From Inflammation to Remission: Exploring Protective Mechanisms in Ulcerative Colitis (PROTECT-UC)

-Henrik Albæk Jacobsen, MD, PhD

Introduction

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic, relapsing disorders often diagnosed in early adulthood. In Denmark, more than 50,000 individuals live with IBD, and the incidence continues to rise.[1] Despite therapeutic advances, disease courses are highly variable, and treatment still follows a "one-size-fits-all" step-up approach based on disease activity.[2]

In my clinical experience as a gastroenterologist, many patients with UC achieve long-term remission on 5-aminosalicylic acid (5-ASA) monotherapy, the cornerstone treatment for mild to moderate disease. In a recent study conducted in collaboration with international experts from Mount Sinai, New York, and Harvard Medical School, Boston, we found that approximately 50% of patients with UC remained in a mild disease state even after 10 years of follow-up.[3] Yet, these patients remain poorly characterized in the literature, as most research and clinical trials have focused on individuals with moderate to severe disease treated in tertiary centers. Consequently, we know little about the mechanisms that allow some patients to maintain remission for years, while others progress to require adcanced biologic therapies or surgical intervention.[4]

The present project focuses on patients with initially mild UC, investigating why some maintain long-term remission on 5-ASA, while others progress. This work continues and expands the international Mild IBD collaboration and aims to generate evidence needed for improved early risk-stratification and personalized treatment strategies.

Background

UC is a heterogeneous disease with variable clinical courses. Early risk stratification is critical to personalize therapy. However, two major unmet needs in UC care are still *improved risk stratification* and *optimization of treatment strategies*.[5] These challenges are interlinked, as improved risk stratification based on disease severity impacts treatment response, whereas treatment response itself shapes long-term outcomes, including longitudinal severity.

While frameworks have been proposed to stratify disease activity, they are still limited in terms of long-term predictive value (disease severity). Disease activity is a reflection of the inflammatory burden of the disease, while the term severity incorporates clinical characteristics derived from retrospective cohort studies associated with long-term outcomes.[6] A limitation of these previous cohort studies is however the use of heterogeneous composite outcomes, such as advanced therapy use, hospitalization, or colectomy as they are each influenced by time period and external factors like healthcare systems and patient preferences. Thus, the modified version of Truelove and Witts criteria first published in 1955 remain on of the most widely used risk stratification tools although originally designed to assess disease activity and predict the need for hospitalization rather than the long-term disease course.[7]

The present project focuses on patients with initially mild UC, investigating why some maintain long-term remission on 5-ASA, while others progress. This work continues and expands the international Mild IBD collaboration and aims to generate evidence needed for improved early risk-stratification and personalized treatment strategies.

Hence, the hypotheses of the present project are:

Study 1: Long-term remission on 5-ASA is associated with distinct phenotypic characteristics.
Study 2: Distinct baseline or early disease features are associated with increased risk of disease progression despite initial response to 5-ASA.

Methods

This project builds on the North Denmark IBD Cohort (NorDIBD), one of the largest unselected population-based IBD cohorts worldwide, including more than 6,000 incident cases since 1978. NorDIBD is based on data captured through GASTROBIO, the regional IBD registry of the North Denmark Region, which integrates real-time input from patients, physicians, and medical staff.[13] The registry includes detailed information on diagnosis, medical therapy, laboratory results, endoscopic findings, surgery, family history, smoking, BMI, quality of life (SHS), and disease activity (SCCAI,

HBI). As part of my PhD, the cohort has been completed, with validation of medical records to be finalized in 2025.[14] Since 2023, a prospective biobanking initiative has been integrated into clinical care, collecting blood and fecal samples from both incident (>200) and prevalent (>1,800) patients with IBD in the North Denmark Region. Using the unique Danish Civil Registration Number, NorDIBD will be linked to nationwide health registries to obtain longitudinal and complementary data. Together, these resources enable detailed clinical and molecular profiling across the full disease spectrum.

Study Designs
The two studies presented below are part of a coherent research project that moves stepwise from clinical phenotyping to biomarker validation and mechanistic exploration. The studies focus specifically on the clinical phenotyping of patients with UC in long-term remission on 5-ASA medication.

Study 1: Clinical Characterization of Ulcerative Colitis in Long-Term Remission with Aminosalicylic Acid

Aim To phenotypically characterize patints with UC who achieve long-term remission on 5-ASA monotherapy. **Activity:** Population-based cohort study using NorDIBD (2002–2025) linked to nationwide Danish health registries. **Participants:** Patients with UC in long-term remission (≥3–5 years) on 5-ASA monotherapy compared with patients requiring early treatment escalation.. **Method:** Descriptive and multivariable logistic regression analyses to identify clinical and demographic factors associated with sustained remission. **Expected results:** Identification of clinical characteristics associated with an increased likelihood of a mild disease course.

Study 2: Predictors of Progression in Initially Mild Ulcerative Colitis

Aim: To identify baseline and early clinical factors associated with later disease progression among patients initially responding to 5-ASA. **Activity:** Longitudinal population-based cohort study using NorDIBD (2015–2025). **Participants:** Patients with UC achieving remission on 5-ASA following diagnosis. **Method:** Cox proportional hazards regression and Kaplan–Meier survival analyses comparing patients who maintain remission versus those who progress to require treatment escalation or surgery. **Expected results:** Identification of early prognostic indicators of progression among initial 5-ASA responders to guide clinical risk stratification.

Management
The project will be led by Henrik Albæk Jacobsen, MD, PhD, Aalborg University Hospital, who has overall responsibility for scientific and administrative management. Dr. Jacobsen combines clinical expertise in gastroenterology with experience in epidemiology and registry-based IBD research, supported by a strong publication record. He will oversee daily operations, including datamanagment and statistical analyses. The work will be conducted at Aalborg University Hospital in collaboration with PREDICT Center of Excellence, Aalborg University. International collaborators provide complementary expertise in translational IBD research and enable comparative studies in mild IBD, enhancing the project's scientific impact and global reach.

Participants: Associate Professor Lone Larsen, MD, PhD - Aalborg University Hospital & PREDICT Center of Excellence, Aalborg University. Professor Tine Jess, MD, DMSc - PREDICT & Aalborg University Hospital.
Collaborators: Professor Jean-Frederic Colombel, MD - Icahn School of Medicine at Mount Sinai, New York. Associate Professor Ashwin Ananthakrishnan, MD - Harvard Medical School, Massachusetts General Hospital, Boston.

Dissemination
This project is expected to yield novel clinical and molecular knowledge about mild UC, with implications for patient management and treatment stratification. Results will be disseminated through publications in leading gastroenterology journals, presenations at international conferences and by sharing findings with patient organizations supporting individuals with IBD.

Ethics
Relevant ethical approvals from the Regional or National Ethics Committees will be obtained before initiation of the studies. We will adhere to the principles of the Helsinki declaration and Good Clinical Practice. For all studies where informed consent is applicable, this will be obtained by standard ethical procedures.

Future Perspectives

This project will generate a detailed clinical characterization of long-term mild UC and early predictors of progression. Results may support development of new risk-stratification tools, inform decision-making on step-up versus early intensive therapy, and help identify patients who can safely continue 5-ASA monotherapy.

Importantly, the work will establish the foundation for later molecular studies integrating clinical phenotypes with biomarkers and microbial signatures to develop more precise stratification models at diagnosis, ultimately improving individualized care for patients with UC

Curriculum Vitae

Henrik Albæk Jacobsen – CV: Born April 7, 1988

Academic Degree

Master of Science in Medicine, Aarhus University 11.06.14

PhD, Faculty of Medicine, Aalborg University 05.11.24

Employment

Period	Position title (Danish)	Afdeling / Institution
01.11.2025 –	Afdelingslæge	Gastroenterologisk Afdeling, Aalborg Universitetshospital

Research Field/-Group

My research focuses on inflammatory bowel disease (IBD), particularly clinical epidemiology and registry-based studies. During my PhD at PREDICT, and The Department of Gastroenterology, Aalborg University Hospital, I worked with national and regional registries and contributed to patient enrollment for a large-scale biobank study collecting fecal and blood samples. I currently work as a clinician at Aalborg University Hospital and will complete my specialization in gastroenterology in November 2025.

I maintain active international collaborations with Mount Sinai, New York, and Harvard Medical School, Boston, studying the disease course and prognosis in patients with IBD. This project is a natural continuation of my previous work, ongoing data collection, and established collaborations.

International Conference Participation and Presentations

United European Gastroenterology Week (UEGW)

- **2024**: October 12–15, Vienna, Austria
- **2023**: October 14–17, Copenhagen, Denmark (poster presentation)

European Crohn's and Colitis Organization (ECCO)

- **2025**: February 19–22, Berlin, Germany (Poster presentation)
- **2024**: February 21–24, Stockholm, Sweden
- **2023**: March 1–4, Copenhagen, Denmark

Digestive Disease Week (DDW) 2024: May 18–21, Washington, D.C., USA (poster presentation)

Press

Medicinsk Tidsskrift – Mild IBD udfordrer lægerne"*Vi viser, at en væsentlig del af IBD-patienterne har vedvarende mild sygdom og ikke oplever forværring. Det er et vigtigt indspark i debatten om, hvordan man skal håndtere nydiagnosticeret IBD."***Sundhedspolitisk Tidsskrift:** Danske forskere: KOL og astma er forbundet med tarmsygdomme **Astma-Allergi Danmark**: En uventet forbindelse mellem astma og tarmsygdomme

Supervision Experience

- Supervised a medical student's master's thesis on the topic of sexual dysfunction in patients with IBD (2024).
- Acted as examiner for the thesis defense.
- Co-first authored and supervised a related research paper based on the thesis findings.

Awards

Poster of Distinction – DDW (2024)

Membership of Scientific Societies

- Commission member, Danish Society of Gastroenterology and Hepatology (Youth), 2018–2023
- Member, Danish Society of Gastroenterology and Hepatology
- Member, European Crohn's and Colitis Organization (ECCO)
- Member, International Bowel Ultrasound Group (IBUS)

Previous Grants

- Region Nordjyllands Sundhedsvidenskabelige Forskningsfond (2025) – 180,000 DKK
- TAKEDA Travel Grant (2021) – 25,000 DKK
- Region Nordjyllands Sundhedsvidenskabelige Forskningsfond (2022) – 90,000 DKK
- Colitis-Crohn Foreningens Forskningslegat (2023) – 50,000 DKK

Peer-Reviewed Journal Articles

1. Sexual Health Challenges in Individuals with and without Inflammatory Bowel Disease: A Population-Based Study in Denmark
   Christina Faaborg Larimore†, **Henrik Albæk Jacobsen**†, Christian Graugaard, Mikael Andersson, Lone Larsen, Morten Frisch
   Inflammatory Bowel Diseases. 2025-10-23.
   https://doi.org/10.1093/ibd/izaf234
   †Authors contributed equally
2. Risk of Colitis in Patients With Inflammatory Bowel Disease or Microscopic Colitis Exposed to Checkpoint Inhibitors: A National Danish Cohort Study
   Emilie Kristine Dahl, Katrine Risager Christensen, **Henrik Albæk Jacobsen**, Anders Kverneland, Anders Dige, Inge Marie Svane, Marco Donia, Jacob Tveiten Bjerrum, Jakob Benedict Seidelin
   JCO Oncology Practice. October 2025.
   https://doi.org/10.1200/OP-25-00390
3. Cross-Sectional Imaging Features Associated With Disease Progression in Crohn's Disease
   Salam P. Bachour, Shravya Srinivas-Rao, Nikitha Uma Baskaran, Manasi Agrawal, **Henrik Albæk Jacobsen**, Lone Larsen, Tine Jess, Jean-Frederic Colombel, Ryan C. Ungaro, Avinash Kambadakone, Ashwin N. Ananthakrishnan
   Inflammatory Bowel Diseases. Published 30 September 2025; izaf219.
   https://doi.org/10.1093/ibd/izaf219
4. Mild Crohn's Disease is Associated with Altered Sphingolipid Metabolism and Reduced Neutrophilic Inflammation
   Arno R. Bourgonje, Susanne Ibing, Palak Rajauria, Jellyana Peraza, **Mild CD Investigation Consortium**, Jean-Frédéric Colombel, Ryan C. Ungaro

Gastroenterology. In Press, Available online 21 July 2025.
https://doi.org/10.1053/j.gastro.2025.07.021

5. Distinct Perturbances in Metabolic Pathways Associate with Disease Progression in Inflammatory Bowel Disease
   Arno R. Bourgonje, Susanne Ibing, Alexandra E. Livanos, Danielle Y. Ganjian, Carmen Argmann, Bruce E. Sands, Marla C. Dubinsky, Drew S. Helmus, **Henrik A. Jacobsen**, Lone Larsen, Tine Jess, Mayte Suarez-Fariñas, Bernhard Y. Renard, Jean-Frédéric Colombel, Ryan C. Ungaro
   Journal of Crohn's and Colitis. 2025; 19(6):jjaf082.
   https://doi.org/10.1093/ecco-jcc/jjaf082
6. A Simple Endoscopic Score for Crohn's Disease (SES-CD) ≥7 Predicts Disease Progression
   Jellyana Peraza, Marco Emilio Kaper, Andre Bargas, Iris Kim, Manasi Agrawal, Lone Larsen, **Henrik Albæk Jacobsen**, Tine Jess, Jean-Frederic Colombel, Joana Torres
   Alimentary Pharmacology & Therapeutics. March 2025.
   https://doi.org/10.1111/apt.18492
7. Prevalence and Prognosis of Mild Inflammatory Bowel Disease: A Population-Based Cohort Study, 1997–2020
   Henrik Albæk Jacobsen, Anastasia Karachalia-Sandri, Anthony C. Ebert, Kristine H. Allin, Ashwin N. Ananthakrishnan, Manasi Agrawal, Ryan C. Ungaro, Jean-Frederic Colombel, Lone Larsen, Tine Jess
   Clinical Gastroenterology and Hepatology. December 2024.
   https://doi.org/10.1016/j.cgh.2024.10.021
8. Increased Risk of Obstructive Lung Disease in Inflammatory Bowel Disease: A Population-Based Cohort Study
   Henrik Albæk Jacobsen, Anastasia Karachalia Sandri, Ulla Møller Weinreich, Tine Jess, Lone Larsen
   United European Gastroenterology Journal. May 2024.
   https://doi.org/10.1002/ueg2.12527
9. Has the Incidence of Inflammatory Bowel Disease Peaked? Evidence From the Population-Based NorDIBD Cohort 1978–2020
   Lone Larsen, Anastasia Karachalia Sandri, Jan Fallingborg, Bent Ascanius Jacobsen**, Henrik Albæk Jacobsen**, Martin Bøgsted, Asbjørn Drewes, Tine Jess
   The American Journal of Gastroenterology. March 2023.
   https://doi.org/10.14309/ajg.0000000000002187
10. Validity of Inflammatory Bowel Disease Diagnoses in the Danish National Patient Registry: A Population-Based Study from the North Denmark Region
    Henrik Albæk Jacobsen, Tine Jess, Lone Larsen
    Clinical Epidemiology. October 2022.
    https://doi.org/10.2147/CLEP.S378003
11. Vedolizumab as First-Line Biological Therapy in Elderly Patients and Those with Contraindications for Anti-TNF Therapy
    Mohamed Attauabi, Camilla Höglund, Janne Fassov, Kenneth Bo Pedersen, Heidi Bansholm Hansen, Signe Wildt, Michael Dam Jensen, Anders Neumann, Cecilie Lind, **Henrik Albæk Jacobsen**, et al.
    Scandinavian Journal of Gastroenterology. September 2021.
    https://doi.org/10.1080/00365521.2021.1946588

Budget

Existing Funding
The applicant's salary for three months, distributed across the 12-month project period (approximately 230,000 DKK), is already fully covered through other funding sources.

Funding Applied for (This Application)
We request 50,000 DKK to cover statistical support, corresponding to approximately one month of full-time work by a statistician. This support is essential to ensure robust and high-quality analyses, enhancing the reliability and validity of the results.

Budget Summary

Budget Item	Amount (DKK)	Funding Source
Applicant salary (3 months, distributed)	230,000	Already funded
Statistician support (approximately 1 month)	50,000	Applied for in this application

Project Period

- Start: Q2 2026
- End: Q2 2027

Lægmandsrapport

-Mild Ulcerøs colitis: Hvem klarer sig godt på 5-ASA?

Hvorfor er projektet vigtigt?
Ulcerøs colitis (UC) er en kronisk tarmbetændelse, som ofte giver tilbagevendende forværringer. Mange patienter behandles med 5-aminosalicsyre (5-ASA). Mens nogle udvikler en svær sygdom med behov for mere avanceret immunmodulerende behandling eller operation, oplever en stor gruppe at forblive symptomfrie i mange år på 5-ASA alene. Alligevel kender vi kun lidt til hvem og hvorfor, disse patienter klarer sig godt på denne medicin.

Det betyder, at læger i dag mangler redskaber til at sige: *"Du har lav risiko for forværring, 5-ASA kan være nok"* eller *"Du har forhøjet risiko, måske skal vi følge dig tæt eller starte avanceret behandling tidligere"*. Det vil vi gerne ændre.

Hvad vil vi undersøge?
Vi vil analysere data fra en meget stor gruppe danske patienter med UC, både dem der har haft mild sygdom i mange år med 5-ASA og dem der hurtigt fik behov for mere avanceret behandling. Formålet er at finde kliniske tegn, der kan forudsige:

- Hvem bliver ved med at have mild sygdom på 5-ASA?
- Hvem forværres hurtigt?
- Hvem ser milde ud i starten, men forværres alligevel senere?

Ved at kende disse mønstre, kan læger bedre rådgive patienter og vælge behandling derefter.

Hvorfor kan vi gøre det?
Via vores unikke database og den opdaterede NorDIBD kohorte, som indeholder data om mere end 6.000 patienter med IBD. Her følger vi sygdomsforløbet over tid og har adgang til detaljerede oplysninger om både demografi og sygdomskarakteristika, herunder sygdomsudbredelse, blodprøver, afføringsprøver, aktivitetsscore, livskvalitet, behandling, bivirkninger, operationer og graviditeter med mere.

Hvad kan det betyde for patienter?
Læger vil få bedre muligheder for tidligt at forudsige, hvilke patienter der trygt kan fortsætte på 5-ASA uden behov for stærkere medicin. Det kan forebygge unødvendige behandlingstrin, reducere bivirkninger, øge trygheden og samtidig mindske både personlige og samfundsmæssige omkostninger.

På længere sigt vil projektets resultater være fundamentet for ny biomarkørforskning baseret på blod- og afføringsprøver fra denne patientkohorte. Ved at kombinere kliniske oplysninger med molekylære fund bliver det forhåbentligt muligt at udvikle endnu mere præcis og personlig behandling i fremtiden.