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Natural history, immunological and genetic characteristics of preclinical inflammatory bowel disease (EARLY): study protocol for a prospective cohort study

Iago Rodríguez-Lago, Urko M. Marigorta, Beatriz Mateos, Míriam Mañosa, Lucía Márquez-Mosquera, Luis Menchén, Francisco Rodríguez-Moranta, Inmaculada Alonso, Mariam Aguas, Horacio Alonso-Galán, Pere Borràs, Beatriz Castro, Eugeni Domènech, Rocío Ferreiro-Iglesias, Ruth de Francisco, Francisco Javier García-Alonso, Natalia García, Orlando García-Bosch, Carla Gargallo, Javier P. Gisbert, Eva Iglesias, Francisco Mesonero, Jone Ortiz de Zárate, Laura Ramos, Empar Sáinz, Pablo Ladrón, Carles Suria, Cristina Suárez Ferrer, Coral Tejido, Pilar Varela, Raquel Vicente, Yamile Zabana, Gisela Castany, Eva Rodríguez, Ana Gutiérrez and Manuel Barreiro-de Acosta; on behalf of the EARLY Study Group from GETECCU

Abstract

Background: The period prior to the diagnosis of inflammatory bowel disease (IBD), defined as the preclinical phase, has emerged as a potential target for disease modification strategies. Despite the relevance of an early diagnosis to the prognosis of the disease, only a limited number of patients are diagnosed during this window of opportunity.

Objectives: To determine the risk of developing symptoms after an incidental diagnosis of IBD and to describe the clinical, genetic, and immunological characteristics of IBD during its preclinical phase.

Design: This study protocol describes a prospective, multicenter cohort study in which incidental (i.e., asymptomatic) IBD within the colorectal cancer screening program will be characterized from a clinical and multi-omic perspective and compared with symptomatic patients and healthy non-IBD controls.

Methods: Samples from blood, urine, stool, and intestinal endoscopic biopsies will be obtained at baseline. A second sample set will be obtained after 52 weeks from those who remain asymptomatic; samples will also be obtained in those with new-onset symptoms. Medical treatment will be prescribed in all patients following current guidelines. Follow-up visits will be performed every 6 months for 10 years, and all new-onset symptoms, changes in disease behavior, extraintestinal manifestations, IBD-related medical therapies, or surgeries will be recorded. Two control cohorts will be included: one including recently diagnosed symptomatic IBD patients (<3 months), and another with healthy non-IBD controls after a normal ileocolonoscopy, in whom samples will be obtained at baseline. Samples from patients and controls will undergo genetic, proteomic, transcriptomic, single-cell RNA sequencing, metabolomic, and microbiome analyses, and integration of data between the different omic perspectives will also be performed. The study has been approved by the Basque Country Ethics Committee (PI2021116).

Conclusion: EARLY will generate a unique dataset addressing a previously unexplored area of IBD, with the final aim of describing the prognosis of patients from its earlier phases on the disease and integrating clinical and omic data into useful tools for the long-term prediction of disease outcomes.

Trial registration: NCT05698745.

Correspondence to:
Iago Rodríguez-Lago
Gastroenterology Department, Hospital Universitario de Galdakao, Biobizkaia Health Research Institute, Galdakao 48960, Spain
iago.r.lago@gmail.com

Urko M. Marigorta
Beatriz Mateos
Integrative Genomics Laboratory, CIC bioGUNE, Derio, Spain

Míriam Mañosa
Gastroenterology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain

Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain

Lucía Márquez-Mosquera
Servei de Aparell Digestiu, Hospital del Mar; IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

Luis Menchén
Gastroenterology Department, Hospital General Universitario e Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

Departamento de Medicina, Universidad Complutense, Madrid, Spain

Francisco Rodríguez-Moranta
Gastroenterology Department, Hospital Universitario Bellvitge, IDIBELL, Hospitalet Llobregat, Barcelona, Spain

Inmaculada Alonso
Laura Ramos
Gastroenterology Department, Hospital Universitario de Canarias, La Laguna, Spain

Mariam Aguas
Gastroenterology Department, Hospital Politécnico y Universitario de la Fe, Valencia, Spain

Horacio Alonso-Galán
Gastroenterology Department, Hospital Universitario Donostia, BioGiopuzkoa Health Research Institute, Donostia, Spain

Pere Borràs
Gastroenterology Department, Hospital Universitari Mútua Terrassa, Terrassa, Spain

Beatriz Castro
Gastroenterology Department, Hospital Universitario Marqués de Valdecilla, Santander, Spain

Eugeni Domènech
Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain

Gastroenterology Department, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain

Rocío Ferreiro-Iglesias
Manuel Barreiro-de Acosta
Gastroenterology Department, Hospital Clínico Universitario de Santiago de Compostela, FIDIS, Santiago de Compostela, Spain

Ruth de Francisco
Gastroenterology Department, Hospital Universitario Central de Asturias, Oviedo, Spain

Francisco Javier García-Alonso
Gastroenterology Department, Hospital Universitario Río Hortega, Valladolid, Spain

Natalia García
Gastroenterology Department, Hospital Álvaro Cunqueiro, Vigo, Spain

Orlando García-Bosch
Gastroenterology Department, Hospital de Sant Joan Despí Moisès Broggi, Sant Joan Despí, Spain

Carla Gargallo
Gastroenterology Department, Hospital Universitario Lozano Blesa, Zaragoza, Spain

Javier P. Gisbert
Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain

Gastroenterology Department, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Universidad Autónoma de Madrid (UAM), Madrid, Spain

Plain language summary

Study protocol of a study on the natural history, immunological and genetic characteristics of the early phases of inflammatory bowel disease (EARLY)

This study focuses on inflammatory bowel disease (IBD) and aims to explore the period before symptoms appear, known as the preclinical phase. Detecting IBD early could improve patient outcomes, but currently, few patients are diagnosed during this phase. The study seeks to determine the risk of developing symptoms after an incidental IBD diagnosis (discovered without symptoms) and to describe the clinical, genetic, and immune characteristics of IBD in this early stage. It involves a prospective, multicenter approach, examining patients who are incidentally diagnosed with IBD during colorectal cancer screening. These patients will be compared to those with symptomatic IBD and healthy individuals without IBD. Researchers will collect samples of blood, urine, stool, and intestinal tissue from participants at the start of the study and again after one year if they remain symptom-free. Additional samples will be taken if symptoms develop. Participants will receive standard medical treatment and have follow-ups every six months for ten years. The study will track new symptoms, changes in disease behavior, extraintestinal symptoms, treatments, and surgeries. Two control groups will be included: one with recently diagnosed symptomatic IBD patients and another with healthy individuals who had normal colonoscopy results. The samples will undergo extensive genetic and molecular analyses to integrate data from different perspectives. The EARLY study will generate a valuable dataset on the early stages of IBD, aiming to understand the prognosis from its earliest phases and to combine clinical and molecular data to predict long-term outcomes.

Keywords: biomarkers, Crohn's disease, early, natural history, prediction, ulcerative colitis

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Background

Inflammatory bowel disease (IBD) is an immune-mediated disease with a progressive and disabling course. Despite the current awareness and improvement in diagnostic procedures, still a significant proportion of patients demonstrate complications even at diagnosis.[1,2] The delay in the diagnosis and its negative impact on structural complications in the long term has been repeatedly demonstrated, in particular through the increased risk of intestinal surgery in these patients.[2] Therefore, strategies focused on earlier diagnosis and intervention are an important unmet need in IBD.

Recently, the preclinical stage of the disease has emerged as a potential target for disease-modification strategies.[3] However, only a limited number of patients with IBD are diagnosed during its early stages or even before the development of symptoms triggered by the inflammatory process in the gut.[4] Some of these cases can be detected as an incidental finding during radiological or endoscopic examinations performed for other indications.[5–8] Despite the interest in new findings from the preclinical phase of the disease, we still have very limited information about this period, both regarding its long-term prognosis and its clinical and molecular characteristics.

The implementation of colorectal cancer (CRC) screening programs has led to the performance of an increasing number of endoscopic examinations in an asymptomatic population.[9] Among these individuals, an incidental diagnosis of IBD has been reported in approximately 0.4% of the participants.[5,8,10–12] Despite the relatively low prevalence and the target population over 45–50 years of age, the diagnosis of IBD in this context represents a unique opportunity to characterize the earliest phases of the disease.[3] A Spanish retrospective study including 110 patients with an incidental diagnosis among 31,005 screening colonoscopies after a positive fecal

immunological test showed a prevalence of IBD of 0.35%.[10] Here, C-reactive protein (CRP) and hemoglobin concentration were within the normal range at diagnosis and, in those cases with Crohn's disease (CD), no structuring or penetrating complications were observed. These data highlight how this subgroup of patients can provide a window of opportunity for early diagnosis and intervention, as 36% and 58% of the patients developed symptoms after a median follow-up of 2 and 7 years, respectively.[10,13] This opportunity has also been highlighted in similar cohorts with incidentally-diagnosed CD patients, where the probability of adverse outcomes was low although not negligible after a median of 4 years.[12] Additionally, the main microscopic features of these patients have been described, including a correlation with the subsequent risk of developing symptoms.[14]

The relevance of these findings has been demonstrated not only through the risk of developing symptoms and the requirement of medical therapy but also through the increased use of healthcare resources, hence highlighting the systemic involvement of the disease even from its early (i.e., preclinical) phase.[13,15] This finding might be associated with the observation of a significant bowel damage even in this subgroup of asymptomatic patients.[16] Recently, international collaborative initiatives have provided significant clinical and omic data on the initial events that precede the clinical onset of the disease. Among the available resources, the GEM cohort and the PREDICTS initiative are among the most important sources for clinical and translational research in this field.[17,18] For instance, certain immunological, microbial, and fecal biomarkers have already been described during this preclinical period.[17,19–25] Therefore, the evaluation of the presymptomatic phases of the disease highlights this unique opportunity of performing a study of the early immune disturbances in the pathophysiology of IBD.[26]

The EARLY cohort will build a multicenter prospective cohort focusing on patients with an incidental diagnosis of IBD during the CRC screening program, that will allow the discovery and characterization of the pathogenic processes that play a more important role in the early stages of the disease, which could be crucial for the identification of new treatment targets. In addition, the availability of two control groups, including an inception cohort of symptomatic patients with IBD and non-IBD healthy controls, may allow the detection of markers with predictive potential, and that might be useful biomarkers in clinical practice. In particular, the prospective design of the cohort will create an opportunity to evaluate the presence of potential predictive markers of the disease course and risk of developing complications from the early period. This is of particular importance considering the relevance of these lesions in the natural history of the disease.

Methods

Aims

The primary aims of this study are to determine the risk of developing symptoms among those patients with preclinical IBD, and to describe the clinical, genetic, and immunological characteristics of IBD during its preclinical phase.

Additionally, a range of secondary aims have been also considered, including the rate of new-onset complications (stricturing, penetrating, or perianal disease) in patients with preclinical CD; the development of a statistical risk model that will combine phenotypic, immunological, and genetic variables to stratify the risk of disease progression, comparing data between patients with and without symptoms from the preclinical cohort, and using as reference those diagnosed after the symptomatic onset and healthy non-IBD controls; to describe the endoscopic features of preclinical ulcerative colitis (UC) at diagnosis and changes in the extent of the lesions during follow-up; to describe the main histological findings of preclinical IBD compared to those diagnosed after the symptomatic onset; and to assess the clinical disease activity over time, the need of medical or surgical therapy and development of extraintestinal manifestations.

Study participants

Patients will be identified at the Gastroenterology Department from the participating sites and also by the close collaboration with the endoscopic unit. All IBD units will actively search for patients with a recent diagnosis of IBD during the CRC screening program. Patients with incidental IBD will be entering cohort A, including all diagnoses after a positive fecal immunological test (subjects between 50 and 69 years) or in whom this

Eva Iglesias Gastroenterology Department, Hospital Universitario Reina Sofía, Córdoba, Spain

Francisco Mesonero Gastroenterology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain

Jone Ortiz de Zárate Gastroenterology Department, Hospital Universitario de Basurto, Bilbao, Spain

Empar Sáinz Gastroenterology Department, Hospital Universitari de Manresa, Manresa, Spain

Pablo Ladrón Gastroenterology Department, Hospital Universitario de Burgos, Burgos, Spain

Carles Suria Gastroenterology Department, Hospital Clínico Universitario de Valencia, Valencia, Spain

Cristina Suárez Ferrer Gastroenterology Department, Hospital Universitario la Paz, Madrid, Spain

Coral Tejido Gastroenterology Department, Complejo Hospitalario de Ourense, Ourense, Spain

Pilar Varela Gastroenterology Department, Hospital Universitario de Cabueñes, Gijón, Spain

Raquel Vicente Gastroenterology Department, Hospital Universitario Miguel Servet, Zaragoza, Spain

Yamile Zabana Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain

Gastroenterology Department, Hospital Universitari Mútua Terrassa, Terrassa, Spain

Gisela Castany
Eva Rodríguez
GETECCU, Spain

Ana Gutiérrez Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain

Gastroenterology Department, Hospital General Universitario Dr Balmis de Alicante; ISABIAL, Alicante, Spain

examination is indicated based on a family history of CRC (usually between 40 and 69 years), only if they are asymptomatic after a detailed evaluation by the responsible physician. Patients will be included in this cohort only within the first 3 months from the index colonoscopy. In addition, only patients without IBD-specific treatment prior to the baseline visit and sample collection (V1) will be recruited.

Two additional control cohorts will be recruited:

- **Cohort B**, including new-onset IBD with a total of 80 adult patients with a recent diagnosis of IBD after developing symptoms. Here, only those with symptom duration <3 months and without previous immunomodulator or biologic use will be included.
- **Cohort C**, with a total of 20 healthy non-IBD controls (i.e., without comorbidities or immune-mediated diseases), identified after the performance of a population-based screening colonoscopy and in whom no signs of IBD are found after a complete ileocolonoscopy. Patients will undergo a detailed evaluation by the responsible gastroenterologist which will ensure that these patients fulfill the inclusion and exclusion criteria.

Study endpoints

For these aims, we have set different endpoints that will address all the primary and secondary aims of the study, including as primary endpoints:

- Development and type of new-onset symptoms during follow-up, for example, rectal bleeding, abdominal pain, diarrhea, rectal syndrome.
- Time to development of symptomatic disease during follow-up.
- IBD characteristics:
  - Type (CD or UC)
  - Disease location (CD) and extent (UC) according to Montreal classification[27]
  - CD behavior at diagnosis (Montreal classification)[27]
  - Endoscopic characteristics at diagnosis (both CD and UC): type of lesions, distribution, and extent
  - Presence and type (simple, complex fistula or abscess) of perianal disease at diagnosis and during follow-up
  - Type and elapsed time of previous extraintestinal manifestations
- Omic findings (i.e., proteomic, transcriptomic, serologic, microbiota, metabolomics, and tissue data)
  - Generation of molecular profiles for each biospecimen through high-throughput technologies
  - Identification of signatures with predictive potential for each molecular layer assayed through single omics
  - Multi-omic integration of signatures to clarify the molecular mechanisms involved and to develop advanced statistical prognosis models

Additionally, we will evaluate the following secondary endpoints:

- IBD characteristics:
  - Development and time to development of changes in CD disease location, according to Montreal classification[27]
  - Development and time to development of new-onset or stricturing, penetrating, or perianal complications, defined as changes in CD behavior
  - Development of proximal disease extension in UC
  - Laboratory parameters: fecal immunological test levels at diagnosis, and CRP, hemoglobin, albumin, fecal calprotectin at diagnosis and during follow-up
- Changes in endoscopic features during follow-up: type of lesions, distribution, and extent
- Microscopic characteristics at diagnosis
- Clinical disease activity during follow-up
- Requirement and time to medical or surgical therapy during follow-up
- Development, type, and time to development of extraintestinal manifestations during follow-up

Patient selection

Inclusion criteria. Patients from **cohort A** will be included if they fulfill all the following inclusion criteria:

- Male or female ⩾18 years of age at baseline
- New diagnosis of IBD during a CRC screening colonoscopy, based on the criteria from the European Crohn's and Colitis Organisation[28,29]
- Presence of a chronic inflammatory infiltrate and histological findings compatible with IBD
- The patient must be asymptomatic at diagnosis and without previous symptoms suggestive of IBD
- Time interval between the index colonoscopy and the baseline visit up to 3 months

Patients from **cohort B** will be included if they fulfill all the following inclusion criteria:

- Male or female ⩾18 years of age at baseline
- Recent diagnosis of IBD, with <3 months from symptoms onset
- Time interval between the index colonoscopy and the baseline visit up to 3 months

Patients from **cohort C** will be included if they fulfill all the following inclusion criteria:

- Male or female ⩾18 years of age at baseline
- No endoscopic signs of IBD after a complete ileocolonoscopy within the CRC screening program
- Time interval between the index colonoscopy and the baseline visit up to 3 months

Exclusion criteria. Patients from **cohort A** will be excluded if they fulfill any of the following exclusion criteria:

- Presence of any enteropathogen in the stool culture
- Isolated findings of acute inflammatory infiltrate without signs of chronicity
- Previous or current diagnosis of microscopic colitis
- Alteration in biomarkers in blood or stool will not constitute an exclusion criterion.

Patients from **cohort B** will be excluded if they fulfill any of the following exclusion criteria:

- Previous use of immunomodulators or biologics for any condition

Patients from **cohort C** will be excluded if they fulfill any of the following exclusion criteria:

- Previous comorbidities or immune-mediated diseases
- Any gastrointestinal symptoms at baseline
- Previous use of immunomodulators or biologics for any condition

Study design and setting of the study

The study started on March 2024 and the recruitment period will last for 4 years (i.e., May 2028). Patients will be followed every 6 months for 10 years, so the study is expected to close in May 2038.

All participating sites and researchers were invited and selected through the GETECCU Research Committee and after the completion of a feasibility assessment regarding the total number of screening colonoscopies performed annually and the available resources for obtaining and processing the study samples. After considering all applications and prioritizing those centers certified by GETECCU quality standards,[30] we have built a collaborative network of 25 IBD Units in Spain.

Ethical considerations

This is a multicenter study with a prospective and observational design. The project will be conducted in accordance with the indications of the Declaration of Taipei (World Medical Association, October 2016), the Standards of Good Clinical Practice, and the Law 14/2007 on Biomedical Research. The information will be obtained from the medical records, and it will be included in an online and encrypted database where only the principal investigator will have access.

The study protocol and all the necessary documents for the inclusion of patients were approved by the Basque Country Ethics Committee (PI2021116, study protocol version 1.1). The study has also been evaluated by the Spanish Agency of Medicine and Sanitary Products (AEMPS) and it was classified as a non-post-authorization observational study. This study has been registered at ClinicalTrials.gov (NCT05698745, last updated December 27, 2024).

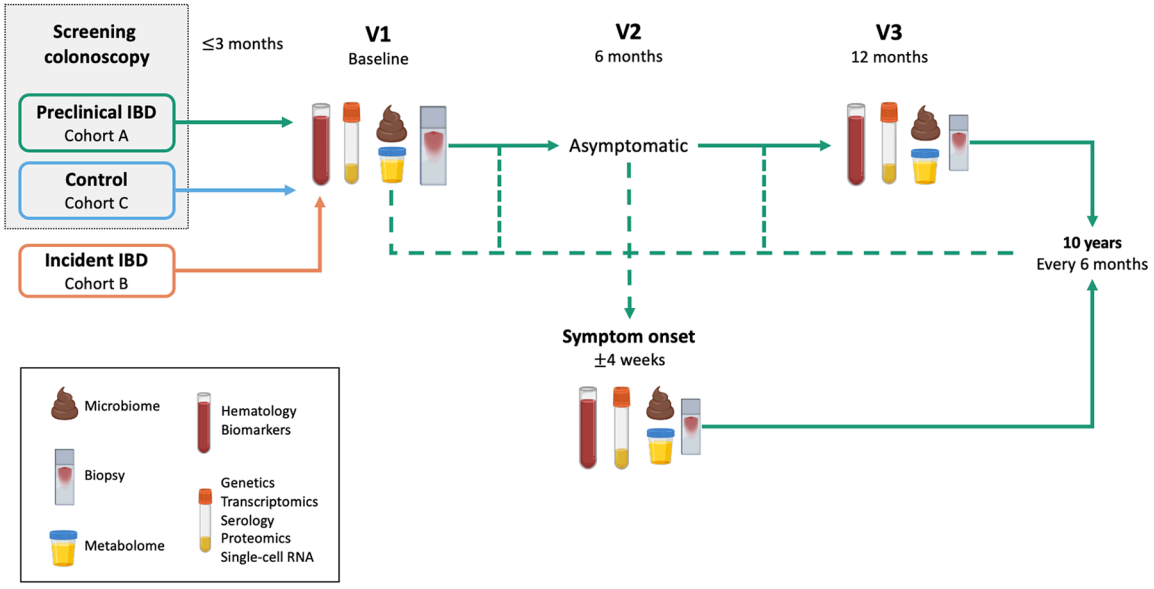

Figure 1. Overview of the study visits, samples, and study procedures during the 10-year follow-up and according to the cohort.

Study visits and procedures

Study visits. Patients with an incidental diagnosis of IBD during a CRC screening colonoscopy during the last 3 months will be recruited (Figure 1). These patients (cohort A) will be followed up every 6 months since the time of diagnosis for a period of 10 years. An additional visit will be performed for those developing new symptoms. These visits may be carried out according to local practice (either in-person or remotely), and according to the responsible physician's criteria (excluding those where it is necessary to obtain biological samples). At each visit, information regarding disease activity and any change in medical therapy will be compiled. Also, data on blood and stool biomarkers following clinical practice standards and closest to the date of consultation (CRP, hemoglobin, albumin, and fecal calprotectin) will also be collected. Due to the long-term follow-up of patients included in cohort A, a proportion of them may be expected to drop out. However, all patients will be referred and recruited at their respective IBD Units located at their reference centers, where their responsible physicians will be in charge of the regular visits. In addition, if loss to follow-up occurs, the unique identification number of each individual in the Spanish healthcare system ensures the identification of major outcomes of interest in the study (e.g., initiation of medical treatment, surgery). Patients from cohorts B (incident IBD) and C (controls) will only undergo the baseline visit (V1), and no follow-up will be necessary for them.

Colonoscopies. The study will be based on CRC screening colonoscopies, which will always follow the usual clinical practice recommendations and the standard procedure at each center and region. In those patients in whom endoscopic findings are compatible with IBD are observed, the terminal ileum will also be examined, and they will undergo the usual differential diagnosis and evaluation of disease location recommended in these cases.[28] The protocol does not establish additional examinations to determine the extent of the disease or endoscopic follow-up of the lesions, which will follow the recommendations of the screening program and the criteria of the responsible physician. However, detailed information regarding the disease extent will be also collected if available.

Biological samples. Blood, stool, and urine baseline samples will be collected at the time of diagnosis, within a maximum of 3 months from the index colonoscopy. Intestinal samples from this endoscopic procedure will also be collected. Patients must be asymptomatic and without any previous or current IBD-related medical therapy at this moment. Patients from cohorts B (incident

IBD) and C (controls) will only undergo this baseline visit and samples.

Blood, urine, and stool samples will be collected during follow-up according to the disease course:

- **Asymptomatic patient**: blood, urine, and stool samples will be collected 52 weeks (±4 weeks) after the date of diagnosis (i.e., the date of the index colonoscopy).
- **Symptomatic patient**: blood, urine, and stool samples will be collected closest to the symptom onset, with a maximum difference of 4 weeks.
    - **If symptoms develop within the first 12 months**, samples will be collected at the time of symptoms onset (±4 weeks) and no additional samples will be collected at the 12-month visit.
    - **If symptoms develop after visit 3 (12 months)**, samples from these patients will be collected at V3 (at 12 months, being asymptomatic) and the closest to symptoms onset (±4 weeks).

Medical treatment. Once the baseline sample is obtained, for patients from cohort A (preclinical IBD), treatment will be indicated by protocol and follow the current National[31] and European[32,33] recommendations. It will be adjusted according to the type of IBD and its extent, according to the usual clinical practice and the Montreal classification[27]:

Ulcerative colitis

- Proctitis (E1): mesalazine suppositories 500–1000 mg/day for 8 weeks.
- Left-sided (E2) or extensive (E3) colitis: oral mesalazine 2.4–4.8 g per day ± mesalazine suppositories 500–1000 mg daily for 8 weeks. This will be followed by 2.4 g of oral mesalazine as maintenance treatment.

Crohn's disease

- Mild-to-moderate ileal or ileocolonic disease: budesonide 9 mg/day for 8 weeks.
- Colonic disease: Since there are no specific indications in the guidelines, these patients will be treated at the discretion of the responsible physician.

Further medical or surgical therapy will be initiated at the discretion of the responsible physician following the current clinical practice guidelines.

Data collection

Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at AEG-REDCap.[34,35] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources. The clinical information from all participating centers will be prospectively and systematically monitored. Only the principal investigators will have access to the whole dataset with de-identified data and omics analyses. Investigators will have access solely to the clinical data from their respective centers.

All data will be handled in an encrypted and confidential manner. All the personal information of the study participants will comply with Organic Law 3/2018 of December 5, on the protection of Personal Data and guarantee of digital rights and the European Directive on Data Privacy.

Definitions

The following definitions will be used in the assessment of clinical disease activity:

- Asymptomatic patient: absence of symptoms associated with IBD after a detailed clinical evaluation and physical examination.
- Symptomatic patient: patient who, previously being asymptomatic, develops new-onset digestive symptoms once other possible causes have been ruled out.
- Clinical remission
    - UC: Partial Mayo score ≤ 2, with a rectal bleeding score of 0.
    - CD: Harvey-Bradshaw Index ≤ 4.
- Active disease
    - UC: Partial Mayo score > 2, with a rectal bleeding score equal or greater than 1.
    - CD: Harvey-Bradshaw Index > 4.

Regarding smoking habits, we will consider the following definitions:

- Active/current smoker: average uptake of >2 cigarettes per day.

- Former smoker: the patient who met the criteria of an active smoker but without the habit for at least 6 months.
- Never smoker: has never met the criteria for an active smoker.

Sample size calculation

Based on data published by the network of cancer screening programs in Spain in 2017, we estimated that 69,416 screening colonoscopies will be performed per year. Therefore, all participating sites will be requested to undergo at least 1000 screening colonoscopies per site (i.e., around 28,000 total screening colonoscopies per year). Based on the previous literature and in order to achieve a sample size to fulfill the main objective regarding the risk of developing new-onset symptoms, we considered an incidence of 0.35% of new diagnoses of IBD,[10] that will lead to the diagnosis of 243 IBD cases per year in the national territory within the screening programs, leading to an estimated sample size of 350 patients in the cohort A (preclinical IBD). This means that each site will be expected to recruit 3–4 patients per year.

In addition, 80 patients from cohort B (incident IBD) and 20 controls from cohort C (healthy controls) will be included. Both cohorts B and C are expected to demonstrate a low interindividual variability based on previous findings in studies of IBD patients and healthy controls, where omic profiles show consistent patterns within groups.[36] These studies highlight that targeted sample selection, rather than sheer volume, is critical for identifying significant features in group comparisons within the disease. Previous studies have successfully identified molecular differences in preclinical stages of CD and UC, further supporting the feasibility of using omic approaches in smaller cohorts.[19] Recruitment in cohort B will be limited to 40 CD patients and 40 UC patients. Calculating sample sizes for multi-omic studies is inherently complex due to the high dimensionality of the data and the need for multiple testing correction.[36] For this aim, we performed a simulation using the MultiPower R package, which allows for joint power studies across different omic datasets. This study was based on the distributional properties of features detected as significant in an internal in-house cohort with transcriptomic and metabolomic cohort profiles (16,393 genes and 232 metabolites, respectively). These analyses indicated that a sample size of 40 patients per group (cohort B) would provide 80% power to detect effect sizes (Cohen's d) of 0.5 or larger. For cohort C ($n = 20$), the lower sample size is justified by the expected high precision and minimal variability among healthy controls. Additionally, we expect high covariance across features in each omic layer, allowing for combining multiple features into predictive signatures, which should further increase the statistical power. In summary, the selected sample sizes for cohorts B and C provide an optimal balance between feasibility and precision in order to identify clinically relevant biological changes. Therefore, the EARLY study will include a total of 450 subjects.

Data analysis

Through descriptive statistics, we will describe the characteristics of IBD during its preclinical phase (cohort A) and descriptively compare it with both control populations (cohorts B and C). Descriptive statistics of the sample will be performed using frequencies and percentages with their corresponding 95% confidence interval (CI) for categorical variables and means and standard deviations, and 95% CI for continuous variables. Continuous variables with asymmetric distributions will be expressed as medians and interquartile ranges (IQR).

Kaplan–Meier survival curves with log-rank analysis and a multivariable Cox regression model will be used to evaluate the risk of development of symptoms during follow-up according to different variables. We will apply multivariable analysis (logistic regression) that will enable the identification of factors associated with this risk. The influence of relevant clinical or disease-related factors (e.g., disease location or extension, behavior, or histologic findings) on the risk of symptomatic disease will be evaluated by Cox proportional regression analysis after adjusting for confounding and clinically relevant factors. Additional comparisons with the same approach will evaluate the rate of complications, disease progression (e.g., proximal disease extension), need for medical therapy or surgery, and development of extraintestinal manifestations. Additional stratification based on selected biomarkers obtained from this cohort will also be applied in further analysis, in addition to clinical data. The correlation between continuous variables like FIT levels, laboratory findings with

some relevant outcomes (e.g., UCEIS) will be analyzed using Spearman's correlation.

Regarding multi-omic analyses, we will follow standard steps. Prior to integration, each omic dataset will undergo rigorous quality control (e.g., removal of low-quality samples and outlier detection) and normalization using methods tailored to each technique. Confounding factors will be addressed using both supervised techniques, adjusting for known covariates (age, sex, disease characteristics), and unsupervised techniques specific to each omic layer, such as surrogate variable analysis for transcriptomics, to minimize bias and ensure accurate downstream integration. Data exploration, dimensionality reduction, and feature selection will be performed using routine methods, such as principal component analysis to identify meta-features of interest, or regularization techniques to create models and identify the most predictive features in each omic layer. For the multi-omic component, we will use an array of tools. This is an active area of research, and we anticipate emerging new frameworks for joint analysis of multiple omic layers. Predictive models, including logistic regression and Cox proportional hazards models, will be developed to assess the probability of symptom development based on baseline multi-omic profiles. These models will be rigorously validated through cross-validation, ensuring robustness, and will be further validated using incoming preclinical cohorts to assess generalizability. Finally, we will assess the predictive utility of models combining clinical risk factors (age, sex, histology, type of IBD, disease location) with identified multi-omic biomarkers (e.g., risk genotypes, gene signatures, protein levels). Internal replication will be performed by reserving a subset of the dataset for validation, and subgroups not included in the initial analysis will be used to ensure robustness of the model for risk stratification and prediction of disease complications (e.g., penetrating or stricturing lesions, perianal disease).

Safety reporting

This noninterventional study is not designed to identify or quantify any safety-related issues associated with any authorized product. For this reason, and in line with Spanish local regulations, safety data will not be collected.

If a patient reports an adverse product-related event to his/her healthcare professional during the data collection period or the healthcare professional identifies an adverse product-related event, which is considered associated to any authorized product, the event will be reported to the Spanish Pharmacovigilance System for Human Use Medicinal Products, and as required by local laws and regulations.

An adverse event is defined as any undesired medical effect in a patient or clinical investigation. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product. A serious adverse event is an adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a birth defect.

Discussion

The EARLY cohort aims to determine the risk of developing symptoms among those patients with incidental IBD, and to describe the clinical, genetic, and immunological characteristics of IBD during its preclinical phase, compared to those patients diagnosed after the symptomatic onset and to healthy non-IBD controls. The results from this cohort will provide a comprehensive description on the initial events that precede the onset of the disease based on clinical and multi-omic data, and based on a multilayered and integrative perspective. This approach to the field of preclinical IBD can lead to the discovery of targets and pathways involved in the initial events that ultimately lead to the diagnosis of the disease.

This prospective cohort will evaluate patients over a period of 10 years, leading to a long-term perspective on the prognosis of patients with an incidental diagnosis of IBD. It is still unknown how the use of different medical therapies may alter the disease course of these patients, so medical treatment will be established based on the type of IBD and the disease extent. This will create a homogeneous patient cohort that will be followed up during the study period and with a reduced risk of bias. The availability of biological samples comprises a unique opportunity to understand the biological processes underlying

the progression of the disease in asymptomatic patients with a subclinical inflammatory process and how they are modified upon the symptomatic onset of the disease. Moreover, two additional control cohorts will also be included, one with recently diagnosed symptomatic patients and a second one with healthy non-IBD controls. Therefore, we will be able to generate a pathological axis in which the immunological environment of each cohort will be compared through a multi-omic perspective. This is the first attempt at the integration of clinical and omic data in a similar cohort of asymptomatic patients with a high risk of developing overt IBD and in whom the mucosal damage has also been evaluated. As no recommendations or guidelines have addressed this clinical scenario, the EARLY cohort will unveil the best approach for stratifying individuals to early intervention according to their risk based on multiple parameters, including genetic, immunological, and microbial factors.

Despite the high number of endoscopic procedures required for the completion of this study, all participating sites will be carefully selected among those with certified quality standards from GETECCU.[30] In addition, educational meetings will be organized with all centers, and a close collaboration will be established in order to ensure the correct performance of all study procedures. Therefore, considering also the multidisciplinary team and support from a scientific society, the EARLY cohort will be able to generate new clinical and omic data about the natural history of the disease. The long-term follow-up of this cohort over 10 years will also be considered as a challenge, but GETECCU has extensive experience in collaborative research and they will support and guarantee the follow-up of all the procedures within the study.[37]

Some limitations might also be considered, including the age of patients undergoing CRC screening procedures, which is expected to be over the age of 50. Despite this limitation, screening programs were considered an ideal setting where asymptomatic individuals undergo endoscopic procedures that allow a detailed evaluation of the mucosa and the obtaining of tissue samples. Also, the absence of reference standards or recommendations for this particular clinical setting and the limited information about the optimal length of follow-up for these patients should be considered.

Conclusion

Therefore, the EARLY study will generate a unique dataset addressing a previously unexplored area of IBD, with the final aim of describing the prognosis of patients from the earlier phases of the disease and integrating clinical and omic data into useful tools for the long-term prediction of disease outcomes.

Author's note

EARLY Study group collaborators: María Rosario Antón Ausejo, Lara Arias García, Guillermo Bastida, María Bellerin Ponce, Iria Bastón-Rey, Lorena Carballo-Folgoso, María José Casanova, Andrés Castaño-García, Jesús Castro-Poceiro, María Chaparro, Pilar Corsino, Cristina Fernández, Emilia Fernández-González, Romina Fernández-Poceiro, Mikel Fiallegas, Cristina García-Pérez, Laura García-Ramírez, Miguel Ángel de Jorge, Marisa Iborra, Dimitrios Kioroglou, Alejo Mancebo, Mercedes Navarro-Llavat, Pilar Nos, Isabel Pérez-Martínez, Sabino Riestra, Ángel de Prado, Cristina Sánchez Gómez, Beatriz Sicilia, María Vaamonde-Lorenzo, Laura Vicente.

Declarations

Ethics approval and consent to participate

This is a multicenter study with a prospective and observational design. The project will be conducted in accordance with the indications of the Declaration of Taipei (World Medical Association, October 2016), the Standards of Good Clinical Practice, and the Law 14/2007 on Biomedical Research. The information will be obtained from the medical records, and it will be included in an online and encrypted database where only the principal investigator will have access. The study protocol and all the necessary documents for the inclusion of patients were approved by the Euskadi Ethics Committee (PI2021116, study protocol version 1.1). The study has also been evaluated by the Spanish Agency of Medicine and Sanitary Products (AEMPS) and it was classified as a non-post-authorization observational study. This study has been registered at ClinicalTrials.gov (NCT05698745, last updated 27/December/2024).

Consent for publication

Consent for publication is included in the informed consent.

Author contributions

Iago Rodríguez-Lago: Conceptualization; Data curation; Formal analysis; Funding acquisition;

Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – original draft.

Urko M. Marigorta: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Resources; Software; Supervision.

Beatriz Mateos: Formal analysis; Investigation; Project administration; Resources.

Míriam Mañosa: Data curation; Investigation; Methodology.

Lucía Márquez-Mosquera: Data curation; Investigation; Methodology.

Luis Menchén: Data curation; Investigation; Methodology.

Francisco Rodríguez-Moranta: Data curation; Investigation; Methodology.

Inmaculada Alonso: Data curation.

Mariam Aguas: Data curation.

Horacio Alonso-Galán: Data curation.

Pere Borràs: Data curation.

Beatriz Castro: Data curation.

Eugeni Domènech: Data curation.

Rocío Ferreiro-Iglesias: Data curation.

Ruth de Francisco: Data curation.

Francisco Javier García-Alonso: Data curation.

Natalia García: Data curation.

Orlando García-Bosch: Data curation.

Carla Gargallo: Data curation.

Javier P. Gisbert: Data curation.

Eva Iglesias: Data curation.

Francisco Mesonero: Data curation.

Jone Ortiz de Zárate: Data curation.

Laura Ramos: Data curation.

Empar Sáinz: Data curation.

Pablo Ladrón: Data curation.

Carles Suria: Data curation.

Cristina Suárez Ferrer: Data curation.

Coral Tejido: Data curation.

Pilar Varela: Data curation.

Raquel Vicente: Data curation.

Yamile Zabana: Data curation; Investigation; Methodology.

Gisela Castany: Project administration; Validation.

Eva Rodríguez: Project administration; Validation.

Ana Gutiérrez: Data curation; Investigation; Methodology.

Manuel Barreiro-de Acosta: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Resources; Supervision; Writing – review & editing.

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Competing interests

IR-L has received financial support for traveling and educational activities from or has served as an advisory board member for AbbVie, Adacyte, Alfasigma, Biogen, Chiesi, Faes Farma, Ferring, Fresenius Kabi, Galapagos, Johnson & Johnson, Eli Lilly, Mirum Pharmaceuticals, Merck, Pfizer, Roche, Takeda, and Tillotts Pharma. MM has received financial support for traveling and educational activities or has served as a speaker or as an advisory member for Janssen, AbbVie, Lilly, Galapagos, Ferring, Takeda, Pfizer, and Tillots Pharma. LM has received financial support for traveling and educational activities from or has served as an advisory board member for Pfizer, MSD, Takeda, AbbVie, Kern, Janssen,

Galapagos, Lilly, Tilllotts Pharma, Ferring, Adacyte, and General Electric. HA has received financial support for traveling and educational activities from or has served as an advisory board member for Janssen, MSD, AbbVie, Takeda, Ferring, Pfizer, and Dr. Falk Pharma. ED has served as a speaker, or has received research or education funding or advisory fees from AbbVie, Adacyte Therapeutics, Biogen, Celltrion, Galapagos, Gilead, GoodGut, Imidomics, Janssen, Kern Pharma, Lilly, MSD, Pfizer, Roche, Samsung, Takeda, Tillotts Pharma. JPG has served as speaker, consultant, and advisory member for or has received research funding from MSD, AbbVie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene/Bristol Myers, Gilead/Galapagos, Lilly, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Norgine and Vifor Pharma. EI has received financial support for traveling and educational activities from or has served as an advisory board member for Adacyte, MSD, Takeda, AbbVie, and Janssen. FM has served as a speaker for and received consulting fees from MSD, AbbVie, Takeda, Janssen, Pfizer, Ferring, Kern Pharma, Dr. Falk Pharma, Galapagos, Chiesi and Faes Farma. CM has received financial support for traveling and educational activities from or participated in research for AbbVie and Janssen. RFI has received financial support for traveling and educational activities from or has served as an advisory board member for AbbVie, MSD, Takeda, Janssen, Kern, Pfizer, Adacyte, Ferring, Faes, Falk, Palex, Casenrecordati, and Shire. LR has served as a speaker or has received funding for educational activities from MSD, AbbVie, Adacyte, Takeda, Pfizer, Janssen, and Ferring. BS has received financial support for traveling and educational activities from or has served as an advisory board member for AbbVie, Faes, Chiesi, Dr. Falk, MSD, Tillotts Pharma, Kern Pharma, Janssen, Pfizer, and Takeda. YZ has received support for conference attendance, speaker fees, research support and consulting fees from AbbVie, Adacyte, Almirall, Amgen, Dr Falk Pharma, Faes Pharma, Ferring, Janssen, Lilly, MSD, Otsuka, Pfizer, Shire, Takeda, Galapagos, Boehringer Ingelheim, Sanofi, and Tillotts Pharma. AGC has received financial support for traveling and educational activities from or has served as an advisory board member for Pfizer, MSD, Takeda, AbbVie, Kern, Janssen, Fresenius Kabi, Galapagos, Lilly, Ferring, Faes Farma, Chiesi, GSK, and Adacyte. MBA has received financial support for traveling and educational activities from or has served as an advisory board member for Pfizer, MSD, Takeda, AbbVie, Kern, Janssen, Fresenius Kabi, Galapagos, Lilly, BMS, Faes Farma, Chiesi, and Adacyte. The remaining authors have no conflicts of interest to declare. All authors have approved the final version of this manuscript.

Availability of data and materials

The data from this study will be shared upon reasonable request and after evaluation by the Scientific Committee from GETECCU.

ORCID iDs

Iago Rodríguez-Lago https://orcid.org/0000-0003-1133-4578

Luis Menchén https://orcid.org/0000-0001-9490-3726

Inmaculada Alonso https://orcid.org/0000-0003-0406-029X

Javier P. Gisbert https://orcid.org/0000-0003-2090-3445

Francisco Mesonero https://orcid.org/0000-0002-7864-8187

Laura Ramos https://orcid.org/0000-0001-7015-1742

Yamile Zabana https://orcid.org/0000-0003-4023-8868

Ana Gutiérrez https://orcid.org/0000-0002-5460-4139

References

1. Chaparro M, Garre A, Nunez Ortiz A, et al. Incidence, clinical characteristics and management of inflammatory bowel disease in spain: large-scale epidemiological study. *J Clin Med* 2021; 10: 2885.

2. Jayasooriya N, Baillie S, Blackwell J, et al. Systematic review with meta-analysis: time to diagnosis and the impact of delayed diagnosis on clinical outcomes in inflammatory bowel disease. *Aliment Pharmacol Ther* 2023; 57: 635–652.

3. Torres J, Halfvarson J, Rodriguez-Lago I, et al. Results of the Seventh Scientific Workshop of ECCO: precision medicine in IBD-prediction and prevention of inflammatory bowel disease. *J Crohns Colitis* 2021; 15: 1443–1454.

4. Sorrentino D. Preclinical and undiagnosed Crohn's disease: the submerged iceberg. *Inflamm Bowel Dis* 2016; 22: 476–486.
5. Butcher RO, Mehta SJ, Ahmad OF, et al. Mo1302 incidental diagnosis of inflammatory bowel disease in a british bowel cancer screening cohort: a multi-centre study. *Gastroenterology* 2013; 144: S-630–S-631.
6. Johnston RD and Logan RF. How often is IBD diagnosed incidentally at screening colonoscopy done for colorectal cancer surveillance or other reasons? *Inflammatory Bowel Dis* 2008; 14(Suppl. 2): S170–S171.
7. Kamel EM, Thumshirn M, Truninger K, et al. Significance of incidental 18F-FDG accumulations in the gastrointestinal tract in PET/CT: correlation with endoscopic and histopathologic results. *J Nuclear Med* 2004; 45: 1804–1810.
8. Park SK, Ye BD, Yang SK, et al. Clinical features and course of ulcerative colitis diagnosed in asymptomatic subjects. *J Crohns Colitis* 2014; 8: 1254–1260.
9. Helsingen LM and Kalager M. Colorectal cancer screening - approach, evidence, and future directions. *NEJM Evid* 2022; 1: EVIDra2100035.
10. Rodriguez-Lago I, Merino O, Azagra I, et al. Characteristics and progression of preclinical inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2018; 16: 1459–1466.
11. Howarth GF, Robinson MHE, Jenkins D, et al. High prevalence of undetected inflammatory bowel disease (IBD): data from the Nottingham faecal occult blood (FOB) screening trial. *Am J Gastroenterol* 2002; 97: 690–694.
12. Grinman A, Ungar B, Lahat A, et al. Incidentally diagnosed asymptomatic Crohn's disease: a retrospective cohort study of long-term clinical outcomes. *Crohns Colitis 360* 2022; 4: otac034.
13. Rodriguez-Lago I, Aguirre U, Ramirez de la Piscina P, et al. Subclinical bowel inflammation increases healthcare resources utilization and steroid use before diagnosis of inflammatory bowel disease. *United European Gastroenterol J* 2023; 11: 9–18.
14. Rodriguez-Lago I, Ramirez C, Merino O, et al. Early microscopic findings in preclinical inflammatory bowel disease. *Dig Liver Dis* 2020; 52: 1467–1472.
15. Rodriguez-Lago I, Aguirre U, Cabriada JL, et al. Increased medication utilization precedes incidentally diagnosed inflammatory bowel disease: a multicenter, case-control study. *Am J Gastroenterol*. Epub ahead of print Dec 2024. DOI: 10.14309/ajg.0000000000003275.
16. Rodriguez-Lago I, Aduna M, Ramirez de la Piscina P, et al. Transmural cross-sectional findings and bowel damage assessment in preclinical Crohn's disease: a case-control study. *Int J Colorectal Dis* 2024; 39: 92.
17. Turpin W, Lee SH, Raygoza Garay JA, et al. Increased intestinal permeability is associated with later development of Crohn's disease. *Gastroenterology* 2020; 159: 2092–2100 e2095.
18. Porter CK, Riddle MS, Gutierrez RL, et al. Cohort profile of the proteomic evaluation and discovery in an IBD cohort of tri-service subjects (PREDICTS) study: rationale, organization, design, and baseline characteristics. *Contemp Clin Trials Commun* 2019; 14: 100345.
19. Torres J, Petralia F, Sato T, et al. Serum biomarkers identify patients who will develop inflammatory bowel diseases up to 5 years before diagnosis. *Gastroenterology* 2020; 159: 96–104.
20. Raygoza Garay JA, Turpin W, Lee SH, et al. Gut microbiome composition is associated with future onset of Crohn's disease in healthy first-degree relatives. *Gastroenterology* 2023; 165: 670–681.
21. Leibovitzh H, Lee SH, Xue M, et al. Altered gut microbiome composition and function are associated with gut barrier dysfunction in healthy relatives of patients with Crohn's disease. *Gastroenterology* 2022; 163: 1364–1376 e1310.
22. Leibovitzh H, Lee SH, Raygoza Garay JA, et al. Immune response and barrier dysfunction-related proteomic signatures in preclinical phase of Crohn's disease highlight earliest events of pathogenesis. *Gut* 2023; 72: 1462–1471.
23. Galipeau HJ, Caminero A, Turpin W, et al. Novel fecal biomarkers that precede clinical diagnosis of ulcerative colitis. *Gastroenterology* 2021; 160: 1532–1545.
24. Mortha A, Remark R, Del Valle DM, et al. Neutralizing anti-granulocyte macrophage-colony stimulating factor autoantibodies recognize post-translational glycosylations on granulocyte macrophage-colony stimulating factor years before diagnosis and predict complicated Crohn's disease. *Gastroenterology* 2022; 163: 659–670.
25. Choung RS, Petralia F, Torres J, et al. Preclinical serological signatures are associated with complicated Crohn's disease phenotype at diagnosis. *Clin Gastroenterol Hepatol* 2023; 21: 2928–2937 e2912.
26. Verstockt B, Noor NM, Marigorta UM, et al. Results of the seventh scientific workshop of ECCO: precision medicine in IBD-disease

outcome and response to therapy. *J Crohns Colitis* 2021; 15: 1431–1442.

27. Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006; 55: 749–753.
28. Magro F, Gionchetti P, Eliakim R, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis* 2017; 11: 649–670.
29. Gomollon F, Dignass A, Annese V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: diagnosis and medical management. *J Crohns Colitis* 2017; 11: 3–25.
30. Barreiro-de Acosta M, Gutierrez A, Zabana Y, et al. Inflammatory bowel disease integral care units: evaluation of a nationwide quality certification programme. The GETECCU experience. *United European Gastroenterol J* 2021; 9: 766–772.
31. Sicilia B, Garcia-Lopez S, Gonzalez-Lama Y, et al. GETECCU 2020 guidelines for the treatment of ulcerative colitis. Developed using the GRADE approach. *Gastroenterol Hepatol* 2020; 43(Suppl 1): 1–57.
32. Raine T, Bonovas S, Burisch J, et al. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. *J Crohns Colitis* 2022; 16: 2–17.
33. Gordon H, Minozzi S, Kopylov U, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis* 2024; 18: 1531–1555.
34. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42: 377–381.
35. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; 95: 103208.
36. Tarazona S, Balzano-Nogueira L, Gomez-Cabrero D, et al. Harmonization of quality metrics and power calculation in multi-omic studies. *Nat Commun* 2020; 11: 3092.
37. Zabana Y, Panes J, Nos P, et al. The ENEIDA registry (Nationwide study on genetic and environmental determinants of inflammatory bowel disease) by GETECCU: Design, monitoring and functions. *Gastroenterol Hepatol* 2020; 43: 551–558.