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BMJ Open

Cohort profile: The Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD)

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1 Cohort profile: The Swedish Inception Cohort in inflammatory

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3

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Abstract

Purpose: There is a need for diagnostic and prognostic biosignatures to improve long-term outcomes in inflammatory bowel disease (IBD). Here, we describe the establishment of the Swedish inception cohort in IBD (SIC-IBD) and demonstrate its potential for the identification of such signatures.

Participants: Patients aged ≥ 18 years with gastrointestinal symptoms who were referred to the gastroenterology unit due to suspected IBD at eight Swedish hospitals between November 2011 and March 2021 were eligible for inclusion.

Findings to date: In total, 368 patients with IBD (Crohn’s disease, $n=143$; ulcerative colitis, $n=201$; IBD-unclassified, $n=24$) and 168 symptomatic controls were included. In addition, 59 healthy controls without gastrointestinal symptoms were recruited as a second control group. Biospecimens and clinical data were collected at inclusion and in patients with IBD also during follow-up to 10 years. Levels of faecal calprotectin and high-sensitivity C-reactive protein were higher in patients with IBD compared to symptomatic controls and healthy controls. Preliminary results highlight the potential of serum protein signatures and autoantibodies, as well as results from faecal markers, to differentiate between IBD and symptomatic controls in the cohort. During the first year of follow-up, 36% (52/143) of the patients with Crohn's disease, 24% (49/201) with ulcerative colitis and 4% (1/24) with IBD-U experienced an aggressive disease course.

Future plans: We have established an inception cohort enabling ongoing initiatives to collect and generate clinical data and multi-omics datasets. The cohort will allow analyses for translation into candidate biosignatures to support clinical decision-making in IBD. Additionally, the data will provide insights into mechanisms of disease pathogenesis.

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Strengths and limitations

- This large, multicentre inception cohort of newly diagnosed adult IBD patients, with integrated biobanking and prospective material collection, enables exploration of IBD pathophysiology and biomarker discovery.
- The inclusion of symptomatic controls with gastrointestinal symptoms mimicking IBD but without evidence of the diagnosis provides a realistic diagnostic setting and addresses limitations of many previous cohorts.
- The use of healthy controls as a second control group offers opportunities to gain insight into IBD pathogenesis.
- The non-population-based study design and the predominance of university hospitals in recruitment may limit the generalisability of findings.
- Suboptimal sample processing at some centres, including delays in serum centrifugation and transportation of faecal samples at ambient temperatures, may have affected the quality of some specific analyses, such as microbiota analyses.

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease, ulcerative colitis and IBD-unclassified (IBD-U), is a chronic disease that predominantly presents during the second and third decades of life. The disease results in an impaired quality of life for patients and substantial societal costs due to sick leave and a high use of healthcare resources [1–3]. Progressive inflammation causes damage to the gastrointestinal tract, and a substantial proportion of patients develop serious disease complications, including bowel obstruction, fistula, abscesses, and colorectal cancer [4–6].

IBD often presents with non-specific symptoms such as diarrhoea, fatigue and abdominal pain and, therefore, presents a diagnostic challenge. Commonly used biomarkers in diagnostic algorithms include C-reactive protein (CRP) and, in some regions, faecal calprotectin (FCP) which help identify patients needing referral for further investigations, including ileocolonoscopy [7]. However, the diagnostic accuracy of CRP is too low for reliably identifying IBD patients, and the utility of FCP is hampered by poor patient adherence to faecal sampling [8,9]. Furthermore, many healthcare systems do not reimburse the use of FCP for diagnostic purposes. The absence of reliable, non-invasive diagnostic biomarkers, occurrence of non-specific symptoms and limited access to ileocolonoscopy, frequently results in a significant diagnostic delay [10,11]. As a consequence, many patients have acquired considerable bowel damage (e.g., fistulas, strictures) already at diagnosis [4,11].

At diagnosis, the heterogeneity in clinical presentation and subsequent disease course make clinicians' attempts to stratify the treatment according to the individual patient's needs very difficult. While some patients experience an indolent disease course with minimal symptoms and low endoscopic activity, a substantial proportion exhibit an aggressive disease phenotype

characterised by treatment refractoriness, corticosteroid dependency, frequent hospital admissions and surgical interventions, including resection surgery and acute colectomy [12–18]. For this latter group, an early effective treatment seems advantageous, as the initial disease phase may provide a "window of opportunity" where prompt suppression of intestinal inflammation could improve long-term outcomes [19–21]. Identifying prognostic biomarkers for this group of patients is therefore critical to facilitate the timely initiation of potent treatment.

To address the need for both diagnostic and prognostic biomarkers, we established the "Swedish Inception Cohort in IBD" (SIC-IBD), a large prospective multicentre cohort involving patients with suspected IBD referred to eight hospitals in Sweden. After a comprehensive diagnostic work-up, patients were classified as incident IBD patients or symptomatic non-IBD controls, i.e., patients presenting with symptoms mimicking IBD but where IBD was ruled out. Alternative diagnoses in this patient group included infectious colitis, irritable bowel syndrome and diverticulitis. As a second control group, healthy controls without gastrointestinal symptoms were recruited. This cohort provides a rich collection of biospecimens together with detailed phenotypic characterisation collected both at diagnosis and during follow-up. Herein, we present the study design and baseline characteristics of the participants in the SIC-IBD.

COHORT DESCRIPTION

Inclusion

This longitudinal multicentre cohort study was conducted across eight Swedish hospitals: Ersta Hospital, Karolinska University Hospital, Linköping University Hospital, Sahlgrenska University Hospital, Skåne University Hospital, Södra Älvsborg Hospital, Uppsala University Hospital, and Örebro University Hospital. Patients aged ≥ 18 years with gastrointestinal

symptoms, such as diarrhoea, abdominal pain and blood or mucus in stools, who were referred to the gastroenterology unit with suspected IBD between November 2011 and March 2021 were eligible for inclusion (Figure 1). Exclusion criteria included a previous diagnosis of Crohn's disease, ulcerative colitis or IBD unclassified, or inability to provide informed consent or to comply with protocol requirements. After obtaining written informed consent, all patients underwent a routine diagnostic work-up for IBD, following clinical practice and international guidelines [22].

Based on the diagnostic work-up, which included magnetic resonance imaging in cases where small bowel involvement was suspected, patients were classified as having incident IBD or as symptomatic controls, i.e., patients with no discernible evidence of IBD at inclusion or during follow-up. The diagnosis of IBD was based on internationally accepted clinical, endoscopic, radiological, and histological criteria [22]. Nine patients were excluded due to suspected or confirmed IBD during follow-up. Patients were followed prospectively according to clinical practice, with data collected after 3 months, 1, 3, 5, 7 and 10 years for those with IBD. In addition, a group of healthy controls, without gastrointestinal disease, was included at baseline.

Demographics of patients and controls

During the inclusion period, 368 patients with IBD (Crohn's disease, n=143; ulcerative colitis, n=201; IBD-U, n=24) and 168 symptomatic controls were included (**Table 1**). The group of symptomatic controls comprised patients who ultimately were diagnosed with various diseases, including microscopic colitis, infectious enteritis, celiac disease, or irritable bowel syndrome. In addition, 59 healthy controls without any history of gastrointestinal disease were recruited as a second control group.

Table 1. Demographics of individuals included in the Swedish Inception Cohort in IBD (SIC-IBD)

	Crohn's disease n=143	Ulcerative colitis n=201	IBD-unclassified n=24	Symptomatic control n=168	Healthy control n=59
Female sex, n (%)	73 (51.1)	81 (40.3)	11 (45.8)	107 (63.7)	33 (55.9)
Median age (IQR)	28 (23-41)	34 (26-45)	33 (30-45)	34 (25-48)	26 (23-31)
Median CRP, mg/L (IQR)*	8.0 (3.3-31.8)	3.6 (1.4-8.6)	3.1 (2-5.6)	1.8 (0.9-5.9)	0.6 (0.3-1.1)
Median FCP, µg/g (IQR)*	448 (236-978)	325 (90-880)	471 (148-621)	68 (19-146)	10 (5-24)
Smoking, n (%)					
Never	70 (49)	95 (48)	12 (50)	71 (42)	41 (69)
Previous	26 (18)	59 (30)	8 (33)	29 (17)	10 (17)
Current	22 (15)	15 (7)	1 (4)	16 (10)	4 (7)
Missing	25 (17)	31 (16)	3 (12)	52 (31)	4 (7)
Median BMI, kg/m² (IQR)	23 (22-26)	24 (22-27)	27 (22-28)	26 (22-30)	23 (21-26)

*Information was missing for CRP in 62 (10%) individuals, faecal calprotectin in 217 (37%) individuals and for Body Mass Index in 198 (33%) individuals
CRP: C-reactive protein; IQR; interquartile range; FCP, faecal calprotectin

181 **Healthcare setting**

182 Sweden has a tax-funded universal healthcare system, and private outpatient healthcare
183 providers are few within the field of gastroenterology. In general, gastroenterologists at
184 secondary or tertiary care centres (rather than primary care) are responsible for diagnosing and
185 managing patients with IBD.

186

187 **Data collection**

188 *Characterisation of disease phenotype and disease activity*

189 Following informed consent, data on patient demographics, disease phenotype according to the
190 Montreal classification[23], extraintestinal manifestations, endoscopic activity (defined as the
191 presence of ulcers in Crohn's disease [yes/no] and the Mayo endoscopic subscore in ulcerative
192 colitis), IBD treatment, IBD-related surgery, and hospital admission were recorded at baseline
193 and prospectively during follow-up. Treatment-naivety was defined as no prior treatment with
194 IBD-related medications, including topical therapies. Previous treatments in patients who were
195 not treatment-naïve included mostly topical therapies but also a few days of corticosteroid
196 treatment. For healthy controls, information about basic demographics was collected. Data on
197 disease characteristics were recorded using case report forms (CRFs), and details on the
198 Montreal classification and clinical disease activity at baseline are provided in **Table 2**.

199

Table 2. Clinical characteristics of patients with Crohn’s disease, ulcerative colitis and IBD-
unclassified in the Swedish Inception Cohort in IBD (SIC-IBD)

	Crohn's Disease n=143	Ulcerative colitis n=201	IBD- unclassified n=24
Disease location, n (%)			
ileal (L1)	48 (33)		
colonic (L2)	50 (35)		
ileocolonic (L3)	34 (24)		
upper GI (L4)	1 (1)		
unknown	10 (7)		
Disease behaviour, n (%)			
non-stricturing, non-penetrating (B1)	115 (80)		
stricturing (B2)	14 (10)		
penetrating (B3)	5 (3)		
unknown	9 (6)		
Perianal disease, n (%)			
	12 (8)		
Disease extent, n (%)			
ulcerative proctitis (E1)		64 (32)	
left-sided colitis (E2)		57 (28)	
extensive colitis (E3)		76 (38)	
unknown		4 (2)	
Treatment-naive, n (%)			
	128 (90)	185 (92)	21 (88)

Upper GI (L4) refers to patients with only upper gastrointestinal Crohn’s disease

IBD-unclassified, Inflammatory bowel disease unclassified; SIC-IBD; GI, gastrointestinal

206 *Patient-reported outcomes*

207 Patient questionnaires were employed to obtain information about clinical disease activity,
208 smoking status, recent antibiotic or non-steroid anti-inflammatory drug use, and any specific
209 dietary restrictions.

210
211 Patients were also asked to complete the Short-Health-Scale and Short Form-36 (SF-36)
212 questionnaire to obtain information about Health-Related Quality of Life (HRQoL) [24–26].
213 SF-36 is a general measure of HRQoL, whereas the Short-Health Scale is a validated measure
214 to address HRQoL in patients with IBD. It includes four dimensions: bowel symptoms, daily
215 life activities, worry and general well-being. Additional quality of life data were collected using
216 the EuroQol-5D (EQ-5D) questionnaire[27,28]. Mental health was evaluated using the Patient-
217 health Questionnaire 9 (PHQ9) [29], the Cognitive Reserve Index (CRI) [30], and the Short-
218 Form Health Survey (SF-36) [26]. Additional data on gastrointestinal symptoms was obtained
219 by using the Gastrointestinal Symptom Rating Scale (GSRS) [31] and the Rome III criteria
220 functional gastrointestinal disorders [32].

221

222 **Sample collection and biobanking**

223 Biospecimens were obtained at baseline and during follow-up, processed and biobanked
224 according to predefined standard operating procedures (SOPs). Blood samples were collected
225 in EDTA and PAX®-tubes. In addition, serum samples were obtained by centrifugation of
226 whole blood at $2400 \times g$ for 5 min at ambient temperature, followed by aliquoting of serum and
227 storing at -80°C . For six centres, blood samples were shipped unprocessed at ambient room
228 temperature and centrifuged upon arrival at the central biobank, Örebro, Sweden. The
229 participants collected faecal samples in plastic tubes at home, brought them to the hospital or

mailed them by postal service. On arrival, the samples were immediately frozen and stored at -80°C . Spot urine samples were collected during study visits, aliquoted and stored at -80°C . In addition to collecting biopsies as part of clinical routine, physicians were instructed to take intestinal biopsies from both inflamed and non-inflamed mucosa according to a predefined protocol. These biopsies were preserved in Allprotect Tissue Reagent (Qiagen, Hilden, Germany) and in a bacterial freezing medium. Biopsies in the freezing medium were immediately stored at -80°C , whereas those in Allprotect Tissue Reagent were handled according to the manufacturer's instructions. Details on the collected biological material are provided in **Table 3**.

Table 3. An overview of biospecimens collected at baseline from individuals within the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD)

	Crohn's Disease n=143	Ulcerative colitis n=201	IBD- unclassified n=24	Symptomatic control n=168	Healthy control n=59
Serum, n (%)	138 (97)	199 (99)	23 (96)	164 (98)	59 (100)
Faecal, n (%)	62 (43)	91 (45)	9 (38)	90 (54)	58 (98)
Urine, n (%)	100 (70)	137 (68)	20 (83)	112 (67)	56 (95)
Intestinal biopsies, n (%)	93 (65)	161 (80)	18 (75)	155 (92)	58 (98)

IBD, inflammatory bowel disease

Measurements of high-sensitivity CRP and faecal calprotectin

After storage, samples for high-sensitivity (hs) CRP (serum) and calprotectin (faeces) were retrieved from the central biobank and sent to Uppsala Clinical Research Center, Uppsala, Sweden and Academic Laboratory, Department of Clinical Chemistry, University Hospital,

Enseignement Supérieur (ABES) .
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Uppsala, Sweden, respectively. hsCRP was assayed in a single batch for all participants at the end of the recruitment period, using a particle-enhanced immunoturbidimetric hsCRP assay (Cardiac C-Reactive Protein (Latex) High Sensitive, Roche Diagnostics) on a Roche Cobas c501. Correspondingly, FCP was extracted and analysed according to the manufacturer's instructions, with a chemiluminescent immunoassay, using the LIASON XL analyser (DiaSorin, Saluggia, Italy). Data on median levels of hsCRP and FCP across the various diagnoses are provided in **Table 1**.

Disease course outcome during follow-up

A composite outcome measure was used to categorise the disease course as aggressive or indolent during follow-up. An aggressive disease course was defined as the presence of any IBD-related surgery, hospital admission for active disease, treatment refractoriness towards targeted therapies, i.e., biologics, Janus kinase (JAK) inhibitors or sphingosine-1-phosphate receptor modulators, and >two courses or high cumulative dosis of systemic corticosteroids within the first year of follow-up (**Table 4**). In addition, Crohn's disease patients with evidence of progression to a complicated disease behaviour, i.e., a new stricture, fistula, or abscess, were also categorised as having an aggressive disease course.

Table 4. Criteria for defining the disease course as aggressive or indolent within the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD). Patients with any of the following events during the first year from the date of diagnosis were defined as having an aggressive disease course.

Difficulty in controlling inflammation in patients with IBD

- Hospital admission for active disease
- Surgical resection (including colectomy) or a stoma
- Use of > 2 courses of corticosteroids* or a cumulative dose of > 2.5 g equivalents of prednisolone
- Use of ≥2 targeted therapies due to poor clinical effectiveness**

Progression to complicated disease behaviour in patients with Crohn’s disease

- New fistula (recto-vaginal, enterocutaneous, internal or proctitis-related perianal fistula), or need for fistula-related surgery
- New abscess (including perianal abscess) or abscess-related surgery
- New stricture or stricture-related surgery

**A corticosteroid course was defined as an episode of treatment with specified start and stop dates. Typically, oral prednisolone was initiated at a starting dose of 40 mg once daily, with a tapering schedule of 5mg per day at weekly intervals, resulting in an 8-week treatment course. For oral budesonide courses, a fixed dose of 9 mg once daily for 8 weeks was most commonly applied.*

***Targeted therapies were defined as biologics, Janus kinase (JAK) inhibitors and sphingosine-1-phosphate receptor modulators*

282 Data management

283 Patients, physicians, or research nurses used CRFs and predefined questionnaires to collect
284 information. All data were imported after pseudonymisation into a central database with reading
285 access for all co-investigators. The database is updated every 6-12 months to allow the import
286 of new data, including follow-up visits, address possible missing information, and correct
287 potential erroneous data entries. To enable backward traceability, a data freeze is created at
288 each update. Each data freeze provides a snapshot of information contained in the database at
289 a given date.

291 Project organisation

292 The SIC-IBD represents a crucial element of the multi-modal national study to identify
293 biomarkers for diagnosis, therapy response and disease progression in IBD (BIO IBD), which
294 aims to bring leading clinicians, clinical researchers and basic scientists within the field of IBD
295 together with corporate partners. The managerial structure and the operational organisation of
296 BIO IBD are shown in **Figure 2**. An executive office has been set up at the Faculty of Health
297 and Medical Sciences, Örebro University, forming the BIO IBD Executive Committee together
298 with representatives of participating universities and university hospitals. The Executive
299 Committee coordinated the efforts of the work packages, clinical departments, biomedical
300 companies, and the Swedish patients' organisation, *Mag- och tarmförbundet* [33].

301
302 The Steering Committee, responsible for the strategic leadership, is formed by representatives
303 from involved universities, biomedical companies and the patient organisation, with equal
304 numbers of basic scientists and clinicians, equal gender, and representation of young scientists.
305 The Advisory Board, composed of internationally renowned representatives of academia and
306 the biomedical industry, provides external review and input.

Patient and Public Involvement statement

During the planning phase of the cohort study, patient representatives from the Swedish patient’s organisation, *Mag- och tarmförbundet* provided input on the study design, including the definition of the disease course during follow-up. Also, they assessed the burden of the collection of biological material and the time required for responding to the questionnaires in the study. Representatives of the patient organisation and the Swedish biomarker manufacturers in the executive committee also provided feedback during the recruitment process and follow-up of study participants. In addition to scientific reporting, key findings of the studies will be communicated to patient organisations, public health policymakers, and the public through various media and news activities. When disseminating the results, the recommendations of the International Committee of Medical Journal Editors (ICMJE) will be applied [34].

FINDINGS TO DATE

At baseline, differences in smoking habits were observed between patients with Crohn’s disease, ulcerative colitis, and IBD-U. Active smoking was more prevalent in patients with Crohn’s disease, while a higher rate of former smokers was found in patients with ulcerative colitis. While hsCRP measurements were available for 90% of all patients and controls, only 63% of patients and controls had available FCP measures in the study. An additional 44 measurements of FCP at diagnosis were available from clinical routine, but these results were excluded from this analysis due to the use of different assays. Both FCP and hsCRP levels were higher in patients with Crohn’s disease and ulcerative colitis compared to symptomatic controls and healthy controls. However, while FCP levels were significantly elevated in IBD unclassified compared to symptomatic controls, the difference in hsCRP levels between these two groups was not statistically significant. No significant differences in FCP levels were

observed between patients with Crohn's disease and ulcerative colitis, but hsCRP levels were higher in Crohn's disease patients. Significant differences in hsCRP and FCP levels were also found between symptomatic controls and healthy controls.

Preliminary results from analyses of serum proteins as well as findings from the analyses of faecal markers have highlighted the potential of these markers to differentiate between patients with IBD and symptomatic controls in this cohort, suggesting their diagnostic value [35,36]. Recent results from the analysis of anti- $\alpha\text{v}\beta 6$ autoantibodies further suggested a high diagnostic value for ulcerative colitis of this marker [37]. Additionally, preliminary data indicate differences in mucosal proteins between patients developing an aggressive course of ulcerative colitis and those with an indolent course [38].

In line with previous studies [19,39], we employed a composite outcome to characterise the disease course within the first year after diagnosis, either as aggressive or indolent (Table 4). An aggressive course was defined by treatment refractoriness, the need for surgical resection, or in the case of Crohn's disease, the development of severe complications such as strictures and fistulas. Based on this definition, 36% (52/143) of the patients with Crohn's disease, 24% (49/201) of those with ulcerative colitis, and 4.2% (1/24) with IBD-U experienced an aggressive disease course within the first year after diagnosis (**Supplementary Table 1**). These results underscore that treatment failure rates and disease complications remain unacceptably high in IBD. Aggressive disease course was associated with more extensive ulcerative colitis, while no association was found between Crohn's disease location and disease course.

STRENGTHS AND LIMITATIONS

In this large nationwide multicentre inception cohort of newly diagnosed patients with IBD, a set of highly relevant biospecimens were collected at inclusion, and patients were prospectively followed. This cohort can be used to gain insights into key pathogenic mechanisms of IBD. Moreover, it provides a valuable resource for biomarker discoveries, particularly the identification of diagnostic biomarkers for IBD and prognostic markers for future disease courses.

This cohort is one of few large-scale IBD inception cohorts of adult patients with integrated biobanking [40–42], as most of the earlier initiatives have included paediatric patients only. Most previous attempts to identify diagnostic biomarkers in inception cohorts have used healthy controls or patients with non-inflammatory conditions (e.g., irritable bowel syndrome) as a control group. These settings do not reflect a diagnostic scenario where patients with gastrointestinal symptoms that are indicative of IBD are examined. Accordingly, evaluations based on these cohorts are likely to overestimate the diagnostic capacity of potential biomarkers [43]. However, this limitation is rarely acknowledged and may partly explain why promising biomarkers fail in replication attempts and do not make their way to the clinic. To allow the identification of diagnostic biomarkers, we have included patients with symptoms indicative of IBD but without any signs of the disease at diagnostic work-up or during follow-up (symptomatic controls) as a reference group. Thus, both cases with IBD and symptomatic controls represented an unselected sample of patients who were referred to secondary care for the suspicion of IBD. In addition, we included healthy controls as a second control group to gain insight into the aetiology of IBD and to characterise pathways related to disease pathogenesis.

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3 380 In this cohort, we did not record the number of eligible patients who were not included, e.g.
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5 381 those who declined to or were not able to give informed consent or were not identified by study
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7 382 personnel. The absence of a population-based cohort design could be a limiting factor when
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10 383 interpreting associations between exposures and clinical outcomes within SIC-IBD. However,
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12 384 the proportion of IBD patients with Crohn's disease in this study (39%), the European Crohn's
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14 385 and Colitis Organization's Epidemiological Committee (EpiCom) inception cohort (37%) and
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16 386 the recent population-based Inflammatory bowel disease in South-Eastern Norway cohort III
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18 387 (35%) were similar. Likewise, the proportions of ulcerative colitis (54%, 52% and 61%) and
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20 388 IBD-U (7%, 11% and 4%) were similar in the three cohorts. Suboptimal procedures in sample
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23 389 collection further limited the study. To enable inclusion at all centres, serum samples collected
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26 390 at centres with limited sample processing capacity were shipped overnight to a central biobank
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28 391 for centrifugation and biobanking. While measured faecal markers such as calprotectin are
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30 392 stable at room temperature for several days, microbiome analyses are sensitive to pre-analytic
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33 393 sample handling [44–46].
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COLLABORATION

We have established an inception cohort of newly diagnosed adult patients with IBD, symptomatic controls and healthy controls with integrated biobanking. Initiatives are underway to generate various multi-omics data from samples collected at baseline and follow-up visits. Analyses of single and multiple datasets, including integration of clinical variables, may discover novel diagnostic and prognostic biosignatures for IBD and its subtypes. Comparisons with healthy controls may also provide insights into IBD pathogenesis and progression mechanisms. We encourage collaborations with researchers from other cohorts and case-control studies to validate findings from the SIC-IBD cohort. Also, researchers can propose new collaborative initiatives and apply for access to data and biospecimens by submitting a proposal to the BIO IBD Executive Office (BIO.IBD@oru.se). All proposals will be reviewed on scientific quality and methodology by the BIOIBD executive committee.

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Authors' contributions

Conception and design: Jonas Halfvarson

Drafting the manuscript: Benita Salomon, Olle Grännö and Jonas Halfvarson

Critical revision for intellectual content: All authors

Final approval: All authors

Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors

Competing interests statement

DB served as a speaker and/or advisory board member for BMS, Janssen, Pfizer, Pharmacosmos, Sandoz, Takeda and Tillotts Pharma. **HS** has served as speaker and/or advisory board member for AbbVie Ferring, Janssen, Pfizer, Takeda, Gilead and Tillotts Pharma. **AC** served as a speaker for Takeda and Ferring. **HH** has served as a speaker, consultant or advisory board member for AbbVie, Ferring, Fresenius Kabi, Janssen, Norgine, Pfizer, Pharmacosmos, Takeda and Tillotts and has received grant support from AbbVie, Ferring, Takeda, and Tillotts. **SA** served as a member for Scientific committee/Advisory board of, Janssen, Pharmacosmos, Takeda, as a consultant for Janssen, OrionPharm, Takeda, and as a speaker: Galapagos, Janssen, Tillotts, received research grants from Janssen and OrionPharma. **FB** has acted as national and/or local principal investigator for clinical trials for Janssen, Ferring and Abbvie. **CE** received grant support/lecture fee/advisory board from Takeda, Janssen Cilag, Pfizer, Abbvie. **OG** served as speaker and/or advisory board member for Abbvie, Bristol Mayer Squibb, Eli Lilly, Ferring, Janssen, Pfizer Takeda, Tillotts Pharma and Vifor Pharma. **JM** has served as a

speaker, consultant or advisory board member for AbbVie, Alfasigma, Amgen, Bayer, Biogen, BMS, Eli Lilly, Ferring, Galapagos, Hospira, ITH, Janssen, Lument, MSD, Otsuka, Pfizer, Sandoz, Takeda, Tillotts and UCB; and has received grant support (not for this study) from AbbVie, BMS, Calpro AS, Carbiotix, Ferring, Fresenius Kabi, Pfizer, Svar Life Science and Takeda. **MKM** has received speaker's fees from Takeda and Janssen. **LÖ** has received a financial support for research by Genetic Analysis AS, Biocodex, Danone Research and AstraZeneca and served as Consultant/Advisory Board member for Genetic Analysis AS, and as a speaker for Biocodex, Ferring Pharmaceuticals, Takeda, AbbVie, Novartis, Janssen-Cilag and Meda. **MC** has received speaker's fees from ViforPharma. She is the national PI for clinical trials for AstraZeneca. **CRHH** has served as a speaker and/or advisory board member for AstraZeneca, Dr Falk Pharma and the Falk Foundation, Galapagos, Janssen, Pfizer, Takeda, Tillotts Pharma, and received grant support from Tillotts and Takeda. **JH** served as speaker and/or advisory board member from AbbVie, Alfasigma, Aqilion, Bristol Myers Squibb, Celgene, Celltrion, Dr Falk Pharma and the Falk Foundation, Eli Lilly, Ferring, Galapagos, Gilead, Hospira, Index Pharma, Janssen, MEDA, Medivir, Medtronic, Merck, MSD, Novartis, Pfizer, Prometheus Laboratories Inc., Sandoz, Shire, STADA, Takeda, Thermo Fisher Scientific, Tillotts Pharma, Vifor Pharma, UCB and received grant support from Janssen, MSD and Takeda. The remaining authors declare no conflicts of interest.

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Ethical approval

The SIC-IBD study was approved by the Regional Ethics Committees (Dnr 2010/313). Written informed consent was obtained from all participants before inclusion.

Provenance and peer review

Not commissioned; externally peer-reviewed.

Data sharing statement

Researchers can apply for access to data and biological specimens by submitting a proposal to the BIO IBD Executive Office (BIO.IBD@oru.se), including a copy of their ethics approval. All proposals will be reviewed by the BIOIBD executive committee based on scientific quality and methodology. This procedure is installed to ensure that the clinical data and biological material are being requested for scientific purposes, in accordance with the informed consent signed by the participants, as the collected data and material cannot be used by purely commercial parties. Additionally, any transfer of data or biological material must comply with Swedish law and the European Union (EU) General Data Protection Regulation (GDPR).

References

1 Lönnfors S, Vermeire S, Avedano L. IBD and health-related quality of life — Discovering the true impact. *J Crohns Colitis*. 2014;8:1281–6. doi: 10.1016/j.crohns.2014.03.005

2 Park KT, Ehrlich OG, Allen JI, et al. The Cost of Inflammatory Bowel Disease: An Initiative From the Crohn’s & Colitis Foundation. *Inflamm Bowel Dis*. 2020;26:1–10. doi: 10.1093/ibd/izz104

3 Khalili H, Everhov ÅH, Halfvarson J, et al. Healthcare use, work loss and total costs in incident and prevalent Crohn’s disease and ulcerative colitis: results from a nationwide study in Sweden. *Aliment Pharmacol Ther*. 2020;52:655–68. doi: 10.1111/apt.15889

4 Peyrin-Biroulet L, Loftus EVJ, Colombel J-F, et al. The Natural History of Adult Crohn’s Disease in Population-Based Cohorts. *Am J Gastroenterol*. 2010;105:289–97. doi: 10.1038/ajg.2009.579

5 Jess T, Rungoe C, Peyrin-Biroulet L. Risk of Colorectal Cancer in Patients With Ulcerative Colitis: A Meta-analysis of Population-Based Cohort Studies. *Clin Gastroenterol and Hepatol*. 2012;10:639–45. doi: 10.1016/j.cgh.2012.01.010

6 Torres J, Billioud V, Sachar DB, et al. Ulcerative Colitis as A Progressive Disease: The Forgotten Evidence. *Inflamm Bowel Dis*. 2012;18:1356–63. doi: 10.1002/ibd.22839

7 Brookes MJ, Whitehead S, Gaya DR, et al. Practical guidance on the use of faecal calprotectin. *Frontline Gastroenterol*. 2018;9:87–91. doi: 10.1136/flgastro-2016-100762

8 Maréchal C, Aimone-Gastin I, Baumann C, et al. Compliance with the faecal calprotectin test in patients with inflammatory bowel disease. *United European Gastroenterol J*. 2017;5:702–7. doi: 10.1177/2050640616686517

9 Khakoo NS, Lewis A, Roldan GA, et al. Patient Adherence to Fecal Calprotectin Testing Is Low Compared to Other Commonly Ordered Tests in Patients With Inflammatory Bowel Disease. *Crohns Colitis* 360. 2021;3:otab028. doi: 10.1093/crocol/otab028

10 Burisch J, Ungaro R, Vind I, et al. Proximal Disease Extension in Patients With Limited Ulcerative Colitis: A Danish Population-based Inception Cohort. *J Crohns Colitis*. 2017;11:1200–4. doi: 10.1093/ecco-jcc/jjx066

11 Schoepfer AM, Dehlavi M-A, Fournier N, et al. Diagnostic Delay in Crohn’s Disease Is Associated With a Complicated Disease Course and Increased Operation Rate. *Am J Gastroenterol*. 2013;108:1744–53. doi: 10.1038/ajg.2013.248

- 12 Solberg IC, Lygren I, Jahnsen J, et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). *Scand J Gastroenterol.* 2009;44:431–40. doi: 10.1080/00365520802600961
- 13 Solberg IC, Vatn MH, Høie O, et al. Clinical Course in Crohn's Disease: Results of a Norwegian Population-Based Ten-Year Follow-Up Study. *Clin Gastroenterol Hepatol.* 2007;5:1430–8. doi: 10.1016/j.cgh.2007.09.002
- 14 Burisch J, Pedersen N, Cukovic-Cavka S, et al. Initial Disease Course and Treatment in an Inflammatory Bowel Disease Inception Cohort in Europe: The ECCO-EpiCom Cohort. *Inflamm Bowel Dis.* 2014;20:36–46. doi: 10.1097/01.MIB.0000436277.13917.c4
- 15 Burisch J, Katsanos KH, Christodoulou DK, et al. Natural Disease Course of Ulcerative Colitis During the First Five Years of Follow-up in a European Population-based Inception Cohort—An Epi-IBD Study. *J Crohns Colitis.* 2019;13:198–208. doi: 10.1093/ecco-jcc/jjy154
- 16 Burisch J, Kiudelis G, Kupcinskis L, et al. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. *Gut.* 2019;68:423–33. doi: 10.1136/gutjnl-2017-315568
- 17 Zhulina Y, Udumyan R, Tysk C, et al. The changing face of Crohn's disease: a population-based study of the natural history of Crohn's disease in Örebro, Sweden 1963–2005. *Scand J Gastroenterol.* 2016;51:304–13. doi: 10.3109/00365521.2015.1093167
- 18 Everhov ÅH, Halfvarson J, Myrelid P, et al. Incidence and Treatment of Patients Diagnosed With Inflammatory Bowel Diseases at 60 Years or Older in Sweden. *Gastroenterology.* 2018;154:518–528.e15. doi: 10.1053/j.gastro.2017.10.034
- 19 Khanna R, Bressler B, Levesque BG, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *Lancet.* 2015;386:1825–34. doi: 10.1016/S0140-6736(15)00068-9
- 20 Colombel J-F, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *The Lancet.* 2017;390:2779–89. doi: 10.1016/S0140-6736(17)32641-7
- 21 Satsangi J, Nowak J, Kalla R, et al. Treatment strategies and biomarkers in Crohn's disease: the PROFILE trial. *Lancet Gastroenterol Hepatol.* 2024;9:591–2. doi: 10.1016/S2468-1253(24)00082-7
- 22 Maaser C, Sturm A, Vavricka SR, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis.* 2019;13:144–164K. doi: 10.1093/ecco-jcc/jjy113

23 Silverberg MS, Satsangi J, Ahmad T, et al. Toward an Integrated Clinical, Molecular and Serological Classification of Inflammatory Bowel Disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol*. 2005;19:5A-36A. doi: 10.1155/2005/269076

24 Hjortswang H, Järnerot G, Curman B, et al. The Short Health Scale: A valid measure of subjective health in ulcerative colitis. *Scand J Gastroenterol*. 2006;41:1196–203. doi: 10.1080/00365520600610618

25 Stjernman H, Grännö C, Järnerot G, et al. Short health scale: A valid, reliable, and responsive instrument for subjective health assessment in Crohn’s disease: *Inflamm Bowel Dis*. 2008;14:47–52. doi: 10.1002/ibd.20255

26 Mchorney CA, John W, Anastasia R. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and Clinical Tests of Validity in Measuring Physical and Mental Health Constructs. *Medical Care*. 1993;31:247–63. doi: 10.1097/00005650-199303000-00006

27 EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199–208. doi: 10.1016/0168-8510(90)90421-9

28 Rabin R, Charro FD. EQ-SD: a measure of health status from the EuroQol Group. *Annals of Medicine*. 2001;33:337–43. doi: 10.3109/07853890109002087

29 Kroenke K, Spitzer RL. The PHQ-9: A New Depression Diagnostic and Severity Measure. *Psychiatric Annals*. 2002;32:509–15. doi: 10.3928/0048-5713-20020901-06

30 Nucci M, Mapelli D, Mondini S. Cognitive Reserve Index questionnaire (CRIq): a new instrument for measuring cognitive reserve. *Aging Clin Exp Res*. 2012;24:218–26. doi: 10.1007/BF03654795

31 Svedlund J, Sjödin I, Dotevall G. GSRS - A clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Digest Dis Sci*. 1988;33:129–34. doi: 10.1007/BF01535722

32 Drossman DA. The Functional Gastrointestinal Disorders and the Rome III Process. *Gastroenterology*. 2006;130:1377–90. doi: 10.1053/j.gastro.2006.03.008

33 Mag- och tarmförbundet. <https://magotarm.se/>. Last Accessed 10 Jan 2025.

34 International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals. Published Online First: 2024.

35 Bazov I, Kruse R, Bergemalm D, et al. P154 A novel serum protein signature as biomarker for Inflammatory Bowel Disease: A diagnostic performance and prediction modelling

- study using data from two independent inception cohorts. *J Crohns Colitis*. 2023;17:i314–5. doi: 10.1093/ecco-jcc/jjac190.0284
- 36 Ling Lundström M, Peterson C, Hedin CRH, et al. Faecal biomarkers for diagnosis and prediction of disease course in treatment-naïve patients with IBD. *Aliment Pharmacol Ther*. 2024;60:765–77. doi: 10.1111/apt.18154
- 37 Pertsinidou E, Salomon B, Bergemalm D, et al. Anti- $\alpha\text{v}\beta 6$ Integrin Autoantibodies associate with a distinct serum inflammatory profile at diagnosis of ulcerative colitis and define a severe phenotype of the disease. *UEG Week 2024 Abstract Issue*. Publisher: Elsevier 2024.
- 38 Salomon B, Carlson M, Bergemalm D, et al. P219 Prognostic potential of mucosal proteins in Ulcerative Colitis. *J Crohns and Colitis*. 2024;18:i549–50. doi: 10.1093/ecco-jcc/jjad212.0349
- 39 Jairath, Vipul R, Khanna R, Guizzetti L, et al. A cluster-randomised controlled trial of an enhanced treatment algorithm for the management of Crohn's disease: REACT-2. *Lancet Gastroenterol Hepatol*. 2022;7:1080. doi: 10.1016/S2468-1253(22)00357-0
- 40 Gevers D, Kugathasan S, Denson LA, et al. The treatment-naïve microbiome in new-onset Crohn's disease. *Cell Host Microbe*. 2014;15:382–92. doi: 10.1016/j.chom.2014.02.005
- 41 Kristensen VA, Opheim R, Perminow G, et al. Inflammatory bowel disease in South-Eastern Norway III (IBSEN III): a new population-based inception cohort study from South-Eastern Norway. *Scand J Gastroenterol*. 2021;56:899–905. doi: 10.1080/00365521.2021.1922746
- 42 Attauabi M, Madsen GR, Bendtsen F, et al. Influence of Genetics, Immunity and the Microbiome on the Prognosis of Inflammatory Bowel Disease (IBD Prognosis Study): the protocol for a Copenhagen IBD Inception Cohort Study. *BMJ Open*. 2022;12:e055779. doi: 10.1136/bmjopen-2021-055779
- 43 Lijmer JG. Empirical Evidence of Design-Related Bias in Studies of Diagnostic Tests. *JAMA*. 1999;282:1061. doi: 10.1001/jama.282.11.1061
- 44 Carstens A, Roos A, Andreasson A, et al. Differential clustering of fecal and mucosa-associated microbiota in 'healthy' individuals. *J Dig Dis*. 2018;19:745–52. doi: 10.1111/1751-2980.12688
- 45 RØseth AG, Fagerhol MK, Aadland E, et al. Assessment of the Neutrophil Dominating Protein Calprotectin in Feces: A Methodologic Study. *Scand J Gastroenterol*. 1992;27:793–8. doi: 10.3109/00365529209011186

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613 46 Lasso A, Stotzer P-O, Öhman L, et al. The intra-individual variability of faecal
614 calprotectin: A prospective study in patients with active ulcerative colitis. J Crohns Colitis.
615 2014;S1873994614001858. doi: 10.1016/j.crohns.2014.06.002

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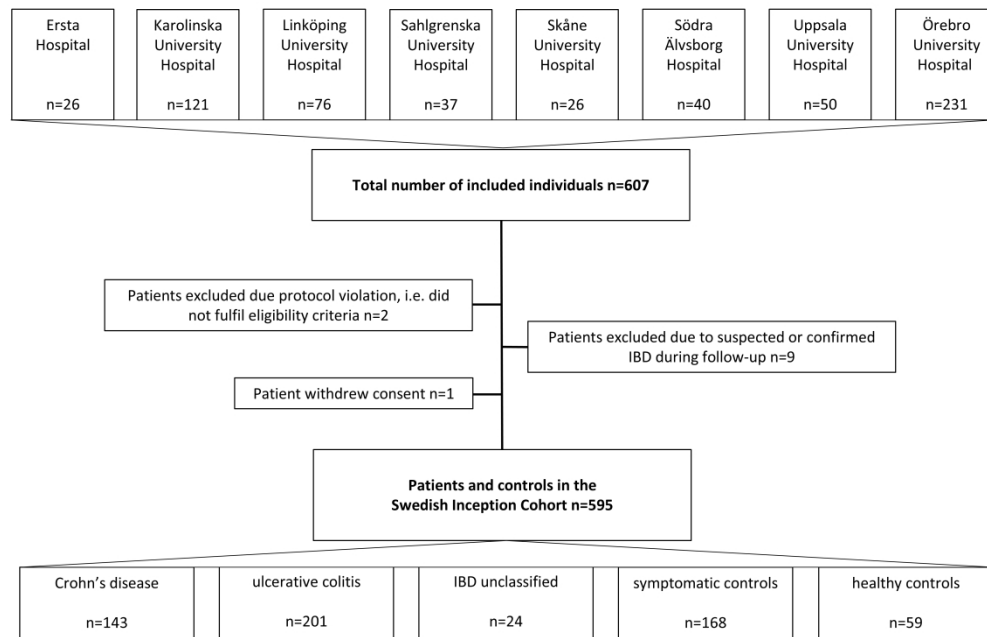


Figure 1. The flow diagram shows the number of included individuals at each hospital, the number of patients excluded and the final number of patients and controls in the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD).

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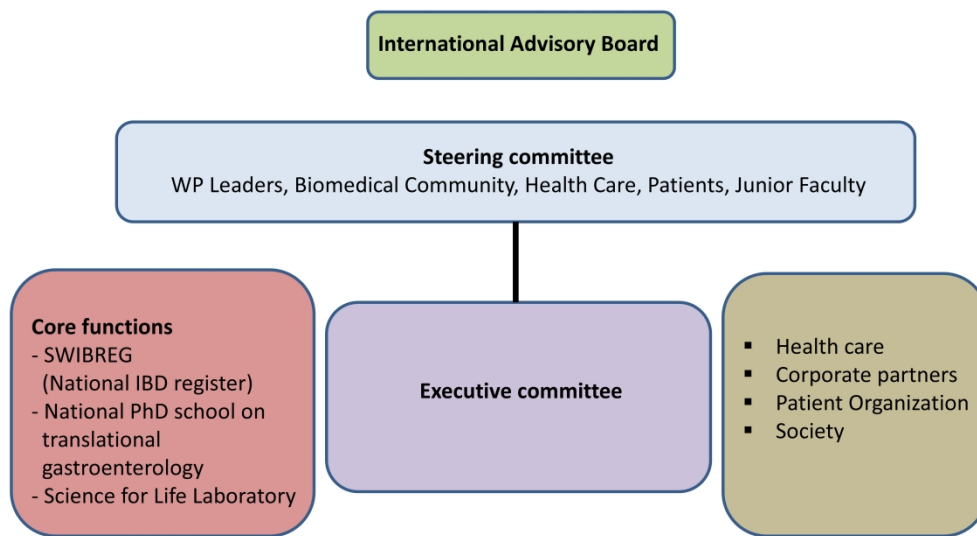


Figure 2. Managerial structure and the operational organisation of the multi-modal national study to identify biomarkers for diagnosis, therapy response and disease progression in inflammatory bowel disease (BIO IBD), where the Swedish inception cohort in IBD (SIC-IBD) represents an important resource.

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Supplementary Table 1

	Crohn's disease n=143	ulcerative colitis n=201	IBD-unclassified n=24
Aggressive disease, n (%)	52 (36.4)	45 (24.4)	1 (4.2)
Indolent disease, n (%)	79 (55.2)	140 (69.7)	22 (91.7)
Unknown*, n (%)	12 (8.4)	12 (6)	1 (4.2)

*Missing information about clinical outcomes due to incomplete follow-up during the first year after diagnosis.

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Cohort profile: The Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD)

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Date Submitted by the Author:	09-Apr-2025
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1 Cohort profile: The Swedish Inception Cohort in inflammatory

2 bowel disease (SIC-IBD)

3

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Abstract

Purpose: There is a need for diagnostic and prognostic biosignatures to improve long-term outcomes in inflammatory bowel disease (IBD). Here, we describe the establishment of the Swedish inception cohort in IBD (SIC-IBD) and demonstrate its potential for the identification of such signatures.

Participants: Patients aged ≥ 18 years with gastrointestinal symptoms who were referred to the gastroenterology unit due to suspected IBD at eight Swedish hospitals between November 2011 and March 2021 were eligible for inclusion.

Findings to date: In total, 367 patients with IBD (Crohn’s disease, $n=142$; ulcerative colitis, $n=201$; IBD-unclassified, $n=24$) and 168 symptomatic controls were included. In addition, 59 healthy controls without gastrointestinal symptoms were recruited as a second control group. Biospecimens and clinical data were collected at inclusion and in patients with IBD also during follow-up to 10 years. Levels of faecal calprotectin and high-sensitivity C-reactive protein were higher in patients with IBD compared to symptomatic controls and healthy controls. Preliminary results highlight the potential of serum protein signatures and autoantibodies, as well as results from faecal markers, to differentiate between IBD and symptomatic controls in the cohort. During the first year of follow-up, 37% (53/142) of the patients with Crohn's disease, 24% (48/201) with ulcerative colitis and 4% (1/24) with IBD-U experienced an aggressive disease course.

Future plans: We have established an inception cohort enabling ongoing initiatives to collect and generate clinical data and multi-omics datasets. The cohort will allow analyses for translation into candidate biosignatures to support clinical decision-making in IBD. Additionally, the data will provide insights into mechanisms of disease pathogenesis.

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Strengths and limitations

- This large, multicentre inception cohort of newly diagnosed adult IBD patients, with integrated biobanking and prospective material collection, enables exploration of IBD pathophysiology and biomarker discovery.
- The inclusion of symptomatic controls with gastrointestinal symptoms mimicking IBD but without evidence of the diagnosis provides a realistic diagnostic setting and addresses limitations of many previous cohorts.
- The use of healthy controls as a second control group offers opportunities to gain insight into IBD pathogenesis.
- The non-population-based study design and the predominance of university hospitals in recruitment may limit the generalisability of findings.
- Suboptimal sample processing at some centres, including delays in serum centrifugation and transportation of faecal samples at ambient temperatures, may have affected the quality of some specific analyses, such as microbiota analyses.

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease, ulcerative colitis and IBD-unclassified (IBD-U), is a chronic disease that predominantly presents during the second and third decades of life. The disease results in an impaired quality of life for patients and substantial societal costs due to sick leave and a high use of healthcare resources [1–3]. Progressive inflammation causes damage to the gastrointestinal tract, and a substantial proportion of patients develop serious disease complications, including bowel obstruction, fistula, abscesses, and colorectal cancer [4–6].

IBD often presents with non-specific symptoms such as diarrhoea, fatigue and abdominal pain and, therefore, presents a diagnostic challenge. Commonly used biomarkers in diagnostic algorithms include C-reactive protein (CRP) and, in some regions, faecal calprotectin (FCP) which help identify patients needing referral for further investigations, including ileocolonoscopy [7]. However, the diagnostic accuracy of CRP is too low for reliably identifying IBD patients, and the utility of FCP is hampered by poor patient adherence to faecal sampling [8,9]. Furthermore, many healthcare systems do not reimburse the use of FCP for diagnostic purposes. The absence of reliable, non-invasive diagnostic biomarkers, occurrence of non-specific symptoms and limited access to ileocolonoscopy, frequently results in a significant diagnostic delay [10,11]. As a consequence, many patients have acquired considerable bowel damage (e.g., fistulas, strictures) already at diagnosis [4,11].

At diagnosis, the heterogeneity in clinical presentation and subsequent disease course make clinicians' attempts to stratify the treatment according to the individual patient's needs very difficult. While some patients experience an indolent disease course with minimal symptoms and low endoscopic activity, a substantial proportion exhibit an aggressive disease phenotype

characterised by treatment refractoriness, corticosteroid dependency, frequent hospital admissions and surgical interventions, including resection surgery and acute colectomy [12–18]. For this latter group, an early effective treatment seems advantageous, as the initial disease phase may provide a "window of opportunity" where prompt suppression of intestinal inflammation could improve long-term outcomes [19–21]. Identifying prognostic biomarkers for this group of patients is therefore critical to facilitate the timely initiation of potent treatment.

To address the need for both diagnostic and prognostic biomarkers, we established the "Swedish Inception Cohort in IBD" (SIC-IBD), a large prospective multicentre cohort involving patients with suspected IBD referred to eight hospitals in Sweden. After a comprehensive diagnostic work-up, patients were classified as incident IBD patients or symptomatic non-IBD controls, i.e., patients presenting with symptoms mimicking IBD but where IBD was ruled out. Alternative diagnoses in this patient group included infectious colitis, irritable bowel syndrome and diverticulitis. As a second control group, healthy controls without gastrointestinal symptoms were recruited. This cohort provides a rich collection of biospecimens together with detailed phenotypic characterisation collected both at diagnosis and during follow-up. Herein, we present the study design and baseline characteristics of the participants in the SIC-IBD.

COHORT DESCRIPTION

Inclusion

This longitudinal multicentre cohort study was conducted across eight Swedish hospitals: Ersta Hospital, Karolinska University Hospital, Linköping University Hospital, Sahlgrenska University Hospital, Skåne University Hospital, Södra Älvsborg Hospital, Uppsala University Hospital, and Örebro University Hospital. Patients aged ≥ 18 years with gastrointestinal

symptoms, such as diarrhoea, abdominal pain and blood or mucus in stools, who were referred to the gastroenterology unit with suspected IBD between November 2011 and March 2021 were eligible for inclusion (Figure 1). Exclusion criteria included a previous diagnosis of Crohn’s disease, ulcerative colitis or IBD unclassified, or inability to provide informed consent or to comply with protocol requirements. After obtaining written informed consent, all patients underwent a routine diagnostic work-up for IBD, following clinical practice and international guidelines [22].

Based on the diagnostic work-up, which included magnetic resonance imaging in cases where small bowel involvement was suspected, patients were classified as having incident IBD or as symptomatic controls, i.e., patients with no discernible evidence of IBD at inclusion or during follow-up. The diagnosis of IBD was based on internationally accepted clinical, endoscopic, radiological, and histological criteria [22]. Nine patients were excluded due to suspected or confirmed IBD during follow-up. Patients were followed prospectively according to clinical practice, with data collected after 3 months, 1, 3, 5, 7 and 10 years for those with IBD. In addition, a group of healthy controls, without gastrointestinal disease, was included at baseline.

168 **Demographics of patients and controls**

169 During the inclusion period, 367 patients with IBD (Crohn's disease, n=142; ulcerative colitis,
170 n=201; IBD-U, n=24) and 168 symptomatic controls were included (**Table 1**). The group of
171 symptomatic controls comprised patients who ultimately were diagnosed with various diseases,
172 including microscopic colitis, infectious enteritis, celiac disease, or irritable bowel syndrome.
173 In addition, 59 healthy controls without any history of gastrointestinal disease were recruited
174 as a second control group.

Table 1. Demographics of individuals included in the Swedish Inception Cohort in IBD (SIC-IBD)

	Crohn's disease n=142	Ulcerative colitis n=201	IBD-unclassified n=24	Symptomatic control n=168	Healthy control n=59
Female sex, n (%)	72 (50.7)	81 (40.3)	11 (45.8)	107 (63.7)	33 (55.9)
Median age (IQR)	28 (23-41)	34 (26-45)	33 (30-45)	34 (25-48)	26 (23-31)
Median CRP, mg/L (IQR)*	8.0 (3.2-32.3)	3.7 (1.4-8.7)	3.1 (2-5.6)	1.8 (0.9-5.9)	0.6 (0.3-1.1)
Median FCP, µg/g (IQR)*	452 (234-981)	325 (90-880)	471 (148-621)	68 (19-146)	10 (5-24)
Smoking, n (%)					
Never	81 (57)	104 (52)	13 (54)	76 (45)	43 (73)
Previous	28 (20)	64 (32)	8 (33)	30 (18)	10 (17)
Current	25 (18)	16 (8)	2 (8)	18 (11)	4 (7)
Missing	8 (6)	17 (8)	1 (4)	44 (26)	2 (3)
Median BMI, kg/m² (IQR)	23 (21-26)	24 (22-27)	27 (22-28)	26 (22-30)	23 (21-25)

*Information was missing for CRP in 62 (10%) individuals, faecal calprotectin in 217 (37%) individuals and for Body Mass Index in 197 (33%) individuals
CRP: C-reactive protein; IQR; interquartile range; FCP, faecal calprotectin

181 Healthcare setting

182 Sweden has a tax-funded universal healthcare system, and private outpatient healthcare
183 providers are few within the field of gastroenterology. In general, gastroenterologists at
184 secondary or tertiary care centres (rather than primary care) are responsible for diagnosing and
185 managing patients with IBD.

187 Data collection

188 *Characterisation of disease phenotype and disease activity*

189 Following informed consent, data on patient demographics, disease phenotype according to the
190 Montreal classification[23], extraintestinal manifestations, endoscopic activity (defined as the
191 presence of ulcers in Crohn's disease [yes/no] and the Mayo endoscopic subscore in ulcerative
192 colitis), IBD treatment, IBD-related surgery, and hospital admission were recorded at baseline
193 and prospectively during follow-up. Treatment-naivety was defined as no prior treatment with
194 IBD-related medications, including topical therapies. Previous treatments in patients who were
195 not treatment-naïve included mostly topical therapies but also a few days of corticosteroid
196 treatment. For healthy controls, information about basic demographics was collected. Data on
197 disease characteristics were recorded using case report forms (CRFs), and details on the
198 Montreal classification and clinical disease activity at baseline are provided in **Table 2**.

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Table 2. Clinical characteristics of patients with Crohn’s disease, ulcerative colitis and IBD-
unclassified in the Swedish Inception Cohort in IBD (SIC-IBD)

	Crohn's Disease n=142	Ulcerative colitis n=201	IBD- unclassified n=24
Disease location, n (%)			
ileal (L1)	48 (34)		
colonic (L2)	50 (35)		
ileocolonic (L3)	34 (24)		
upper GI (L4)	1 (1)		
unknown	9 (6)		
Disease behaviour, n (%)			
non-stricturing, non-penetrating (B1)	115 (80)		
stricturing (B2)	14 (10)		
penetrating (B3)	5 (3)		
unknown	8 (6)		
Perianal disease, n (%)			
	12 (8)		
Disease extent, n (%)			
ulcerative proctitis (E1)		64 (32)	
left-sided colitis (E2)		57 (28)	
extensive colitis (E3)		76 (38)	
unknown		4 (2)	
Treatment-naïve, n (%)			
	128 (90)	185 (92)	21 (88)

Upper GI (L4) refers to patients with only upper gastrointestinal Crohn’s disease
IBD-unclassified, Inflammatory bowel disease unclassified; SIC-IBD; GI, gastrointestinal

206 *Patient-reported outcomes*

207 Patient questionnaires were employed to obtain information about clinical disease activity,
208 smoking status, recent antibiotic or non-steroid anti-inflammatory drug use, and any specific
209 dietary restrictions.

210
211 Patients were also asked to complete the Short-Health-Scale and Short Form-36 (SF-36)
212 questionnaire to obtain information about Health-Related Quality of Life (HRQoL) [24–26].
213 SF-36 is a general measure of HRQoL, whereas the Short-Health Scale is a validated measure
214 to address HRQoL in patients with IBD. It includes four dimensions: bowel symptoms, daily
215 life activities, worry and general well-being. Additional quality of life data were collected using
216 the EuroQol-5D (EQ-5D) questionnaire [27,28]. Mental health was evaluated using the Patient-
217 health Questionnaire 9 (PHQ9) [29], the Cognitive Reserve Index (CRI) [30], and the Short-
218 Form Health Survey (SF-36) [26]. Additional data on gastrointestinal symptoms was obtained
219 by using the Gastrointestinal Symptom Rating Scale (GSRS) [31] and the Rome III criteria
220 functional gastrointestinal disorders [32].

221

222 **Sample collection and biobanking**

223 Biospecimens were obtained at baseline and during follow-up, processed and biobanked
224 according to predefined standard operating procedures (SOPs). Blood samples were collected
225 in EDTA and PAX®-tubes. In addition, serum samples were obtained by centrifugation of
226 whole blood at $2400 \times g$ for 5 min at ambient temperature, followed by aliquoting of serum and
227 storing at -80°C . For six centres, blood samples were shipped unprocessed at ambient room
228 temperature and centrifuged upon arrival at the central biobank, Örebro, Sweden. The
229 participants collected faecal samples in plastic tubes at home, brought them to the hospital or

mailed them by postal service. On arrival, the samples were immediately frozen and stored at -80°C . Spot urine samples were collected during study visits, aliquoted and stored at -80°C . In addition to collecting biopsies as part of clinical routine, physicians were instructed to take intestinal biopsies from both inflamed and non-inflamed mucosa according to a predefined protocol. These biopsies were preserved in Allprotect Tissue Reagent (Qiagen, Hilden, Germany) and in a bacterial freezing medium. Biopsies in the freezing medium were immediately stored at -80°C , whereas those in Allprotect Tissue Reagent were handled according to the manufacturer's instructions. Details on the collected biological material are provided in **Table 3**.

Table 3. An overview of biospecimens collected at baseline from individuals within the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD)

	Crohn's Disease n=142	Ulcerative colitis n=201	IBD- unclassified n=24	Symptoma tic control n=168	Healthy control n=59
Serum, n (%)	137 (96)	199 (99)	23 (96)	164 (98)	59 (100)
Faecal, n (%)*	99 (70)	137 (68)	20 (83)	112 (67)	56 (95)
Intestinal biopsies, n (%)	92 (65)	161 (80)	18 (75)	155 (92)	58 (98)
Urine, n (%)	62 (44)	91 (45)	9 (38)	90 (54)	58 (98)

*Faecal samples for microbiome analyses and for additional faecal marker. Samples for faecal calprotectin were handled separately.
IBD, inflammatory bowel disease

Measurements of high-sensitivity CRP and faecal calprotectin

After storage, samples for high-sensitivity (hs) CRP (serum) and calprotectin (faeces) were retrieved from the central biobank and sent to Uppsala Clinical Research Center, Uppsala, Sweden and Academic Laboratory, Department of Clinical Chemistry, University Hospital,

Uppsala, Sweden, respectively. hsCRP was assayed in a single batch for all participants at the end of the recruitment period, using a particle-enhanced immunoturbidimetric hsCRP assay (Cardiac C-Reactive Protein (Latex) High Sensitive, Roche Diagnostics) on a Roche Cobas c501. Correspondingly, FCP was extracted and analysed according to the manufacturer's instructions, with a chemiluminescent immunoassay, using the LIASON XL analyser (DiaSorin, Saluggia, Italy). Data on median levels of hsCRP and FCP across the various diagnoses are provided in **Table 1**.

Disease course outcome during follow-up

A composite outcome measure was used to categorise the disease course as aggressive or indolent during follow-up. An aggressive disease course was defined as the presence of any IBD-related surgery, hospital admission for active disease, treatment refractoriness towards targeted therapies, i.e., biologics, Janus kinase (JAK) inhibitors or sphingosine-1-phosphate receptor modulators, and >two courses or high cumulative dosis of systemic corticosteroids within the first year of follow-up (**Table 4**). In addition, Crohn's disease patients with evidence of progression to a complicated disease behaviour, i.e., a new stricture, fistula, or abscess, were also categorised as having an aggressive disease course.

Table 4. Criteria for defining the disease course as aggressive or indolent within the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD). Patients with any of the following events during the first year from the date of diagnosis were defined as having an aggressive disease course.

Difficulty in controlling inflammation in patients with IBD

- Hospital admission for active disease
- Surgical resection (including colectomy) or a stoma
- Use of > 2 courses of corticosteroids* or a cumulative dose of > 2.5 g equivalents of prednisolone
- Use of ≥2 targeted therapies due to poor clinical effectiveness**

Progression to complicated disease behaviour in patients with Crohn’s disease

- New fistula (recto-vaginal, enterocutaneous, internal or proctitis-related perianal fistula), or need for fistula-related surgery
- New abscess (including perianal abscess) or abscess-related surgery
- New stricture or stricture-related surgery

**A corticosteroid course was defined as an episode of treatment with specified start and stop dates. Typically, oral prednisolone was initiated at a starting dose of 40 mg once daily, with a tapering schedule of 5mg per day at weekly intervals, resulting in an 8-week treatment course. For oral budesonide courses, a fixed dose of 9 mg once daily for 8 weeks was most commonly applied.*

***Targeted therapies were defined as biologics, Janus kinase (JAK) inhibitors and sphingosine-1-phosphate receptor modulators*

284 **Data management**

285 Patients, physicians, or research nurses used CRFs and predefined questionnaires to collect
286 information. All data were imported after pseudonymisation into a central database with reading
287 access for all co-investigators. The database is updated every 6-12 months to allow the import
288 of new data, including follow-up visits, address possible missing information, and correct
289 potential erroneous data entries. To enable backward traceability, a data freeze is created at
290 each update. Each data freeze provides a snapshot of information contained in the database at
291 a given date.

293 **Project organisation**

294 The SIC-IBD represents a crucial element of the multi-modal national study to identify
295 biomarkers for diagnosis, therapy response and disease progression in IBD (BIO IBD), which
296 aims to bring leading clinicians, clinical researchers and basic scientists within the field of IBD
297 together with corporate partners. The managerial structure and the operational organisation of
298 BIO IBD are shown in **Figure 2**. An executive office has been set up at the Faculty of Health
299 and Medical Sciences, Örebro University, forming the BIO IBD Executive Committee together
300 with representatives of participating universities and university hospitals. The Executive
301 Committee coordinated the efforts of the work packages, clinical departments, biomedical
302 companies, and the Swedish patients' organisation, *Mag- och tarmförbundet* [33].

303
304 The Steering Committee, responsible for the strategic leadership, is formed by representatives
305 from involved universities, biomedical companies and the patient organisation, with equal
306 numbers of basic scientists and clinicians, equal gender, and representation of young scientists.
307 The Advisory Board, composed of internationally renowned representatives of academia and
308 the biomedical industry, provides external review and input.

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Patient and Public Involvement statement

During the planning phase of the cohort study, patient representatives from the Swedish patient’s organisation, *Mag- och tarmförbundet* provided input on the study design, including the definition of the disease course during follow-up. Also, they assessed the burden of the collection of biological material and the time required for responding to the questionnaires in the study. Representatives of the patient organisation and the Swedish biomarker manufacturers in the executive committee also provided feedback during the recruitment process and follow-up of study participants. In addition to scientific reporting, key findings of the studies will be communicated to patient organisations, public health policymakers, and the public through various media and news activities. When disseminating the results, the recommendations of the International Committee of Medical Journal Editors (ICMJE) will be applied [34].

FINDINGS TO DATE

At baseline, differences in smoking habits were observed between patients with Crohn’s disease and ulcerative colitis. Active smoking was more prevalent in patients with Crohn’s disease, while a higher rate of former smokers was found in patients with ulcerative colitis. While hsCRP measurements were available for 90% of all patients and controls, only 63% of patients and controls had available FCP measures in the study. An additional 44 measurements of FCP at diagnosis were available from clinical routine, but these results were excluded from this analysis due to the use of different assays. Both FCP and hsCRP levels were higher in patients with Crohn’s disease and ulcerative colitis compared to symptomatic controls and healthy controls. However, while FCP levels were significantly elevated in IBD unclassified compared to symptomatic controls, the difference in hsCRP levels between these two groups was not statistically significant. No significant differences in FCP levels were observed between

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patients with Crohn's disease and ulcerative colitis, but hsCRP levels were higher in Crohn's disease patients. Significant differences in hsCRP and FCP levels were also found between symptomatic controls and healthy controls.

Preliminary results from analyses of serum proteins as well as findings from the analyses of faecal markers have highlighted the potential of these markers to differentiate between patients with IBD and symptomatic controls in this cohort, suggesting their diagnostic value [35,36]. Recent results from the analysis of anti- $\alpha\beta 6$ autoantibodies further suggested a high diagnostic value for ulcerative colitis of this marker [37]. Additionally, preliminary data indicate differences in mucosal proteins between patients developing an aggressive course of ulcerative colitis and those with an indolent course [38].

In line with previous studies [19,39], we employed a composite outcome to characterise the disease course within the first year after diagnosis, either as aggressive or indolent (Table 4). An aggressive course was defined by treatment refractoriness, the need for surgical resection, or in the case of Crohn's disease, the development of severe complications such as strictures and fistulas. Based on this definition, 37% (53/142) of the patients with Crohn's disease, 24% (48/201) of those with ulcerative colitis, and 4% (1/24) with IBD-U experienced an aggressive disease course within the first year after diagnosis (**Supplementary Table 1**). These results underscore that treatment failure rates and disease complications remain unacceptably high in IBD. Aggressive disease course was associated with more extensive ulcerative colitis, while no association was found between Crohn's disease location and disease course.

STRENGTHS AND LIMITATIONS

In this large nationwide multicentre inception cohort of newly diagnosed patients with IBD, a set of highly relevant biospecimens were collected at inclusion, and patients were prospectively followed. This cohort can be used to gain insights into key pathogenic mechanisms of IBD. Moreover, it provides a valuable resource for biomarker discoveries, particularly the identification of diagnostic biomarkers for IBD and prognostic markers for future disease courses.

This cohort is one of few large-scale IBD inception cohorts of adult patients with integrated biobanking [40–42], as most of the earlier initiatives have included paediatric patients only. Most previous attempts to identify diagnostic biomarkers in inception cohorts have used healthy controls or patients with non-inflammatory conditions (e.g., irritable bowel syndrome) as a control group. These settings do not reflect a diagnostic scenario where patients with gastrointestinal symptoms that are indicative of IBD are examined. Accordingly, evaluations based on these cohorts are likely to overestimate the diagnostic capacity of potential biomarkers [43]. However, this limitation is rarely acknowledged and may partly explain why promising biomarkers fail in replication attempts and do not make their way to the clinic. To allow the identification of diagnostic biomarkers, we have included patients with symptoms indicative of IBD but without any signs of the disease at diagnostic work-up or during follow-up (symptomatic controls) as a reference group. Thus, both cases with IBD and symptomatic controls represented an unselected sample of patients who were referred to secondary care for the suspicion of IBD. In addition, we included healthy controls as a second control group to gain insight into the aetiology of IBD and to characterise pathways related to disease pathogenesis.

A composite outcome was chosen to categorise disease course since no established gold standard for defining or classifying IBD course currently exists. The Montreal classification provides a framework for Crohn's disease location and behaviour, and extent of ulcerative colitis but does not capture disease progression over time [23]. Several other cohorts, including the European Crohn's and Colitis Organization's Epidemiological Committee (EpiCom) inception cohort [14] and Inflammatory bowel disease in South-Eastern Norway cohort III (IBSEN III) [41], have recorded disease-related events such as IBD-related surgery, disease complications, and hospital admissions to assess disease severity over time. Similarly, the Randomised Evaluation of an Algorithm for Crohn's Treatment (REACT) [19] and REACT-2 [39] trials employed a composite outcome to define disease course in Crohn's disease using similar criteria. While a single criterion, such as treatment escalation or new disease complications in Crohn's disease [44,45], may facilitate interpretability, a composite outcome allows a more comprehensive assessment of disease severity over time. This approach captures multiple dimensions, including difficulties in controlling inflammation, fibrosis-related complications, and poor treatment response, thereby offering a broader perspective on disease course.

In this cohort, we did not record the number of eligible patients who were not included, e.g. those who declined to or were not able to give informed consent or were not identified by study personnel. The absence of a population-based cohort design could be a limiting factor when interpreting associations between exposures and clinical outcomes within SIC-IBD, as selection bias may have been introduced. However, the proportion of IBD patients with Crohn's disease in this study (39%), the EpiCom inception cohort (37%) and the recent population-based Inflammatory bowel disease in South-Eastern Norway cohort III (35%) were similar. Likewise, the proportions of ulcerative colitis (55%, 52% and 61%) and IBD-U (7%, 11% and 4%) were

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406 similar in the three cohorts. Suboptimal procedures in sample collection further limited the
407 study. To enable inclusion at all centres, serum samples collected at centres with limited sample
408 processing capacity were shipped overnight to a central biobank for centrifugation and
409 biobanking. While measured faecal markers such as calprotectin are stable at room temperature
410 for several days, microbiome analyses are sensitive to pre-analytic sample handling [46–48].
411 Furthermore, not all included patients were treatment-naïve, which could influence the
412 molecular data and may warrant sensitivity analyses. Approximately 9% of patients had
413 initiated treatment before inclusion, most commonly with one or a few doses of corticosteroids
414 in the days preceding inclusion.

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COLLABORATION

We have established an inception cohort of newly diagnosed adult patients with IBD, symptomatic controls and healthy controls with integrated biobanking. Initiatives are underway to generate various multi-omics data from samples collected at baseline and follow-up visits. Analyses of single and multiple datasets, including integration of clinical variables, may discover novel diagnostic and prognostic biosignatures for IBD and its subtypes. Comparisons with healthy controls may also provide insights into IBD pathogenesis and progression mechanisms. We encourage collaborations with researchers from other cohorts and case-control studies to validate findings from the SIC-IBD cohort. Also, researchers can propose new collaborative initiatives and apply for access to data and biospecimens by submitting a proposal to the BIO IBD Executive Office (BIO.IBD@oru.se). All proposals will be reviewed on scientific quality and methodology by the BIOIBD executive committee.

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443 **Competing interests statement**

444

445 **DB** served as a speaker and/or advisory board member for Abbvie, BMS, Johnson and Johnson,

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The SIC-IBD study was approved by the Regional Ethics Committees (Dnr 2010/313). Written informed consent was obtained from all participants before inclusion.

Provenance and peer review

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Data sharing statement

Researchers can apply for access to data and biological specimens by submitting a proposal to the BIO IBD Executive Office (BIO.IBD@oru.se), including a copy of their ethics approval. All proposals will be reviewed by the BIOIBD executive committee based on scientific quality and methodology. This procedure is installed to ensure that the clinical data and biological material are being requested for scientific purposes, in accordance with the informed consent signed by the participants, as the collected data and material cannot be used by purely commercial parties. Additionally, any transfer of data or biological material must comply with Swedish law and the European Union (EU) General Data Protection Regulation (GDPR).

References

- 1 Lönnfors S, Vermeire S, Avedano L. IBD and health-related quality of life — Discovering the true impact. *J Crohns Colitis*. 2014;8:1281–6. doi: 10.1016/j.crohns.2014.03.005
- 2 Park KT, Ehrlich OG, Allen JI, et al. The Cost of Inflammatory Bowel Disease: An Initiative From the Crohn's & Colitis Foundation. *Inflamm Bowel Dis*. 2020;26:1–10. doi: 10.1093/ibd/izz104
- 3 Khalili H, Everhov ÅH, Halfvarson J, et al. Healthcare use, work loss and total costs in incident and prevalent Crohn's disease and ulcerative colitis: results from a nationwide study in Sweden. *Aliment Pharmacol Ther*. 2020;52:655–68. doi: 10.1111/apt.15889
- 4 Peyrin-Biroulet L, Loftus EVJ, Colombel J-F, et al. The Natural History of Adult Crohn's Disease in Population-Based Cohorts. *Am J Gastroenterol*. 2010;105:289–97. doi: 10.1038/ajg.2009.579
- 5 Jess T, Rungoe C, Peyrin-Biroulet L. Risk of Colorectal Cancer in Patients With Ulcerative Colitis: A Meta-analysis of Population-Based Cohort Studies. *Clin Gastroenterol and Hepatol*. 2012;10:639–45. doi: 10.1016/j.cgh.2012.01.010
- 6 Torres J, Billioud V, Sachar DB, et al. Ulcerative Colitis as A Progressive Disease: The Forgotten Evidence. *Inflamm Bowel Dis*. 2012;18:1356–63. doi: 10.1002/ibd.22839
- 7 Brookes MJ, Whitehead S, Gaya DR, et al. Practical guidance on the use of faecal calprotectin. *Frontline Gastroenterol*. 2018;9:87–91. doi: 10.1136/flgastro-2016-100762
- 8 Maréchal C, Aimone-Gastin I, Baumann C, et al. Compliance with the faecal calprotectin test in patients with inflammatory bowel disease. *United European Gastroenterol J*. 2017;5:702–7. doi: 10.1177/2050640616686517
- 9 Khakoo NS, Lewis A, Roldan GA, et al. Patient Adherence to Fecal Calprotectin Testing Is Low Compared to Other Commonly Ordered Tests in Patients With Inflammatory Bowel Disease. *Crohns Colitis* 360. 2021;3:otab028. doi: 10.1093/crocol/otab028
- 10 Burisch J, Ungaro R, Vind I, et al. Proximal Disease Extension in Patients With Limited Ulcerative Colitis: A Danish Population-based Inception Cohort. *J Crohns Colitis*. 2017;11:1200–4. doi: 10.1093/ecco-jcc/jjx066
- 11 Schoepfer AM, Dehlavi M-A, Fournier N, et al. Diagnostic Delay in Crohn's Disease Is Associated With a Complicated Disease Course and Increased Operation Rate. *Am J Gastroenterol*. 2013;108:1744–53. doi: 10.1038/ajg.2013.248

12 Solberg IC, Lygren I, Jahnsen J, et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). *Scand J Gastroenterol.* 2009;44:431–40. doi: 10.1080/00365520802600961

13 Solberg IC, Vatn MH, Høie O, et al. Clinical Course in Crohn’s Disease: Results of a Norwegian Population-Based Ten-Year Follow-Up Study. *Clin Gastroenterol Hepatol.* 2007;5:1430–8. doi: 10.1016/j.cgh.2007.09.002

14 Burisch J, Pedersen N, Cukovic-Cavka S, et al. Initial Disease Course and Treatment in an Inflammatory Bowel Disease Inception Cohort in Europe: The ECCO-EpiCom Cohort. *Inflamm Bowel Dis.* 2014;20:36–46. doi: 10.1097/01.MIB.0000436277.13917.c4

15 Burisch J, Katsanos KH, Christodoulou DK, et al. Natural Disease Course of Ulcerative Colitis During the First Five Years of Follow-up in a European Population-based Inception Cohort—An Epi-IBD Study. *J Crohns Colitis.* 2019;13:198–208. doi: 10.1093/ecco-jcc/jjy154

16 Burisch J, Kiudelis G, Kupcinskis L, et al. Natural disease course of Crohn’s disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. *Gut.* 2019;68:423–33. doi: 10.1136/gutjnl-2017-315568

17 Zhulina Y, Udumyan R, Tysk C, et al. The changing face of Crohn’s disease: a population-based study of the natural history of Crohn’s disease in Örebro, Sweden 1963–2005. *Scand J Gastroenterol.* 2016;51:304–13. doi: 10.3109/00365521.2015.1093167

18 Everhov ÅH, Halfvarson J, Myrelid P, et al. Incidence and Treatment of Patients Diagnosed With Inflammatory Bowel Diseases at 60 Years or Older in Sweden. *Gastroenterology.* 2018;154:518-528.e15. doi: 10.1053/j.gastro.2017.10.034

19 Khanna R, Bressler B, Levesque BG, et al. Early combined immunosuppression for the management of Crohn’s disease (REACT): a cluster randomised controlled trial. *Lancet.* 2015;386:1825–34. doi: 10.1016/S0140-6736(15)00068-9

20 Colombel J-F, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn’s disease (CALM): a multicentre, randomised, controlled phase 3 trial. *The Lancet.* 2017;390:2779–89. doi: 10.1016/S0140-6736(17)32641-7

21 Satsangi J, Nowak J, Kalla R, et al. Treatment strategies and biomarkers in Crohn’s disease: the PROFILE trial. *Lancet Gastroenterol Hepatol.* 2024;9:591–2. doi: 10.1016/S2468-1253(24)00082-7

22 Maaser C, Sturm A, Vavricka SR, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis.* 2019;13:144-164K. doi: 10.1093/ecco-jcc/jjy113

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

- 23 Silverberg MS, Satsangi J, Ahmad T, et al. Toward an Integrated Clinical, Molecular and Serological Classification of Inflammatory Bowel Disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol*. 2005;19:5A-36A. doi: 10.1155/2005/269076
- 24 Hjortswang H, Järnerot G, Curman B, et al. The Short Health Scale: A valid measure of subjective health in ulcerative colitis. *Scand J Gastroenterol*. 2006;41:1196–203. doi: 10.1080/00365520600610618
- 25 Stjernman H, Grännö C, Järnerot G, et al. Short health scale: A valid, reliable, and responsive instrument for subjective health assessment in Crohn's disease: *Inflamm Bowel Dis*. 2008;14:47–52. doi: 10.1002/ibd.20255
- 26 Mchorney CA, John W, Anastasia R. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and Clinical Tests of Validity in Measuring Physical and Mental Health Constructs. *Medical Care*. 1993;31:247–63. doi: 10.1097/00005650-199303000-00006
- 27 EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199–208. doi: 10.1016/0168-8510(90)90421-9
- 28 Rabin R, Charro FD. EQ-SD: a measure of health status from the EuroQol Group. *Annals of Medicine*. 2001;33:337–43. doi: 10.3109/07853890109002087
- 29 Kroenke K, Spitzer RL. The PHQ-9: A New Depression Diagnostic and Severity Measure. *Psychiatric Annals*. 2002;32:509–15. doi: 10.3928/0048-5713-20020901-06
- 30 Nucci M, Mapelli D, Mondini S. Cognitive Reserve Index questionnaire (CRIq): a new instrument for measuring cognitive reserve. *Aging Clin Exp Res*. 2012;24:218–26. doi: 10.1007/BF03654795
- 31 Svedlund J, Sjödin I, Dotevall G. GSRS - A clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Digest Dis Sci*. 1988;33:129–34. doi: 10.1007/BF01535722
- 32 Drossman DA. The Functional Gastrointestinal Disorders and the Rome III Process. *Gastroenterology*. 2006;130:1377–90. doi: 10.1053/j.gastro.2006.03.008
- 33 Mag- och tarmförbundet. <https://magotarm.se/>. Last Accessed 10 Jan 2025.
- 34 International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals. Updated 2025. Last Accessed 09 April 2025.
- 35 Bazov I, Kruse R, Bergemalm D, et al. P154 A novel serum protein signature as biomarker for Inflammatory Bowel Disease: A diagnostic performance and prediction modelling

study using data from two independent inception cohorts. *J Crohns Colitis*. 2023;17:i314–5. doi: 10.1093/ecco-jcc/jjac190.0284

36 Ling Lundström M, Peterson C, Hedin CRH, et al. Faecal biomarkers for diagnosis and prediction of disease course in treatment-naïve patients with IBD. *Aliment Pharmacol Ther*. 2024;60:765–77. doi: 10.1111/apt.18154

37 Pertsinidou E, Salomon B, Bergemalm D, et al. et al. Anti-integrin $\alpha\text{v}\beta 6$ IgG antibody as a diagnostic and prognostic marker in ulcerative colitis: A cross-sectional and longitudinal study defining a specific disease phenotype. (Accepted for publication in *J Crohns and Colitis* on March 14, 2025)

38 Salomon B, Carlson M, Bergemalm D, et al. P219 Prognostic potential of mucosal proteins in Ulcerative Colitis. *J Crohns and Colitis*. 2024;18:i549–50. doi: 10.1093/ecco-jcc/jjad212.0349

39 Jairath, Vipul R, Khanna R, Guizzetti L, et al. A cluster-randomised controlled trial of an enhanced treatment algorithm for the management of Crohn’s disease: REACT-2. *Lancet Gastroenterol Hepatol*. 2022;7:1080. doi: 10.1016/S2468-1253(22)00357-0

40 Gevers D, Kugathasan S, Denson LA, et al. The treatment-naïve microbiome in new-onset Crohn’s disease. *Cell Host Microbe*. 2014;15:382–92. doi: 10.1016/j.chom.2014.02.005

41 Kristensen VA, Opheim R, Perminow G, et al. Inflammatory bowel disease in South-Eastern Norway III (IBSEN III): a new population-based inception cohort study from South-Eastern Norway. *Scand J Gastroenterol*. 2021;56:899–905. doi: 10.1080/00365521.2021.1922746

42 Attauabi M, Madsen GR, Bendtsen F, et al. Influence of Genetics, Immunity and the Microbiome on the Prognosis of Inflammatory Bowel Disease (IBD Prognosis Study): the protocol for a Copenhagen IBD Inception Cohort Study. *BMJ Open*. 2022;12:e055779. doi: 10.1136/bmjopen-2021-055779

43 Lijmer JG. Empirical Evidence of Design-Related Bias in Studies of Diagnostic Tests. *JAMA*. 1999;282:1061. doi: 10.1001/jama.282.11.1061

44 Kalla R, Adams AT, Bergemalm D, et al. Serum proteomic profiling at diagnosis predicts clinical course, and need for intensification of treatment in inflammatory bowel disease. *Journal of Crohn’s and Colitis*. 2021;15:699–708. doi: 10.1093/ecco-jcc/jjaa230

45 Ungaro RC, Hu L, Ji J, et al. Machine learning identifies novel blood protein predictors of penetrating and stricturing complications in newly diagnosed paediatric Crohn’s disease. *Aliment Pharmacol Ther*. 2020. doi: 10.1111/apt.16136

635 46 Carstens A, Roos A, Andreasson A, et al. Differential clustering of fecal and mucosa-
636 associated microbiota in 'healthy' individuals. *J Dig Dis*. 2018;19:745–52. doi:
637 10.1111/1751-2980.12688

638 47 RØseth AG, Fagerhol MK, Aadland E, et al. Assessment of the Neutrophil Dominating
639 Protein Calprotectin in Feces: A Methodologic Study. *Scandinavian Journal of*
640 *Gastroenterology*. 1992;27:793–8. doi: 10.3109/00365529209011186

641 48 Lasso A, Stotzer P-O, Öhman L, et al. The intra-individual variability of faecal
642 calprotectin: A prospective study in patients with active ulcerative colitis. *Journal of*
643 *Crohn's and Colitis*. 2014;S1873994614001858. doi: 10.1016/j.crohns.2014.06.002

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646 Figure 1. The flow diagram shows the number of included individuals at each hospital, the
647 number of patients excluded and the final number of patients and controls in the Swedish
648 Inception Cohort in inflammatory bowel disease (SIC-IBD).

649

650 Figure 2. Managerial structure and the operational organisation of the multi-modal national
651 study to identify biomarkers for diagnosis, therapy response and disease progression in
652 inflammatory bowel disease (BIO IBD), where the Swedish inception cohort in IBD (SIC-
653 IBD) represents an important resource.

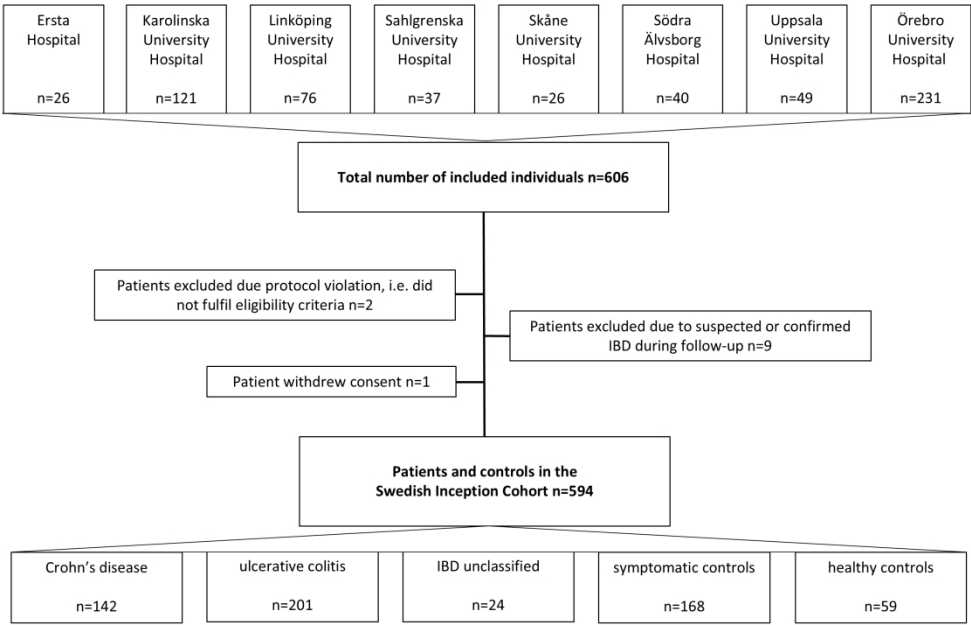


Figure 1. The flow diagram shows the number of included individuals at each hospital, the number of patients excluded and the final number of patients and controls in the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD).

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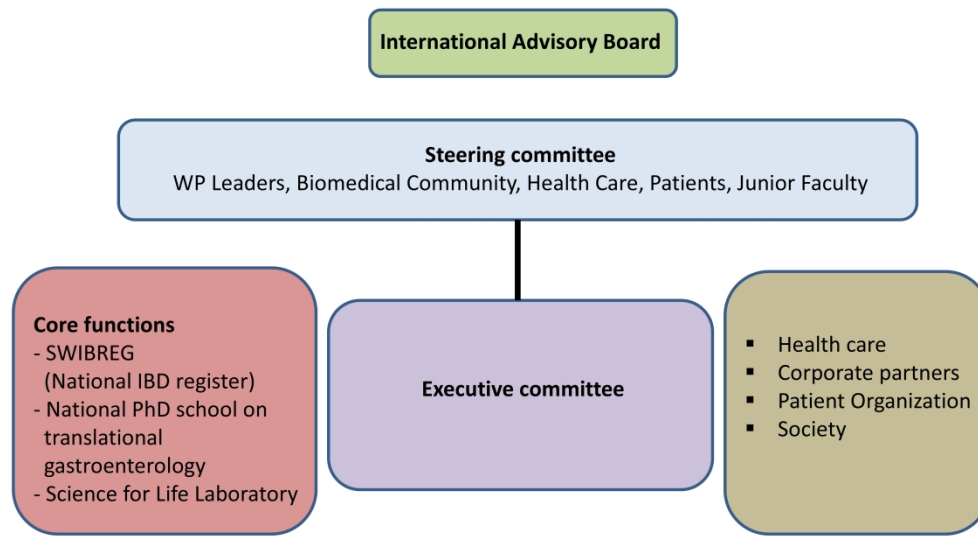


Figure 2. Managerial structure and the operational organisation of the multi-modal national study to identify biomarkers for diagnosis, therapy response and disease progression in inflammatory bowel disease (BIO IBD), where the Swedish inception cohort in IBD (SIC-IBD) represents an important resource.

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Supplementary Table 1

	Crohn's disease n=142	ulcerative colitis n=201	IBD-unclassified n=24
Aggressive disease, n (%)	53 (37.3)	48 (23.9)	1 (4.2)
Indolent disease, n (%)	83 (58.5)	144 (71.6)	22 (91.7)
Unknown*, n (%)	6 (4.2)	9 (4.5)	1 (4.2)

*Missing information about clinical outcomes due to incomplete follow-up during the first year after diagnosis.

BMJ Open

Cohort profile: The Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD)

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59 **Abstract**

60 **Purpose:** There is a need for diagnostic and prognostic biosignatures to improve long-term
61 outcomes in inflammatory bowel disease (IBD). Here, we describe the establishment of the
62 Swedish inception cohort in IBD (SIC-IBD) and demonstrate its potential for the identification
63 of such signatures.

64 **Participants:** Patients aged ≥ 18 years with gastrointestinal symptoms who were referred to the
65 gastroenterology unit due to suspected IBD at eight Swedish hospitals between November 2011
66 and March 2021 were eligible for inclusion.

67 **Findings to date:** In total, 367 patients with IBD (Crohn’s disease, $n=142$; ulcerative colitis,
68 $n=201$; IBD-unclassified, $n=24$) and 168 symptomatic controls were included. In addition, 59
69 healthy controls without gastrointestinal symptoms were recruited as a second control group.
70 Biospecimens and clinical data were collected at inclusion and in patients with IBD also during
71 follow-up to 10 years. Levels of faecal calprotectin and high-sensitivity C-reactive protein were
72 higher in patients with IBD compared to symptomatic controls and healthy controls.
73 Preliminary results highlight the potential of serum protein signatures and autoantibodies, as
74 well as results from faecal markers, to differentiate between IBD and symptomatic controls in
75 the cohort. During the first year of follow-up, 37% (53/142) of the patients with Crohn's disease,
76 24% (48/201) with ulcerative colitis and 4% (1/24) with IBD-U experienced an aggressive
77 disease course.

78 **Future plans:** We have established an inception cohort enabling ongoing initiatives to collect
79 and generate clinical data and multi-omics datasets. The cohort will allow analyses for
80 translation into candidate biosignatures to support clinical decision-making in IBD.
81 Additionally, the data will provide insights into mechanisms of disease pathogenesis.

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Strengths and limitations of this study

- This large, multicentre inception cohort of newly diagnosed adult patients with inflammatory bowel disease (IBD), with integrated biobanking and prospective material collection, enables exploration of IBD pathophysiology and biomarker discovery.
- The inclusion of symptomatic controls with gastrointestinal symptoms mimicking IBD but without evidence of the diagnosis provides a realistic diagnostic setting and addresses limitations of many previous cohorts.
- The use of healthy controls as a second control group offers opportunities to gain insight into IBD pathogenesis.
- The non-population-based study design and the predominance of university hospitals in recruitment may limit the generalisability of findings.
- Suboptimal sample processing at some centres, including delays in serum centrifugation and transportation of faecal samples at ambient temperatures, may have affected the quality of some specific analyses, such as microbiota analyses.

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease, ulcerative colitis and IBD-unclassified (IBD-U), is a chronic disease that predominantly presents during the second and third decades of life. The disease results in an impaired quality of life for patients and substantial societal costs due to sick leave and a high use of healthcare resources [1–3]. Progressive inflammation causes damage to the gastrointestinal tract, and a substantial proportion of patients develop serious disease complications, including bowel obstruction, fistula, abscesses, and colorectal cancer [4–6].

IBD often presents with non-specific symptoms such as diarrhoea, fatigue and abdominal pain and, therefore, presents a diagnostic challenge. Commonly used biomarkers in diagnostic algorithms include C-reactive protein (CRP) and, in some regions, faecal calprotectin (FCP) which help identify patients needing referral for further investigations, including ileocolonoscopy [7]. However, the diagnostic accuracy of CRP is too low for reliably identifying IBD patients, and the utility of FCP is hampered by poor patient adherence to faecal sampling [8,9]. Furthermore, many healthcare systems do not reimburse the use of FCP for diagnostic purposes. The absence of reliable, non-invasive diagnostic biomarkers, occurrence of non-specific symptoms and limited access to ileocolonoscopy, frequently results in a significant diagnostic delay [10,11]. As a consequence, many patients have acquired considerable bowel damage (e.g., fistulas, strictures) already at diagnosis [4,11].

At diagnosis, the heterogeneity in clinical presentation and subsequent disease course make clinicians' attempts to stratify the treatment according to the individual patient's needs very difficult. While some patients experience an indolent disease course with minimal symptoms and low endoscopic activity, a substantial proportion exhibit an aggressive disease phenotype

characterised by treatment refractoriness, corticosteroid dependency, frequent hospital admissions and surgical interventions, including resection surgery and acute colectomy [12–18]. For this latter group, an early effective treatment seems advantageous, as the initial disease phase may provide a "window of opportunity" where prompt suppression of intestinal inflammation could improve long-term outcomes [19–21]. Identifying prognostic biomarkers for this group of patients is therefore critical to facilitate the timely initiation of potent treatment.

To address the need for both diagnostic and prognostic biomarkers, we established the "Swedish Inception Cohort in IBD" (SIC-IBD), a large prospective multicentre cohort involving patients with suspected IBD referred to eight hospitals in Sweden. After a comprehensive diagnostic work-up, patients were classified as incident IBD patients or symptomatic non-IBD controls, i.e., patients presenting with symptoms mimicking IBD but where IBD was ruled out. Alternative diagnoses in this patient group included infectious colitis, irritable bowel syndrome and diverticulitis. As a second control group, healthy controls without gastrointestinal symptoms were recruited. This cohort provides a rich collection of biospecimens together with detailed phenotypic characterisation collected both at diagnosis and during follow-up. Herein, we present the study design and baseline characteristics of the participants in the SIC-IBD.

COHORT DESCRIPTION

Inclusion

This longitudinal multicentre cohort study was conducted across eight Swedish hospitals: Ersta Hospital, Karolinska University Hospital, Linköping University Hospital, Sahlgrenska University Hospital, Skåne University Hospital, Södra Älvsborg Hospital, Uppsala University Hospital, and Örebro University Hospital. Patients aged ≥ 18 years with gastrointestinal

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3 145 symptoms, such as diarrhoea, abdominal pain and blood or mucus in stools, who were referred
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5 146 to the gastroenterology unit with suspected IBD between November 2011 and March 2021 were
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8 147 eligible for inclusion (Figure 1). Exclusion criteria included a previous diagnosis of Crohn's
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10 148 disease, ulcerative colitis or IBD unclassified, or inability to provide informed consent or to
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12 149 comply with protocol requirements. After obtaining written informed consent, all patients
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14 150 underwent a routine diagnostic work-up for IBD, following clinical practice and international
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16 151 guidelines [22].
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21 153 Based on the diagnostic work-up, which included magnetic resonance imaging in cases where
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23 154 small bowel involvement was suspected, patients were classified as having incident IBD or as
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25 155 symptomatic controls, i.e., patients with no discernible evidence of IBD at inclusion or during
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27 156 follow-up. The diagnosis of IBD was based on internationally accepted clinical, endoscopic,
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29 157 radiological, and histological criteria [22]. Nine patients were excluded due to suspected or
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31 158 confirmed IBD during follow-up. Patients are followed prospectively according to clinical
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33 159 practice, with data collected after 3 months, 1, 3, 5, 7 and 10 years for those with IBD. At
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35 160 present, follow-up is ongoing for many patients. In addition, a group of healthy controls,
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37 161 without gastrointestinal disease, was included at baseline.
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44 162 **Demographics of patients and controls**
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46 163 During the inclusion period, 367 patients with IBD (Crohn's disease, n=142; ulcerative colitis,
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48 164 n=201; IBD-U, n=24) and 168 symptomatic controls were included (**Table 1**). The group of
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50 165 symptomatic controls comprised patients who ultimately were diagnosed with various diseases,
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52 166 including microscopic colitis, infectious enteritis, celiac disease, or irritable bowel syndrome.
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54 167 In addition, 59 healthy controls without any history of gastrointestinal disease were recruited
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56 168 as a second control group.
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Table 1. Demographics of individuals included in the Swedish Inception Cohort in IBD (SIC-IBD)

	Crohn's disease n=142	Ulcerative colitis n=201	IBD- unclassified n=24	Symptomatic control n=168	Healthy control n=59
Female sex, n (%)	72 (50.7)	81 (40.3)	11 (45.8)	107 (63.7)	33 (55.9)
Median age (IQR)	28 (23-41)	34 (26-45)	33 (30-45)	34 (25-48)	26 (23-31)
Median CRP, mg/L (IQR)*	8.0 (3.2-32.3)	3.7 (1.4-8.7)	3.1 (2-5.6)	1.8 (0.9-5.9)	0.6 (0.3-1.1)
Median FCP, µg/g (IQR)*	452 (234-981)	325 (90-880)	471 (148-621)	68 (19-146)	10 (5-24)
Smoking, n (%)					
Never	81 (57)	104 (52)	13 (54)	76 (45)	43 (73)
Previous	28 (20)	64 (32)	8 (33)	30 (18)	10 (17)
Current	25 (18)	16 (8)	2 (8)	18 (11)	4 (7)
Missing	8 (6)	17 (8)	1 (4)	44 (26)	2 (3)
Median BMI, kg/m ² (IQR)	23 (21-26)	24 (22-27)	27 (22-28)	26 (22-30)	23 (21-25)

*Information was missing for CRP in 62 (10%) individuals, faecal calprotectin in 217 (37%) individuals and for Body Mass Index in 197 (33%) individuals.
CRP: C-reactive protein; IQR; interquartile range; FCP, faecal calprotectin.

Healthcare setting

Sweden has a tax-funded universal healthcare system, and private outpatient healthcare providers are few within the field of gastroenterology. In general, gastroenterologists at secondary or tertiary care centres (rather than primary care) are responsible for diagnosing and managing patients with IBD.

Data collection

Characterisation of disease phenotype and disease activity

Following informed consent, data on patient demographics, disease phenotype according to the Montreal classification[23], extraintestinal manifestations, endoscopic activity (defined as the presence of ulcers in Crohn's disease [yes/no] and the Mayo endoscopic subscore in ulcerative colitis), IBD treatment, IBD-related surgery, and hospital admission were recorded at baseline and prospectively during follow-up. Treatment-naivety was defined as no prior treatment with IBD-related medications, including topical therapies. Previous treatments in patients who were not treatment-naïve included mostly topical therapies but also a few days of corticosteroid treatment. For healthy controls, information about basic demographics was collected. Data on disease characteristics were recorded using case report forms (CRFs), and details on the Montreal classification and clinical disease activity at baseline are provided in **Table 2**.

Table 2. Clinical characteristics of patients with Crohn's disease, ulcerative colitis and IBD-unclassified in the Swedish Inception Cohort in IBD (SIC-IBD)

	Crohn's Disease n=142	Ulcerative colitis n=201	IBD-unclassified n=24
Disease location, n (%)			
ileal (L1)	48 (34)		
colonic (L2)	50 (35)		
ileocolonic (L3)	34 (24)		
upper GI (L4)	1 (1)		
unknown	9 (6)		
Disease behaviour, n (%)			
non-stricturing, non-penetrating (B1)	115 (80)		
stricturing (B2)	14 (10)		
penetrating (B3)	5 (3)		
unknown	8 (6)		
Perianal disease, n (%)	12 (8)		
Disease extent, n (%)			
ulcerative proctitis (E1)		64 (32)	
left-sided colitis (E2)		57 (28)	
extensive colitis (E3)		76 (38)	
Unknown		4 (2)	
Treatment-naïve, n (%)	128 (90)	185 (92)	21 (88)

Upper GI (L4) refers to patients with only upper gastrointestinal Crohn's disease.

IBD-unclassified, Inflammatory bowel disease unclassified; SIC-IBD; GI, gastrointestinal.

Patient-reported outcomes

Patient questionnaires were employed to obtain information about clinical disease activity, smoking status, recent antibiotic or non-steroid anti-inflammatory drug use, and any specific dietary restrictions.

Patients were also asked to complete the Short-Health-Scale and Short Form-36 (SF-36) questionnaire to obtain information about Health-Related Quality of Life (HRQoL) [24–26]. SF-36 is a general measure of HRQoL, whereas the Short-Health Scale is a validated measure to address HRQoL in patients with IBD. It includes four dimensions: bowel symptoms, daily life activities, worry and general well-being. Additional quality of life data were collected using the EuroQol-5D (EQ-5D) questionnaire[27,28]. Mental health was evaluated using the Patient-health Questionnaire 9 (PHQ9) [29], the Cognitive Reserve Index (CRI) [30], and the Short-Form Health Survey (SF-36) [26]. Additional data on gastrointestinal symptoms was obtained by using the Gastrointestinal Symptom Rating Scale (GSRS) [31] and the Rome III criteria functional gastrointestinal disorders [32].

Sample collection and biobanking

Biospecimens were obtained at baseline and during follow-up, processed and biobanked according to predefined standard operating procedures (SOPs). Blood samples were collected in EDTA and PAX®-tubes. In addition, serum samples were obtained by centrifugation of whole blood at $2400 \times g$ for 5 min at ambient temperature, followed by aliquoting of serum and storing at $-80^{\circ} C$. For six centres, blood samples were shipped unprocessed at ambient room temperature and centrifuged upon arrival at the central biobank, Örebro, Sweden. The participants collected faecal samples in plastic tubes at home, brought them to the hospital or

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mailed them by postal service. On arrival, the samples were immediately frozen and stored at -80°C. Spot urine samples were collected during study visits, aliquoted and stored at -80°C. In addition to collecting biopsies as part of clinical routine, physicians were instructed to take intestinal biopsies from both inflamed and non-inflamed mucosa according to a predefined protocol. These biopsies were preserved in Allprotect Tissue Reagent (Qiagen, Hilden, Germany) and in a bacterial freezing medium. Biopsies in the freezing medium were immediately stored at -80°C, whereas those in Allprotect Tissue Reagent were handled according to the manufacturer's instructions. Details on the collected biological material are provided in **Table 3**.

Table 3. An overview of biospecimens collected at baseline from individuals within the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD)

	Crohn's Disease n=142	Ulcerative colitis n=201	IBD- unclassified n=24	Symptomatic control n=168	Healthy control n=59
Serum, n (%)	137 (96)	199 (99)	23 (96)	164 (98)	59 (100)
Faecal, n (%)*	99 (70)	137 (68)	20 (83)	112 (67)	56 (95)
Intestinal biopsies, n (%)	92 (65)	161 (80)	18 (75)	155 (92)	58 (98)
Urine, n (%)	62 (44)	91 (45)	9 (38)	90 (54)	58 (98)

*Faecal samples for microbiome analyses and for additional faecal marker. Samples for faecal calprotectin were handled separately.
IBD, inflammatory bowel disease.

Measurements of high-sensitivity CRP and faecal calprotectin

After storage, samples for high-sensitivity (hs) CRP (serum) and calprotectin (faeces) were retrieved from the central biobank and sent to Uppsala Clinical Research Center, Uppsala, Sweden and Academic Laboratory, Department of Clinical Chemistry, University Hospital,

Uppsala, Sweden, respectively. hsCRP was assayed in a single batch for all participants at the end of the recruitment period, using a particle-enhanced immunoturbidimetric hsCRP assay (Cardiac C-Reactive Protein (Latex) High Sensitive, Roche Diagnostics) on a Roche Cobas c501. Correspondingly, FCP was extracted and analysed according to the manufacturer's instructions, with a chemiluminescent immunoassay, using the LIASON XL analyser (DiaSorin, Saluggia, Italy). Data on median levels of hsCRP and FCP across the various diagnoses are provided in **Table 1**.

Disease course outcome during follow-up

A composite outcome measure was used to categorise the disease course as aggressive or indolent during follow-up. An aggressive disease course was defined as the presence of any IBD-related surgery, hospital admission for active disease, treatment refractoriness towards targeted therapies, i.e., biologics, Janus kinase (JAK) inhibitors or sphingosine-1-phosphate receptor modulators, and >two courses or high cumulative dosis of systemic corticosteroids within the first year of follow-up (**Table 4**). In addition, Crohn's disease patients with evidence of progression to a complicated disease behaviour, i.e., a new stricture, fistula, or abscess, were also categorised as having an aggressive disease course.

Table 4. Criteria for defining the disease course as aggressive or indolent within the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD). Patients with any of the following events during the first year from the date of diagnosis were defined as having an aggressive disease course.

Difficulty in controlling inflammation in patients with IBD

- Hospital admission for active disease
- Surgical resection (including colectomy) or a stoma
- Use of > 2 courses of corticosteroids* or a cumulative dose of > 2.5 g equivalents of prednisolone
- Use of ≥ 2 targeted therapies due to poor clinical effectiveness**

Progression to complicated disease behaviour in patients with Crohn's disease

- New fistula (recto-vaginal, enterocutaneous, internal or proctitis-related perianal fistula), or need for fistula-related surgery
- New abscess (including perianal abscess) or abscess-related surgery
- New stricture or stricture-related surgery

*A corticosteroid course was defined as an episode of treatment with specified start and stop dates. Typically, oral prednisolone was initiated at a starting dose of 40 mg once daily, with a tapering schedule of 5mg per day at weekly intervals, resulting in an 8-week treatment course. For oral budesonide courses, a fixed dose of 9 mg once daily for 8 weeks was most commonly applied.

**Targeted therapies were defined as biologics, Janus kinase (JAK) inhibitors and sphingosine-1-phosphate receptor modulators.

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Data management

Patients, physicians, or research nurses used CRFs and predefined questionnaires to collect information. All data were imported after pseudonymisation into a central database with reading access for all co-investigators. The database is updated every 6-12 months to allow the import of new data, including follow-up visits, address possible missing information, and correct potential erroneous data entries. To enable backward traceability, a data freeze is created at each update. Each data freeze provides a snapshot of information contained in the database at a given date.

Project organisation

The SIC-IBD represents a crucial element of the multi-modal national study to identify biomarkers for diagnosis, therapy response and disease progression in IBD (BIO IBD), which aims to bring leading clinicians, clinical researchers and basic scientists within the field of IBD together with corporate partners. The managerial structure and the operational organisation of BIO IBD are shown in **Figure 2**. An executive office has been set up at the Faculty of Health and Medical Sciences, Örebro University, forming the BIO IBD Executive Committee together with representatives of participating universities and university hospitals. The Executive Committee coordinated the efforts of the work packages, clinical departments, biomedical companies, and the Swedish patients' organisation, *Mag- och tarmförbundet* [33].

The Steering Committee, responsible for the strategic leadership, is formed by representatives from involved universities, biomedical companies and the patient organisation, with equal numbers of basic scientists and clinicians, equal gender, and representation of young scientists. The Advisory Board, composed of internationally renowned representatives of academia and the biomedical industry, provides external review and input.

295 Patient and public involvement

296 During the planning phase of the cohort study, patient representatives from the Swedish
297 patient's organisation, *Mag- och tarmförbundet* provided input on the study design, including
298 the definition of the disease course during follow-up. Also, they assessed the burden of the
299 collection of biological material and the time required for responding to the questionnaires in
300 the study. Representatives of the patient organisation and the Swedish biomarker manufacturers
301 in the executive committee also provided feedback during the recruitment process and follow-
302 up of study participants. In addition to scientific reporting, key findings of the studies will be
303 communicated to patient organisations, public health policymakers, and the public through
304 various media and news activities. When disseminating the results, the recommendations of the
305 International Committee of Medical Journal Editors (ICMJE) will be applied [34].

307 FINDINGS TO DATE

308 At baseline, differences in smoking habits were observed between patients with Crohn's disease
309 and ulcerative colitis. Active smoking was more prevalent in patients with Crohn's disease,
310 while a higher rate of former smokers was found in patients with ulcerative colitis. While
311 hsCRP measurements were available for 90% of all patients and controls, only 63% of patients
312 and controls had available FCP measures in the study. An additional 44 measurements of FCP
313 at diagnosis were available from clinical routine, but these results were excluded from this
314 analysis due to the use of different assays. Both FCP and hsCRP levels were higher in patients
315 with Crohn's disease and ulcerative colitis compared to symptomatic controls and healthy
316 controls. However, while FCP levels were significantly elevated in IBD unclassified compared
317 to symptomatic controls, the difference in hsCRP levels between these two groups was not
318 statistically significant. No significant differences in FCP levels were observed between
319 patients with Crohn's disease and ulcerative colitis, but hsCRP levels were higher in Crohn's

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disease patients. Significant differences in hsCRP and FCP levels were also found between symptomatic controls and healthy controls.

Preliminary results from analyses of serum proteins as well as findings from the analyses of faecal markers have highlighted the potential of these markers to differentiate between patients with IBD and symptomatic controls in this cohort, suggesting their diagnostic value [35,36]. Recent results from the analysis of anti- $\alpha\text{v}\beta 6$ autoantibodies further suggested a high diagnostic value for ulcerative colitis of this marker [37]. Additionally, preliminary data indicate differences in mucosal proteins between patients developing an aggressive course of ulcerative colitis and those with an indolent course [38].

In line with previous studies [19,39], we employed a composite outcome to characterise the disease course within the first year after diagnosis, either as aggressive or indolent (Table 4). An aggressive course was defined by treatment refractoriness, the need for surgical resection, or in the case of Crohn’s disease, the development of severe complications such as strictures and fistulas. Based on this definition, 37% (53/142) of the patients with Crohn's disease, 24% (48/201) of those with ulcerative colitis, and 4% (1/24) with IBD-U experienced an aggressive disease course within the first year after diagnosis (**Supplementary Table 1**). These results underscore that treatment failure rates and disease complications remain unacceptably high in IBD. Aggressive disease course was associated with more extensive ulcerative colitis, while no association was found between Crohn’s disease location and disease course.

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343 **Future plans**

344 Research projects and collaborations based on the SIC-IBD are ongoing. The diagnostic and
345 prognostic value of multiple molecular datasets is being further investigated, both separately
346 and in combination, using a multi-omics approach. Additionally, correlations across data layers,
347 such as between levels of faecal marker, serum and mucosal proteins, and compositional
348 microbiome data may provide further insights into disease mechanisms. The evaluation of the
349 patient-reported outcomes aims to improve our understanding of the impact of IBD on patients'
350 quality of life, and can be integrated with clinical and molecular data to explore potential
351 associations.

352
353 If single biomarkers or biomarker signatures of markers are identified, we aim to validate these
354 in independent cohorts. For example, preliminary findings on serum proteins and results on
355 anti- $\alpha\text{v}\beta 6$ autoantibodies have been validated in the Inflammatory bowel disease in South-
356 Eastern Norway III (IBSEN III) cohort [35,37,40]. Conversely, SIC-IBD may also serve as a
357 validation cohort for findings from other cohorts. For instance, recent results on serum proteins
358 in preclinical IBD were examined in SIC-IBD to evaluate their relevance in incident IBD [41].
359 Finally, promising markers from the SIC-IBD should be further tested in prospective clinical
360 trials, such as the NORDTREAT trial [42].

361 362 **STRENGTHS AND LIMITATIONS**

363 In this large nationwide multicentre inception cohort of newly diagnosed patients with IBD, a
364 set of highly relevant biospecimens were collected at inclusion, and patients were prospectively
365 followed. This cohort can be used to gain insights into key pathogenic mechanisms of IBD.
366 Moreover, it provides a valuable resource for biomarker discoveries, particularly the

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identification of diagnostic biomarkers for IBD and prognostic markers for future disease courses.

This cohort is one of few large-scale IBD inception cohorts of adult patients with integrated biobanking [40,43,44], as most of the earlier initiatives have included paediatric patients only. Most previous attempts to identify diagnostic biomarkers in inception cohorts have used healthy controls or patients with non-inflammatory conditions (e.g., irritable bowel syndrome) as a control group. These settings do not reflect a diagnostic scenario where patients with gastrointestinal symptoms that are indicative of IBD are examined. Accordingly, evaluations based on these cohorts are likely to overestimate the diagnostic capacity of potential biomarkers [45]. However, this limitation is rarely acknowledged and may partly explain why promising biomarkers fail in replication attempts and do not make their way to the clinic. To allow the identification of diagnostic biomarkers, we have included patients with symptoms indicative of IBD but without any signs of the disease at diagnostic work-up or during follow-up (symptomatic controls) as a reference group. Thus, both cases with IBD and symptomatic controls represented an unselected sample of patients who were referred to secondary care for the suspicion of IBD. In addition, we included healthy controls as a second control group to gain insight into the aetiology of IBD and to characterise pathways related to disease pathogenesis.

A composite outcome was chosen to categorise disease course since no established gold standard for defining or classifying IBD course currently exists. The Montreal classification provides a framework for Crohn’s disease location and behaviour, and extent of ulcerative colitis but does not capture disease progression over time [23]. Several other cohorts, including the European Crohn’s and Colitis Organization’s Epidemiological Committee (EpiCom) inception cohort [14] and the IBSSEN III cohort [40], have recorded disease-related events such as IBD-related surgery, disease complications, and hospital admissions to assess disease

severity over time. Similarly, the Randomised Evaluation of an Algorithm for Crohn's Treatment (REACT) [19] and REACT-2 [39] trials employed a composite outcome to define disease course in Crohn's disease using similar criteria. While a single criterion, such as treatment escalation or new disease complications in Crohn's disease [46,47], may facilitate interpretability, a composite outcome allows a more comprehensive assessment of disease severity over time. This approach captures multiple dimensions, including difficulties in controlling inflammation, fibrosis-related complications, and poor treatment response, thereby offering a broader perspective on disease course.

In this cohort, we did not record the number of eligible patients who were not included, e.g. those who declined to or were not able to give informed consent or were not identified by study personnel. The absence of a population-based cohort design could be a limiting factor when interpreting associations between exposures and clinical outcomes within SIC-IBD, as selection bias may have been introduced. However, the proportion of IBD patients with Crohn's disease in this study (39%), the EpiCom inception cohort (37%) and the recent population-based IBSEN III cohort (35%) were similar. Likewise, the proportions of ulcerative colitis (55%, 52% and 61%) and IBD-U (7%, 11% and 4%) were similar in the three cohorts. Suboptimal procedures in sample collection further limited the study. To enable inclusion at all centres, serum samples collected at centres with limited sample processing capacity were shipped overnight to a central biobank for centrifugation and biobanking. While measured faecal markers such as calprotectin are stable at room temperature for several days, microbiome analyses are sensitive to pre-analytic sample handling [48–50]. Furthermore, not all included patients were treatment-naïve, which could influence the molecular data and may warrant sensitivity analyses. Approximately 9% of patients had initiated treatment before inclusion, most commonly with one or a few doses of corticosteroids in the days preceding inclusion.

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COLLABORATION

419 We have established an inception cohort of newly diagnosed adult patients with IBD,
420 symptomatic controls and healthy controls with integrated biobanking. Initiatives are underway
421 to generate various multi-omics data from samples collected at baseline and follow-up visits.
422 Analyses of single and multiple datasets, including integration of clinical variables, may
423 discover novel diagnostic and prognostic biosignatures for IBD and its subtypes. Comparisons
424 with healthy controls may also provide insights into IBD pathogenesis and progression
425 mechanisms. We encourage collaborations with researchers from other cohorts and case-
426 control studies to validate findings from the SIC-IBD cohort. Also, researchers can propose
427 new collaborative initiatives and apply for access to data and biospecimens by submitting a
428 proposal to the BIO IBD Executive Office (BIO.IBD@oru.se). All proposals will be reviewed
429 on scientific quality and methodology by the BIOIBD executive committee.

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Contributors

Conception and design: JH. Drafting the manuscript: BS, OGrännö and JH. Critical revision for intellectual content, final approval, and accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved: BS, OGrännö, DB, HS, AC, HH, MLL, JPH, SA, FB, CE, OGrip, AB, JM, NN, SB, CML, EHH, MKM, ÅVK, MD'A, DR, LÖ, JDS, MC, CRHH, RK, and JH. Guarantor: JH.

Competing interests

DB served as a speaker and/or advisory board member for Abbvie, BMS, Johnson and Johnson, Pfizer, Pharmacosmos, Sandoz, Takeda and Tillotts Pharma. HS has served as speaker and/or advisory board member for AbbVie Ferring, Janssen, Pfizer, Takeda, Gilead and Tillotts Pharma. AC served as a speaker for Takeda and Ferring. HH has served as a speaker, consultant or advisory board member for AbbVie, Ferring, Fresenius Kabi, Janssen, Norgine, Pfizer, Pharmacosmos, Takeda and Tillotts and has received grant support from AbbVie, Ferring, Takeda, and Tillotts. SA served as a member for Scientific committee/Advisory board of, Janssen, Pharmacosmos, Takeda, as a consultant for Janssen, OrionPharm, Takeda, and as a speaker: Galapagos, Janssen, Tillotts, received research grants from Janssen and OrionPharma. FB has acted as national and/or local principal investigator for clinical trials for Janssen, Ferring and Abbvie. CE received grant support/lecture fee/advisory board from Takeda, Janssen Cilag, Pfizer, Abbvie. OGrip served as speaker and/or advisory board member for Abbvie, Bristol Mayer Squibb, Eli Lilly, Ferring, Janssen, Pfizer Takeda, Tillotts Pharma and Vifor Pharma. JM has served as a speaker, consultant or advisory board member for AbbVie, Alfasigma, Amgen, Bayer, Biogen, BMS, Eli Lilly, Ferring, Galapagos, Hospira, ITH, Janssen, Lument, MSD, Otsuka, Pfizer, Sandoz, Takeda, Tillotts and UCB; and has received grant support (not for this study) from AbbVie, BMS, Calpro AS, Carbiotix, Ferring, Fresenius Kabi, Pfizer, Svar

Life Science and Takeda. MKM has received speaker's fees from Takeda and Janssen. LÖ has received a financial support for research by Genetic Analysis AS, Biocodex, Danone Research and AstraZeneca and served as Consultant/Advisory Board member for Genetic Analysis AS, and as a speaker for Biocodex, Ferring Pharmaceuticals, Takeda, AbbVie, Novartis, Janssen-Cilag and Meda. MC has received speaker's fees from ViforPharma. She is the national PI for clinical trials for AstraZeneca. CRHH has served as a speaker and/or advisory board member for AstraZeneca, Dr Falk Pharma and the Falk Foundation, Galapagos, Janssen, Pfizer, Takeda, Tillotts Pharma, and received grant support from Tillotts and Takeda. JH served as speaker and/or advisory board member from AbbVie, Alfasigma, Aqilion, Bristol Myers Squibb, Celgene, Celltrion, Dr Falk Pharma and the Falk Foundation, Eli Lilly, Ferring, Galapagos, Gilead, Hospira, Index Pharma, Janssen, MEDA, Medivir, Medtronic, Merck, MSD, Novartis, Pfizer, Prometheus Laboratories Inc., Sandoz, Shire, STADA, Takeda, Thermo Fisher Scientific, Tillotts Pharma, Vifor Pharma, UCB and received grant support from Janssen, MSD and Takeda. The remaining authors declare no conflicts of interest.

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Ethical approval

The SIC-IBD study was approved by the Regional Ethics Committees (Dnr 2010/313). Written informed consent was obtained from all participants before inclusion.

Provenance and peer review

Not commissioned; externally peer-reviewed.

490 Data availability statement

491 Researchers can apply for access to data and biological specimens by submitting a proposal to
492 the BIO IBD Executive Office (BIO.IBD@oru.se), including a copy of their ethics approval.
493 All proposals will be reviewed by the BIOIBD executive committee based on scientific quality
494 and methodology. This procedure is installed to ensure that the clinical data and biological
495 material are being requested for scientific purposes, in accordance with the informed consent
496 signed by the participants, as the collected data and material cannot be used by purely
497 commercial parties. Additionally, any transfer of data or biological material must comply with
498 Swedish law and the European Union (EU) General Data Protection Regulation (GDPR).
499

References

1 Lönnfors S, Vermeire S, Avedano L. IBD and health-related quality of life — Discovering
the true impact. *J Crohns Colitis*. 2014;8:1281–6. doi: 10.1016/j.crohns.2014.03.005

2 Park KT, Ehrlich OG, Allen JI, et al. The Cost of Inflammatory Bowel Disease: An
Initiative From the Crohn’s & Colitis Foundation. *Inflamm Bowel Dis*. 2020;26:1–10. doi:
10.1093/ibd/izz104

3 Khalili H, Everhov ÅH, Halfvarson J, et al. Healthcare use, work loss and total costs in
incident and prevalent Crohn’s disease and ulcerative colitis: results from a nationwide
study in Sweden. *Aliment Pharmacol Ther*. 2020;52:655–68. doi: 10.1111/apt.15889

4 Peyrin-Biroulet L, Loftus EVJ, Colombel J-F, et al. The Natural History of Adult Crohn’s
Disease in Population-Based Cohorts. *Am J Gastroenterol*. 2010;105:289–97. doi:
10.1038/ajg.2009.579

5 Jess T, Rungoe C, Peyrin-Biroulet L. Risk of Colorectal Cancer in Patients With
Ulcerative Colitis: A Meta-analysis of Population-Based Cohort Studies. *Clin
Gastroenterol and Hepatol*. 2012;10:639–45. doi: 10.1016/j.cgh.2012.01.010

6 Torres J, Billioud V, Sachar DB, et al. Ulcerative Colitis as A Progressive Disease: The
Forgotten Evidence. *Inflamm Bowel Dis*. 2012;18:1356–63. doi: 10.1002/ibd.22839

7 Brookes MJ, Whitehead S, Gaya DR, et al. Practical guidance on the use of faecal
calprotectin. *Frontline Gastroenterol*. 2018;9:87–91. doi: 10.1136/flgastro-2016-100762

8 Maréchal C, Aimone-Gastin I, Baumann C, et al. Compliance with the faecal calprotectin
test in patients with inflammatory bowel disease. *United European Gastroenterol J*.
2017;5:702–7. doi: 10.1177/2050640616686517

9 Khakoo NS, Lewis A, Roldan GA, et al. Patient Adherence to Fecal Calprotectin Testing
Is Low Compared to Other Commonly Ordered Tests in Patients With Inflammatory
Bowel Disease. *Crohns Colitis 360*. 2021;3:otab028. doi: 10.1093/crocol/otab028

10 Burisch J, Ungaro R, Vind I, et al. Proximal Disease Extension in Patients With Limited
Ulcerative Colitis: A Danish Population-based Inception Cohort. *J Crohns Colitis*.
2017;11:1200–4. doi: 10.1093/ecco-jcc/jjx066

11 Schoepfer AM, Dehlavi M-A, Fournier N, et al. Diagnostic Delay in Crohn’s Disease Is
Associated With a Complicated Disease Course and Increased Operation Rate. *Am J
Gastroenterol*. 2013;108:1744–53. doi: 10.1038/ajg.2013.248

12 Solberg IC, Lygren I, Jahnsen J, et al. Clinical course during the first 10 years of ulcerative
colitis: results from a population-based inception cohort (IBSEN Study). *Scand J
Gastroenterol*. 2009;44:431–40. doi: 10.1080/00365520802600961

- 13 Solberg IC, Vatn MH, Høie O, et al. Clinical Course in Crohn's Disease: Results of a Norwegian Population-Based Ten-Year Follow-Up Study. *Clin Gastroenterol Hepatol*. 2007;5:1430–8. doi: 10.1016/j.cgh.2007.09.002
- 14 Burisch J, Pedersen N, Cukovic-Cavka S, et al. Initial Disease Course and Treatment in an Inflammatory Bowel Disease Inception Cohort in Europe: The ECCO-EpiCom Cohort. *Inflamm Bowel Dis*. 2014;20:36–46. doi: 10.1097/01.MIB.0000436277.13917.c4
- 15 Burisch J, Katsanos KH, Christodoulou DK, et al. Natural Disease Course of Ulcerative Colitis During the First Five Years of Follow-up in a European Population-based Inception Cohort—An Epi-IBD Study. *J Crohns Colitis*. 2019;13:198–208. doi: 10.1093/ecco-jcc/jjy154
- 16 Burisch J, Kiudelis G, Kupcinskas L, et al. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. *Gut*. 2019;68:423–33. doi: 10.1136/gutjnl-2017-315568
- 17 Zhulina Y, Udumyan R, Tysk C, et al. The changing face of Crohn's disease: a population-based study of the natural history of Crohn's disease in Örebro, Sweden 1963–2005. *Scand J Gastroenterol*. 2016;51:304–13. doi: 10.3109/00365521.2015.1093167
- 18 Everhov ÅH, Halfvarson J, Myrelid P, et al. Incidence and Treatment of Patients Diagnosed With Inflammatory Bowel Diseases at 60 Years or Older in Sweden. *Gastroenterology*. 2018;154:518–528.e15. doi: 10.1053/j.gastro.2017.10.034
- 19 Khanna R, Bressler B, Levesque BG, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *Lancet*. 2015;386:1825–34. doi: 10.1016/S0140-6736(15)00068-9
- 20 Colombel J-F, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *The Lancet*. 2017;390:2779–89. doi: 10.1016/S0140-6736(17)32641-7
- 21 Satsangi J, Nowak J, Kalla R, et al. Treatment strategies and biomarkers in Crohn's disease: the PROFILE trial. *Lancet Gastroenterol Hepatol*. 2024;9:591–2. doi: 10.1016/S2468-1253(24)00082-7
- 22 Maaser C, Sturm A, Vavricka SR, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis*. 2019;13:144–164K. doi: 10.1093/ecco-jcc/jjy113
- 23 Silverberg MS, Satsangi J, Ahmad T, et al. Toward an Integrated Clinical, Molecular and Serological Classification of Inflammatory Bowel Disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol*. 2005;19:5A–36A. doi: 10.1155/2005/269076

1
2
3 569 24 Hjortswang H, Järnerot G, Curman B, et al. The Short Health Scale: A valid measure of
4 570 subjective health in ulcerative colitis. *Scand J Gastroenterol*. 2006;41:1196–203. doi:
5 571 10.1080/00365520600610618
6
7
8 572 25 Stjernman H, Grännö C, Järnerot G, et al. Short health scale: A valid, reliable, and
9 573 responsive instrument for subjective health assessment in Crohn’s disease: *Inflamm Bowel*
10 574 *Dis*. 2008;14:47–52. doi: 10.1002/ibd.20255
11
12
13 575 26 Mchorney CA, John W, Anastasia R. The MOS 36-Item Short-Form Health Survey (SF-
14 576 36): II. Psychometric and Clinical Tests of Validity in Measuring Physical and Mental
15 577 Health Constructs. *Medical Care*. 1993;31:247–63. doi: 10.1097/00005650-199303000-
16 578 00006
17
18
19 579 27 EuroQol - a new facility for the measurement of health-related quality of life. *Health*
20 580 *Policy*. 1990;16:199–208. doi: 10.1016/0168-8510(90)90421-9
21
22
23 581 28 Rabin R, Charro FD. EQ-SD: a measure of health status from the EuroQol Group. *Annals*
24 582 *of Medicine*. 2001;33:337–43. doi: 10.3109/07853890109002087
25
26
27 583 29 Kroenke K, Spitzer RL. The PHQ-9: A New Depression Diagnostic and Severity Measure.
28 584 *Psychiatric Annals*. 2002;32:509–15. doi: 10.3928/0048-5713-20020901-06
29
30 585 30 Nucci M, Mapelli D, Mondini S. Cognitive Reserve Index questionnaire (CRIq): a new
31 586 instrument for measuring cognitive reserve. *Aging Clin Exp Res*. 2012;24:218–26. doi:
32 587 10.1007/BF03654795
33
34
35 588 31 Svedlund J, Sjödin I, Dotevall G. GSRS - A clinical rating scale for gastrointestinal
36 589 symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Digest Dis*
37 590 *Sci*. 1988;33:129–34. doi: 10.1007/BF01535722
38
39
40 591 32 Drossman DA. The Functional Gastrointestinal Disorders and the Rome III Process.
41 592 *Gastroenterology*. 2006;130:1377–90. doi: 10.1053/j.gastro.2006.03.008
42
43
44 593 33 Mag- och tarmförbundet. <https://magotarm.se/>. Last Accessed 10 Jan 2025.
45
46 594 34 International Committee of Medical Journal Editors. Recommendations for the Conduct,
47 595 Reporting, Editing, and Publication of Scholarly work in Medical Journals. Updated 2025.
48 596 Last Accessed 09 April 2025
49
50
51 597 35 Bazov I, Kruse R, Bergemalm D, et al. P154 A novel serum protein signature as biomarker
52 598 for Inflammatory Bowel Disease: A diagnostic performance and prediction modelling
53 599 study using data from two independent inception cohorts. *J Crohns Colitis*. 2023;17:i314–
54 600 5. doi: 10.1093/ecco-jcc/jjac190.0284
55
56
57 601 36 Ling Lundström M, Peterson C, Hedin CRH, et al. Faecal biomarkers for diagnosis and
58 602 prediction of disease course in treatment-naïve patients with IBD. *Aliment Pharmacol*
59 603 *Ther*. 2024;60:765–77. doi: 10.1111/apt.18154

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- 37 Pertsinidou E, Salomon B, Bergemalm D, et al. et al. Anti-integrin $\alpha\text{v}\beta 6$ IgG antibody as a diagnostic and prognostic marker in ulcerative colitis: A cross-sectional and longitudinal study defining a specific disease phenotype. (Accepted for publication in J Crohns and Colitis on March 14, 2025)
- 38 Salomon B, Carlson M, Bergemalm D, et al. P219 Prognostic potential of mucosal proteins in Ulcerative Colitis. J Crohns and Colitis. 2024;18:i549–50. doi: 10.1093/ecco-jcc/jjad212.0349
- 39 Jairath, Vipul R, Khanna R, Guizzetti L, et al. A cluster-randomised controlled trial of an enhanced treatment algorithm for the management of Crohn's disease: REACT-2. The Lancet Gastroenterology & Hepatology. 2022;7:1080. doi: 10.1016/S2468-1253(22)00357-0
- 40 Kristensen VA, Opheim R, Perminow G, et al. Inflammatory bowel disease in South-Eastern Norway III (IBSEN III): a new population-based inception cohort study from South-Eastern Norway. Scand J Gastroenterol. 2021;56:899–905. doi: 10.1080/00365521.2021.1922746
- 41 Grännö O, Bergemalm D, Salomon B, et al. Preclinical Protein Signatures of Crohn's Disease and Ulcerative Colitis: A Nested Case-Control Study Within Large Population-Based Cohorts. Gastroenterology. 2025;168:741–53. doi: 10.1053/j.gastro.2024.11.006
- 42 Rejler M, Füchtbauer JD, Davíðsdóttir LG, et al. Nordic inflammatory bowel disease treatment strategy trial: protocol for the NORDTREAT randomised controlled biomarker-strategy trial. BMJ Open. 2024;14:e083163. doi: 10.1136/bmjopen-2023-083163
- 43 Gevers D, Kugathasan S, Denson LA, et al. The treatment-naïve microbiome in new-onset Crohn's disease. Cell Host Microbe. 2014;15:382–92. doi: 10.1016/j.chom.2014.02.005
- 44 Attauabi M, Madsen GR, Bendtsen F, et al. Influence of Genetics, Immunity and the Microbiome on the Prognosis of Inflammatory Bowel Disease (IBD Prognosis Study): the protocol for a Copenhagen IBD Inception Cohort Study. BMJ Open. 2022;12:e055779. doi: 10.1136/bmjopen-2021-055779
- 45 Lijmer JG. Empirical Evidence of Design-Related Bias in Studies of Diagnostic Tests. JAMA. 1999;282:1061. doi: 10.1001/jama.282.11.1061
- 46 Kalla R, Adams AT, Bergemalm D, et al. Serum proteomic profiling at diagnosis predicts clinical course, and need for intensification of treatment in inflammatory bowel disease. Journal of Crohn's and Colitis. 2021;15:699–708. doi: 10.1093/ecco-jcc/jjaa230
- 47 Ungaro RC, Hu L, Ji J, et al. Machine learning identifies novel blood protein predictors of penetrating and stricturing complications in newly diagnosed paediatric Crohn's disease. Aliment Pharmacol Ther. Published Online First: 1 November 2020. doi: 10.1111/apt.16136

1
2
3
4
5
6
7
8
9
10
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42
43
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47
48
49
50
51
52
53
54
55
56
57
58
59
60

48 Carstens A, Roos A, Andreasson A, et al. Differential clustering of fecal and mucosa-associated microbiota in ‘healthy’ individuals. *J Dig Dis*. 2018;19:745–52. doi: 10.1111/1751-2980.12688

49 RØseth AG, Fagerhol MK, Aadland E, et al. Assessment of the Neutrophil Dominating Protein Calprotectin in Feces: A Methodologic Study. *Scandinavian Journal of Gastroenterology*. 1992;27:793–8. doi: 10.3109/00365529209011186

50 Lasso A, Stotzer P-O, Öhman L, et al. The intra-individual variability of faecal calprotectin: A prospective study in patients with active ulcerative colitis. *Journal of Crohn’s and Colitis*. 2014;S1873994614001858. doi: 10.1016/j.crohns.2014.06.002

FIGURE CAPTIONS

Figure 1. Flow diagram showing the number of included individuals at each hospital, the number of patients excluded and the final number of patients and controls in the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD).

Figure 2. Managerial structure and the operational organisation of the multi-modal national study to identify biomarkers for diagnosis, therapy response and disease progression in inflammatory bowel disease (BIO IBD), where the Swedish inception cohort in IBD (SIC-IBD) represents an important resource.

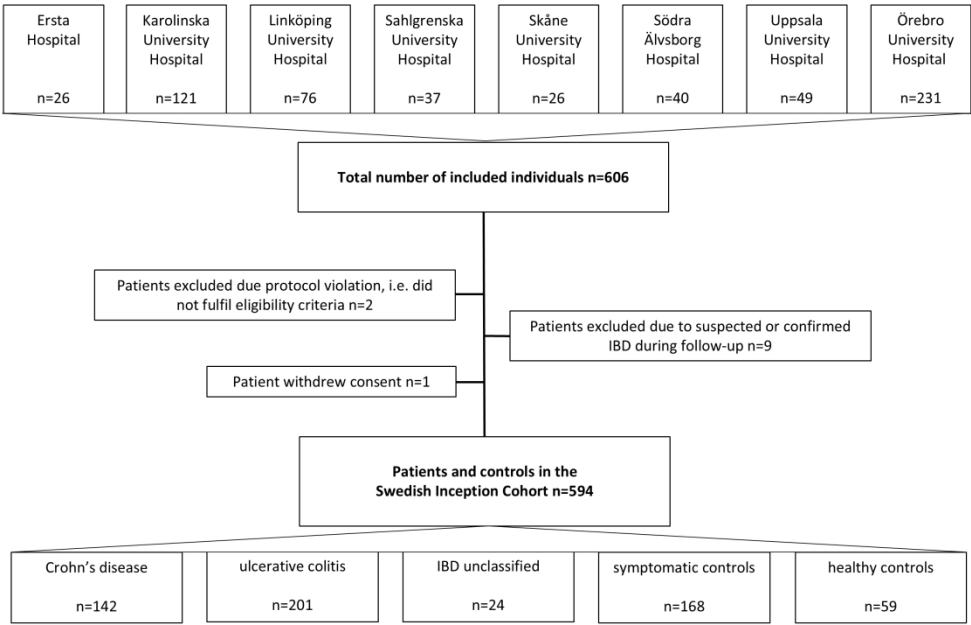


Figure 1. The flow diagram shows the number of included individuals at each hospital, the number of patients excluded and the final number of patients and controls in the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD).

609x395mm (118 x 118 DPI)

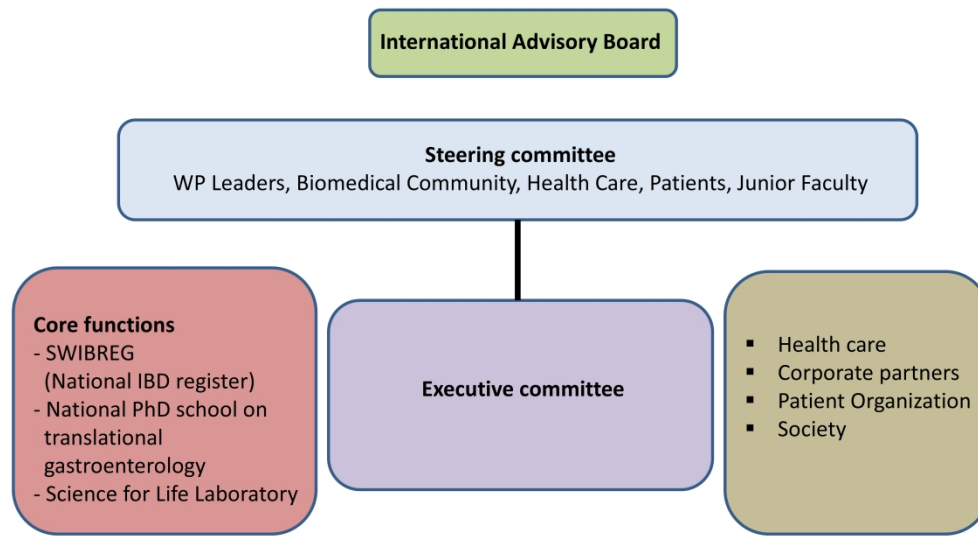


Figure 2. Managerial structure and the operational organisation of the multi-modal national study to identify biomarkers for diagnosis, therapy response and disease progression in inflammatory bowel disease (BIO IBD), where the Swedish inception cohort in IBD (SIC-IBD) represents an important resource.

611x334mm (236 x 236 DPI)

Supplementary Table 1

	Crohn's disease n=142	ulcerative colitis n=201	IBD-unclassified n=24
Aggressive disease, n (%)	53 (37.3)	48 (23.9)	1 (4.2)
Indolent disease, n (%)	83 (58.5)	144 (71.6)	22 (91.7)
Unknown*, n (%)	6 (4.2)	9 (4.5)	1 (4.2)

*Missing information about clinical outcomes due to incomplete follow-up during the first year after diagnosis.