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General Information

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Requires Data Access? Yes

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
https://yoda.yale.edu/wp-content/uploads/2024/06/PD-COI.pdf
https://yoda.yale.edu/wp-content/uploads/2024/06/SS-COI.pdf
https://yoda.yale.edu/wp-content/uploads/2024/06/AS-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. 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

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, 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 a phase 3 trial of ustekinumab for the treatment of UC. 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 a phase 3 trias of ustekinumab for UC 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 a phase 3 trial of ustekinumab for UC 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 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, race 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.
2) To determine the ability for our AI model to accurately predict patient characteristics such as age, sex, race, 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

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 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 the phase 3 ustekinumab study. 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
-Subscores of the Mayo Score (e.g. stool frequency, rectal bleeding, and physician global assessment)
-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)

The purpose of studying whether our AI model is capable of predicting patient characteristics such as age, sex, race/ethnicity, and comorbidities is to serve as a proof of concept for whether there may also be other available biomarker signals in endoscopy that are not readily apparent to human experts. To our knowledge, no prior study has been made as to whether these types of patient characteristics can be ascertained from endoscopy data. If successful, our results would help advance scientific understanding of endoscopic differences between patient demographics that are clinically relevant. Analogous work has been done in retinal imaging to predict cardiovascular risk, age, gender, and smoking status [7].

Statistical Analysis Plan:

Study selection: phase 3 clinical trial of ustekinumab for the treatment of UC 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.

It is important to note that the prediction of patient characteristics such as age, sex, race/ethnicity, and comorbidities will only use the already provided de-identified trial data. No attempts will be made to re-identify the de-identified data that is provided, nor would this be possible.

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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Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2024/08/YODA-Project-Protocol-2024-0668-Additional-Information-Statement.docx