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**Requires Data Access?** Yes

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**Requires Data Access?** Yes

**Are external grants or funds being used to support this research?:** External grants or funds are being used to support this research.
**Project Funding Source:** This research was supported by the National Natural Science Foundation of China (#82270555, #82070538, #82000520).
**How did you learn about the YODA Project?:** Colleague

## Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/04/COI-Jieqi-Zheng.pdf
https://yoda.yale.edu/wp-content/uploads/2024/04/DOI_Rirong_Chen.pdf
https://yoda.yale.edu/wp-content/uploads/2024/04/COI-Shenghong-Zhang.pdf

## Certification

**Certification:** All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
**Data Use Agreement Training:** As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT00036439 - C0168T37 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate

the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
2. NCT00487539 - C0524T17 - A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Subcutaneously, in Subjects with Moderately to Severely Active Ulcerative Colitis
3. NCT00488774 - C0524T16 - A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Intravenously, in Subjects With Moderately to Severely Active Ulcerative Colitis
4. NCT00488631 - C0524T18 - A Phase 3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Maintenance Therapy, Administered Subcutaneously, in Subjects With Moderately to Severely Active Ulcerative Colitis
5. NCT02407236 - CNTO1275UCO3001 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis

**What type of data are you looking for?:** Individual Participant-Level Data, which includes Full CSR and all supporting documentation

## Research Proposal

## Project Title

Dynamics of Disease Activity in Monitoring Therapeutic Outcomes and Predicting Prognosis for Ulcerative Colitis

**Narrative Summary:**

Ulcerative colitis (UC) is a chronic, recurrent inflammatory bowel disease (IBD). Recent years have witnessed a significant surge in the development of targeted therapies, which has expanded the therapeutic options for UC. However, although biologics have improve the prognosis of UC, 30-50% patients may still encounter poor therapeutic outcomes such as primary non-response, secondary loss of response, or potential immunogenicity. Therefore, timely monitoring disease activity and predicting therapeutic response are vital processes during biologics, especially in the initial year of treatment. Describing trajectories of disease course is a promising topic in current clinical research, while relatively limited studies towards this have been reported in UC patients with biologics treatment. Therefore, this project aims to investigate the role of disease activity dynamic trajectories in therapeutic efficacy monitoring and prognosis predicting in UC.

**Scientific Abstract:**

Background: As the emergence of novel therapeutic options like biologics, monitoring disease activity and predicting therapeutic efficacy has become essential processes in UC management. However, longitudinal dynamics of clinical activity have not been fully understood. This study aims to explore distinct trajectories of clinical activity within one year of biologic therapy in UC patients, so as to provide evidence for disease monitoring and personalized medicine.
Objective: This study aims to reveal the overall dynamics of disease activity during biologics therapy. The scientific hypothesis of this study is that the trajectories of major predictors could help to monitor disease courses and predict different therapeutic outcomes in UC.
Study design: This is a post-hoc analysis study including data from one or more of the five clinical trials (UNIFI, PURSUIT, ACT 1, GEMINI 1 and VARSITY). The major predictors include Mayo score, partial Mayo score, patient-reported outcome 2, Mayo subscore, serum and fecal biomarkers (e.g., C-

reactive protein, hemoglobin, albumin, fecal calprotectin and lactoferrin), endoscopic socres, histological findings, patient report outcomes (e.g., IBDQ scores), and their long-term trajectories.
Participants: Moderate-to-severe UC patients with at least three time of disease activity assessment would be included. Participants who meet any of the following criteria are not eligible for study inclusion: lacking data of corresponding predictors during induction therapy; having concomitant intestinal infection disease when assessing predictors after induction therapy.
Main Outcome Measure(s): Outcomes include therapeutic efficacy (such as clinical response, clinical remission, mucosal healing, endoscopic improvement, histological remission, histological improvement, histo-endoscopic improvement, patient-reported outcomes etc.) at the end of maintenance treatment, as well as colorectal resection during long-term follow-up.
Statistical analysis: The latent class growth mixed model is performed to fit the trajectory of disease activity dynamic trajectory. Cross-lagged structural equation models are used to explore temporal relationships of the predictors. Multivariate logistic regression is conducted to adjust potential confounders and to analyze the association of candidate predictors and outcomes.

**Brief Project Background and Statement of Project Significance:**

Ulcerative colitis (UC) is a chronic, recurrent inflammatory bowel disease (IBD) with an unknown etiology, which usually manifests as bloody diarrhea, frequent defecation, and tenesmus. Although biologics have improve the prognosis of UC, 30-50% patients may still encounter poor therapeutic outcomes such as primary non-response, secondary loss of response, or potential immunogenicity. Therefore, timely monitoring disease activity and predicting therapeutic response are vital processes during biologics, especially in the initial year of treatment. Describing trajectories of disease course is a promising topic in current clinical research. Recently, trajectories of clinical symptoms, psychological evaluations, health-related quality of life and biomarkers were explored in newly diagnosed UC patients. Besides, temporal relationships were disentangled during this process. Moreover, one of our previous studies has observed that trajectories of fecal lactoferrin during biologic induction were associated with one-year clinical, endoscopic and histological remission of UC patients. In this way, trajectories could be a promising method for disease course monitoring and prognosis predicting in various disease, while relatively limited studies towards this have been reported in UC patients with biologics treatment. Therefore, in order to investigate the role of disease activity dynamic trajectories in therapeutic efficacy monitoring and prognosis predicting, we will perform post-hoc analysis based on one or more of the five randomized clinical trials, including UNIFI, PURSUIT, ACT 1, GEMINI 1 and VARSITY.

**Specific Aims of the Project:**

This study aims to reveal the overall dynamics of disease activity during biologics therapy. The scientific hypothesis of this study is that the trajectories of major predictors could help to monitor disease courses and predict different therapeutic outcomes in UC.

**Study Design:**

Individual trial analysis

**Study Design Explanation:**

post-hoc analysis using participant-level data from one or more trials

**What is the purpose of the analysis being proposed? Please select all that apply.**

Research on clinical prediction or risk prediction

## Research Methods

**Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:**

Participants from one or more clinical trials (UNIFI, PURSUIT, and ACT 1 from the YODA Project, GEMINI 1 and VARSITY from the Vivli Project) will be included in the study as either a development cohort for trajectory fitting or a external validation cohort. Moderate-to-severe UC patients with at least three time of disease activity assessment would be included. Participants who meet any of the following criteria are not eligible for study inclusion: lacking data of corresponding predictors during induction therapy; having concomitant intestinal infection disease when assessing predictors after induction therapy.

**Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:**

Outcomes include therapeutic efficacy (such as clinical response, clinical remission, mucosal healing, endoscopic improvement, histological remission, histological improvement, histo-endoscopic improvement, patient-reported outcomes etc.) at the end of maintenance treatment, as well as colorectal resection during long-term follow-up.
Clinical response is defined as a decrease from baseline in the total Mayo score of ≥3 points and ≥30% decrease, with an accompanying decrease in the subscore for rectal bleeding of ≥1 point or an absolute subscore for rectal bleeding ≤1. Clinical remission is defined as a partial Mayo score ≤ 2 and all subscores ≤ 1. Mucosal healing is defined as Mayo endoscopic score [MES]=0, and endoscopic improvement is defined as MES ≤1. As for histological outcomes, histologic improvement and histologic remission are defined as Geboes grade <3.2 and <2, respectively. And histo-endoscopic improvement defined as Geboes grade 20 points and IBDQ ≥170 points, respectively.

**Main Predictor/Independent Variable and how it will be categorized/defined for your study:**

The major predictors include Mayo score, partial Mayo score, patient-reported outcome 2, Mayo subscore, serum and fecal biomarkers (e.g., C-reactive protein, hemoglobin, albumin, fecal calprotectin and lactoferrin), endoscopic socres, histological findings, patient report outcomes (e.g., IBDQ scores), and their long-term trajectories. They will be collected at several time points during one-year biologic treatment and before the end of maintenance therapy, which differs from efficacy outcomes collected at the end of maintenance treatment.

**Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:**

Other variables of interest include baseline characteristics (e.g., gender, age, disease duration, body mass index, medication history, treatment allocation and concomitant therapy) and baseline disease activity evaluation (e.g., partial mayo score, endoscopic mayo score, fecal calprotectin and C-reactive protein).

**Statistical Analysis Plan:**

Continuous and categorical variables are described as median (interquartile range) or frequency (percentage), respectively.
The latent class growth mixed model (LCGMM) is performed to fit the trajectory of disease activity dynamic trajectory. LCGMM is a validated approach used to analyze longitudinal data and identify subgroups with distinct trajectories,which has been applied in various diseases. Based on lcmm package in R software, LCGMM usually uses linear, quadratic, or cubic polynomial functions with different class numbers ranging from 2 to 5 for identifying subgroups with distinct trajectories. The optimal trajectory was selected based on (1) the lowest Bayesian information criterion, (2) a minimum of 5% of patients in each class, and (3) the posterior probability of assignments being >0.7 in each class. Cross-lagged structural equation models are used to explore temporal relationships of the predictors.
Taking account of differences among studies and individuals, multivariate logistic regression is conducted to adjust potential confounders (such as age, sex, medications, and baseline partial mayo score) and assess whether variables of interest could independently predict outcomes. Besides, we

will perform subgroup analysis stratified by different trials to assess the interaction between predictors and trials. Sensitivity analyses in patients with same disease activity, range of age, disease duration or type of biologics (anti-Tumor necrosis factor agents, vedolizumab or ustekinumab) will be performed to verify the consistency of our results.
Statistical significance was set at p-value ≤0.05. All statistical analysis is performed via R software within the secure platform to which the YODA project or the Vivli project remote desktop is connected.

**Software Used:**

RStudio

**Project Timeline:**

Anticipated project start: 2024/7/15
Analysis completion: 2025/2/15
Manuscript drafted: 2025/2/15
First submitted for publication: 2025/3/15
Results reported back to the YODA Project: 2025/6/15

**Dissemination Plan:**

The products of this project will be submitted to scientific conference, such as Digestive Disease Week, European Crohn's and Colitis Organization and Asian Crohn's and Colitis Organization. A manuscript will also be submitted for publication in peer-reviewed journals, such as Clinical Gastroenterology and Hepatology (CGH), Journal of Crohn's and Colitis (JCC), American Journal of Gastroenterology (AJG) and Inflammatory Bowel Diseases (IBD) and others. The acknowledgement for the YODA Project and the Vivli Project will be presented in all products of this study.

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