The YODA Project
Research Proposal Review

The following page contains the final YODA Project review approving this proposal.

The Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
195 Church Street, 5th Floor, New Haven, CT 06510

The YODA Project
Research Proposal Review - Final
(Protocol #: 2024-0668)

Reviewers:

- ☐ Nihar Desai
- ☒ Cary Gross
- ☐ Harlan Krumholz
- ☒ Richard Lehman
- ☒ Joseph Ross
- ☐ Joshua Wallach

Review Questions:	**Decision:**
1. Is the scientific purpose of the research proposal clearly described?	Yes
2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?	Yes
3. Can the proposed research be reasonably addressed using the requested data?	Yes, or it's highly likely
4. Recommendation for this data request:	Approve

Comments:

No additional comments.

The YODA Project
Research Proposal Review

Revisions were requested during review of this proposal.
The following pages contain the original YODA Project review and the original submitted proposal.

The Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
195 Church Street, 5th Floor, New Haven, CT 06510

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2024-0668)

Reviewers:

- ☐ Nihar Desai
- ☒ Cary Gross
- ☐ Harlan Krumholz
- ☒ Richard Lehman
- ☒ Joseph Ross
- ☐ Joshua Wallach

Review Questions:	**Decision:**
1. Is the scientific purpose of the research proposal clearly described?	Yes
2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?	Yes
3. Can the proposed research be reasonably addressed using the requested data?	Yes, or it's highly likely
4. Recommendation for this data request:	Not Approve

Comments:

Very interesting study to analyze endoscopy videos and images to predict endoscopic disease scoring and drug response in patients with Ulcerative Colitis and Crohn's disease. Before approving the proposal, we need a better understanding of why the investigators will also attempt to predict patient characteristics, like age, sex and race/ethnicity, as well as comorbidities. This potentially raises concerns about patient privacy and re-identification. Why would the AI model need to be able to predict this patient information?

Principal Investigator

First Name: Matt
Last Name: Schwartz
Degree: B.E.
Primary Affiliation: Virgo Surgical Video Solutions, Inc.
E-mail: matt@virgosvs.com
State or Province: CA
Country: United States

General Information

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/07/MattSchwartz-YODA-COI.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. 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
2. 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
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. NCT01863771 - CNTO148UCO3001 - A Safety and Effectiveness Study of Golimumab in Japanese Patients With Moderately to Severely Active Ulcerative Colitis
5. NCT01988961 - CNTO148UCO2001 - A Study to Evaluate the Accuracy of a Subset of the Length-109 Probe Set Panel (a Genetic Test) in Predicting Response to Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis
6. NCT00036439 - C0168T37 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
7. NCT00096655 - C0168T46 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
8. NCT00207675 - C0168T47 - A Randomized, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNF a Chimeric Monoclonal Antibody (Infliximab, REMICADE) in

Pediatric Subjects With Moderate to Severe CROHN'S Disease

9. NCT00094458 - C0168T67 - Multicenter, Randomized, Double-Blind, Active Controlled Trial Comparing REMICADE® (infliximab) and REMICADE plus Azathioprine to Azathioprine in the Treatment of Patients with Crohn's Disease Naive to both Immunomodulators and Biologic Therapy (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease)
10. NCT00336492 - C0168T72 - A Phase 3, Randomized, Open-label, Parallel-group, Multicenter Trial to Evaluate the Safety and Efficacy of Infliximab (REMICADE) in Pediatric Subjects With Moderately to Severely Active Ulcerative Colitis
11. NCT00207662 - C0168T21 - ACCENT I - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNFa Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long-term Treatment of Patients With Moderately to Severely Active Crohn's Disease
12. NCT00207766 - C0168T26 - ACCENT II - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long Term Treatment of Patients With Fistulizing CROHN'S Disease
13. NCT00004941 - C0168T20 - A Placebo-controlled, Repeated-dose Study of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients with Enterocutaneous Fistulae as a Complication of Crohn's Disease
14. NCT01551290 - CR018769; REMICADEUCO3001 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Infliximab in Chinese Subjects With Active Ulcerative Colitis
15. NCT00771667 - C0743T26 - A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Ustekinumab Therapy in Subjects With Moderately to Severely Active Crohn's Disease Previously Treated With TNF Antagonist Therapy
16. NCT01369329 - CNTO1275CRD3001 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist Therapy (UNITI-1)
17. NCT01369342 - CNTO1275CRD3002 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease (UNITI-2)
18. NCT01369355 - CNTO1275CRD3003 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease
19. NCT00265122 - C0379T07 - A Multicenter, Randomized, Phase 2a Study of Human Monoclonal Antibody to IL-12p40 (CNTO 1275) in Subjects With Moderately to Severely Active Crohn's Disease
20. 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
21. NCT01190839 - REMICADECRD3001 - Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE (Infliximab) and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at Increased Risk of Recurrence

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

Research Proposal

Project Title

Predicting likelihood of achieving remission from baseline information including endoscopy using an

artificial intelligence model

Narrative Summary:

Currently available pharmaceutical treatments for ulcerative colitis (UC) and Crohn's disease (CD) are known to achieve relatively low rates of remission (30% - 40%). Despite efforts to develop treatment algorithms and predictive biomarkers, clinicians lack tools to accurately predict drug response. While the Mayo Endoscopic Score (MES) and Simple Endoscopic Score for Crohn's disease (SES-CD) standardize disease severity scoring, they do not provide predictive capabilities. We have developed an AI model that extracts information-dense feature representations from endoscopy. This study will assess the ability to use this AI model to predictively classify drug responders vs. non-responders.

Scientific Abstract:

Background:
We have developed an AI model capable of extracting meaningful representational features from endoscopy videos, which can then be used to make predictions or classifications about those procedures. If this model can accurately predict endoscopic disease scoring, patient characteristics, and drug response in patients with UC and CD, it could help advance clinical trial design and treatment algorithms.

Objective:
We aim to study the efficacy of this AI model to take baseline information, including endoscopy imaging, as input, and output predictions of endoscopic disease score, patient characteristics, and drug response.

Study Design:
This is a retrospective analysis of endoscopy videos and images from phase 2 and phase 3 trials of ustekinumab, golimumab, and infliximab for the treatment of UC and CD. All videos and images will be processed by our AI model to extract visual features. These features will be used to classify endoscopic disease score, patient characteristics, and drug response.

Participants:
All participants from phase 2 and phase 3 trials of ustekinumab, golimumab, and infliximab for UC and CD with endoscopy data.

Primary Outcomes:
The area under the receiver operating characteristic (AUROC) will be reported for all classification evaluations.

Secondary Outcomes:
Sensitivity, specificity, precision, and recall will be reported as secondary evaluation metrics.

Statistical Analysis:
Full confusion matrix including AUROC, F1 score, sensitivity, specificity, precision, and recall. Random split 80/10/10 into training, validation, and test sets.

Brief Project Background and Statement of Project Significance:

Currently available treatment options for UC and CD patients achieve only modest rates of clinical and endoscopic response. For example, in its phase 3 UC induction study, patients assigned to golimumab (200/100mg and 400/200mg) achieved 51.0% and 54.9% clinical response, respectively at six weeks, compared to 30.3% for placebo [1]. Furthermore, in the phase 3 UC maintenance study of golimumab (50mg and 100mg), clinical response was maintained in only 47.0% and 49.7% of patients, respectively at 54 weeks, compared to 31.2% for placebo [2]. Combined, this means we

can expect only 24.0% to 27.3% of golimumab UC patients to successfully achieve and maintain clinical response over 54 weeks. Similar results are seen across a wide range of UC and CD treatment options.

Attempts to characterize UC and CD based on genetic sequencing have advanced scientific understanding of these diseases and contributing genes, but they have not yet yielded any predictive capabilities for drug response [3]. Current FDA guidelines for developing drugs to treat UC and CD define clinical remission in part based on endoscopic disease activity scoring using the MES and SES-CD, respectively [4,5]. These scoring systems (and many others) have been extensively studied as measurement tools for disease activity in UC and CD; however, they have not been fully validated or established as tools for measuring responsiveness [6].

We have developed an AI model to extract information-dense visual features from endoscopy. This model was trained in a self-supervised fashion on a curated dataset of frames sampled from a pool of over 120,000 unique endoscopic procedures, representing over 3.2 billion total frames. Because it has been trained on an extremely diverse endoscopy dataset, our model serves as a powerful backbone feature extractor for training new models with limited data.

In this study, we will leverage endoscopy data from the phase 2 and phase 3 trials of ustekinumab, golimumab, and infliximab for UC and CD who have undergone endoscopic evaluation to assess the efficacy of our AI model in predicting endoscopic disease score, patient characteristics, and drug response. For all prediction tasks, we will split the available data into random splits of 80/10/10 for training, validation, and testing. For tasks where data is limited, we will conduct k-fold cross validation.

This study will determine whether our AI model is capable of automatically replicating the MES and SES-CD with high efficacy. It will also help determine whether there are other visual features present in endoscopy that can predict patient characteristics such as age, sex, and comorbidities. Finally and most importantly, this study will examine whether there are visual endoscopic features present at baseline that can help determine which patients are most likely to respond to specific drugs. If true, this could help advance future trial design and ultimately lead to significantly higher response rates for IBD treatments.

Specific Aims of the Project:

1) To evaluate the efficacy of our AI model for predicting the centrally read MES or SES-CD.
2) To determine the ability for our AI model to accurately predict patient characteristics such as age, sex, and comorbidities.
3) To evaluate the efficacy of our AI model for predicting which trial subjects will respond to treatment based on their baseline endoscopy.

Study Design:

Methodological research

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

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Participant-level data meta-analysis

Meta-analysis using only data from the YODA Project

Research on clinical trial methods

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:

Only trial data made available through the YODA Project will be used.

Inclusion criteria: patients with endoscopic images/video
Exclusion criteria: none

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

Primary Outcome Measures:

The area under the receiver operating curve (AUROC) for predicting:
1) Centrally read MES and SES-CD scores
2) Patient characteristics such as age, sex, gender, race, comorbidities, and biomarker panel
3) Response to treatment based on baseline endoscopy

An AUROC that is statistically significantly greater than 0.5 will be classified as better than chance. An AUROC of 0.6 to 0.7 will be considered of interest and worth additional study, 0.7 to 0.8 will be considered good, 0.8 to 0.9 will be considered excellent, and >0.9 will be considered outstanding.

Secondary Outcome Measures:

For each category of classification, we will report the full confusion matrix, sensitivity, specificity, precision, and recall for training, validation, and test subsets.

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

The main independent variable will be achievement of clinical or endoscopic response or remission as defined in each of the golimumab, infliximab, and ustekinumab studies. These are generally defined based on clinical and endoscopic scoring indices.

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 will include:
-MES and SES-CD
-Subscores of the Mayo Score (e.g. stool frequency, rectal bleeding, and physician global assessment)
-Crohn’s Disease Activity Index (CDAI)
-Age and sex
-Race and ethnicity
-Other comorbidities
-Biomarker panels
-Disease duration
-Previous and concomitant treatment exposures
-Disease extent UC (left sided vs. extensive/pancolitis for UC)
-Disease extent CD (ileal vs. ileocolonic vs. colonic disease for CD, as defined by the involved segments on the SES-CD)

Statistical Analysis Plan:

Study selection: phase 2 and 3 clinical trials of infliximab, golimumab, and ustekinumab for the treatment of UC and CD with endoscopy data.

We will apply the following statistical analyses through a full confusion matrix: AUROC, sensitivity, specificity, precision, recall, and F1 score. We will also report inference results from our AI model for select examples of true positives, false positives, true negatives, and false negatives to provide representative examples of the model working and not working.

Software Used:

Python

Project Timeline:

Project Start Date: August 1, 2024
Initial Analysis: August 15, 2024
Analysis Completion: August 30, 2024
Manuscript Drafted: September 15, 2024
Abstract Submitted to ECCO: November 15, 2024
Manuscript Submitted for Publication: November 30, 2024
Results Reported to YODA: December 15, 2024
Project Completed: December 30, 2024

Dissemination Plan:

We anticipate that this project will lead to a manuscript submitted in either a clinical gastroenterology or artificial intelligence journal. We intend to submit the draft manuscript to medrxiv.org (founded by Cold Spring Harbor Laboratory, Yale University, and BMJ). We also plan to share our results at relevant conferences, such as European Crohn's and Colitis Organization, Crohn's and Colitis Congress, Digestive Disease Week, and American College of Gastroenterology.

Bibliography:

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2. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, Adedokun OJ, Guzzo C, Colombel JF, Reinisch W, Gibson PR, Collins J, Järnerot G, Rutgeerts P; PURSUIT-Maintenance Study Group. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014 Jan;146(1):96-109.e1. doi: 10.1053/j.gastro.2013.06.010. Epub 2013 Jun 14. PMID: 23770005.
3. Dubinsky MC, Collins R, Abreu MT; International Organization for the Study of Inflammatory Bowel Diseases (IOIBD). Challenges and Opportunities in IBD Clinical Trial Design. Gastroenterology. 2021 Aug;161(2):400-404. doi: 10.1053/j.gastro.2021.03.065. Epub 2021 Apr 20. PMID: 33864796.
4. Ulcerative Colitis: Developing Drugs for Treatment Guidance for Industry. FDA Draft Guidance. 2022 April. https://www.fda.gov/media/158016/download.
5. Crohn's Disease: Developing Drugs for Treatment Guidance for Industry. FDA Draft guidance. 2022 April. https://www.fda.gov/media/158001/download.
6. Mohammed Vashist N, Samaan M, Mosli MH, Parker CE, MacDonald JK, Nelson SA, Zou GY, Feagan BG, Khanna R, Jairath V. Endoscopic scoring indices for evaluation of disease activity in ulcerative colitis. Cochrane Database Syst Rev. 2018 Jan 16;1(1):CD011450. doi: 10.1002/14651858.CD011450.pub2. PMID: 29338066; PMCID: PMC6491285.