td>Distention/Bloating</td>
<td>0.5 1.25</td>
<td>0.75 0.75</td>
<td>0.63 0.63</td>
</tr>
<tr>
<td>Fecal Soilage</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 0.5</td>
<td>0.0 0.5</td>
<td>0 0</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>0 0.5</td>
<td>0.17 0.5</td>
<td>0 0.25</td>
</tr>
<tr>
<td>Emotional Well-being</td>
<td>0 0.22</td>
<td>0 0.22</td>
<td>0.06 0.22</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 0.5</td>
<td>0 0.5</td>
<td>0 0.5</td>
</tr>
</tbody>
</table>
Systemic Sclerosis (SSc) patient consented

Standardized Assessment

Central International SSc Database

Treatment Groups Identified based on GIT Questionnaire

- GERD
- Disrupted swallowing
- Diarrhea
- Bowel incontinence/soilage
- Constipation
- Belly pain
- Gas/bloat/flatulence
- Nausea and vomiting

• Standardized algorithms implemented.
• Local institution diagnostics and biobank.
• Treatment regimens recorded.
• Serial questionnaires.

Central International SSc Database

Outcomes assessment of treatments and diagnostics on GIT symptoms
INVESTIGATIONAL PROCEDURES:

Upper GIT

Esophageal Motility

- Modified barium swallow
- Manometry
- Impedance
- pH monitoring
- Scintigraphy
- Tissue Evaluation
  - Endoscopy
  - Traditional
  - Capsule

Stomach Motility

- Scintigraphy
- Electrogastrography
- Gastric Emptying
- Breath test
- Single Photon Emission CT
- Wireless pH monitoring
- MRI
- Tissue evaluation
  - Endoscopy
  - Traditional
  - Capsule

Small Bowel Motility

- Manometry
- Scintigraphy
- Breath Testing
- MRI

Tissue Evaluation

- Enteroscopy
  - Capsule

Large Bowel Motility

- Radio-opaque markers
- Scintigraphy
- Wireless Motility capsule
- MRI

Tissue evaluation

- Colonoscopy
  - Capsule

Anorectal

- Manometry
- Endosonography
- Scintigraphy
- Electromyography
- Dynamic MRI
- Defecography
- Balloon Expulsion Test

Tissue evaluation

- Colonoscopy
THE PROBLEM WITH GIT PROCEDURES

- Invasive
- Expensive
- Often times do not provide guidance:
  - “Findings consistent with Systemic Sclerosis”
- Empiric treatments often the standard of care
Probiotics
- Live microorganisms that, when administered in adequate amounts, have shown potential benefits in SSc patients.

Malnutrition
- Prevalent in 25% of our SSc population across GIT symptoms and body habitus.

Therapeutics
- Worsening of GIT symptoms in patients on certain types immunosuppression.

Metabolomics
- Esophageal tissue micro-molecules of the metabolome as cellular imagery.

Frech T, et al. Rheumatol Int. 2014
Frech TM. Clin Exp Rheumatol 2011
Pilot Project

Three female SSc patients.
- All ANA positive.
- Moderate-severe GIT 2.0 score.
- Different auto-antibodies.
- Different SSc disease durations.

Two healthy controls.
- All on PPI.

Distal esophageal biopsies obtained by same methodology and processing.
Computational Molecular Phenotyping

CMP Software vs Mass Spectrometry

- MassSpec presumes large-scale tissue homogeneity

- CMP reveals metabolic diversity and fingerprints cells
Two HC specimens were similar in expression levels and distribution of cells in all metabolites. Arginine, a rate-limiting substrate for nitric oxide synthase, which is a critical mediator of vasodilation, was abnormal in all SSc samples.

Early disease, SCL-70 esophageal specimen was different in distribution of cells and expression levels of all metabolites compared to HC.

< 2 years disease duration  5 years disease duration  10 years disease duration
Biomarkers and Structured Care for SSc

- Microbiome characterization.
- Improved natural history studies.
- Concurrent skin and esophageal longitudinal examination.
- Definitions of disease and treatment algorithms.

Acknowledgements

- Telehealth and SSc Patients
- Utah SSc Clinical Care Team
  - Kathryn Peterson, MD
  - Erinn Downs-Kelly, MD
  - Bryan Jones, PhD
- Donato Lab

- Funding:
  - CCTS Pilot Personalized Health Care
  - Office of the Rural Health Initiative
  - VA Merit Award
  - Scleroderma Foundation
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