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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

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ABSTRACT

Introduction Inflammatory bowel diseases (IBD), encompassing Crohn’s disease and ulcerative colitis, are chronic, inflammatory diseases of the gastrointestinal tract. We have initiated a Danish population-based inception cohort study aiming to investigate the underlying mechanisms for the heterogeneous course of IBD, including need for, and response to, treatment.

Methods and analysis IBD Prognosis Study is a prospective, population-based inception cohort study of unsolicited, newly diagnosed adult, adolescent and paediatric patients with IBD within the uptake area of Hvidovre University Hospital and Herlev University Hospital, Denmark, which covers approximately 1 050 000 inhabitants (~20% of the Danish population). The diagnosis of IBD will be according to the Porto diagnostic criteria in paediatric and adolescent patients or the Copenhagen diagnostic criteria in adult patients. All patients will be followed prospectively with regular clinical examinations including ileocolonoscopies, MRI of the small intestine, validated patient-reported measures and objective examinations with intestinal ultrasound. In addition, intestinal biopsies from ileocolonoscopies, stool, rectal swabs, saliva samples, swabs of the oral cavity and blood samples will be collected systematically for the analysis of biomarkers, microbiome and genetic profiles. Environmental factors and quality of life will be assessed using questionnaires and, when available, automatic registration of purchase data. The occurrence and course of extraintestinal manifestations will be evaluated by rheumatologists, dermatologists and dentists, and assessed by MR cholangiopancreatography, MR of the spine and sacroiliac joints, ultrasonography of peripheral joints and entheses, clinical oral examination, as well as panoramic radiography of the jaws. Fibroscans and dual-energy X-ray absorptiometry scans will be performed to monitor occurrence and course of chronic liver diseases, osteopenia and osteoporosis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study is a prospective population-based inception cohort study of all newly diagnosed patients with inflammatory bowel diseases patients, both adult, adolescent and paediatric, within a well-described geographical area, ensuring the cohort represents the whole spectrum of disease presentation and course.

⇒ The longitudinal study design, with regular collection of biological material, will enable investigations of the underlying mechanisms of the heterogeneous courses of IBD.

⇒ In this study population, the occurrence and course of some of the most common subclinical and clinical extraintestinal rheumatological, dermatological, oral and hepatobiliary manifestations will be thoroughly described.

⇒ Although well described, the cohort is limited by its sample size when compared with existing prospective population-based cohorts.

⇒ Due to the nature of the study design, missing data and biological samples are expected in some patients.
INTRODUCTION

Inflammatory bowel diseases (IBD), encompassing Crohn’s disease (CD) and ulcerative colitis (UC), are chronic, progressive, inflammatory diseases of the gastrointestinal (GI) tract. The pathogenesis of CD and UC is not fully understood but is thought to be the result of a complex interplay between genetic and environmental factors, epithelial barrier defects and altered gut microbiota, resulting in chronic relapsing innate and adaptive immune responses. The incidence of IBD is increasing worldwide, and in Europe alone, more than 1.3 million people are affected. Denmark has one of the highest prevalence in the world, with 0.8% of its population diagnosed with IBD. The disease course of IBD is highly heterogeneous with some patients experiencing only mild inflammation and few symptoms, while others develop severe inflammation and complications. Prospective population-based studies have recently demonstrated that a significant proportion of patients experience disease progression within the first 5 years of their diagnosis that requires hospitalisation, IBD-related surgery, and advanced therapy. Patients diagnosed in childhood (20%), and specifically those with a very early onset of IBD, have more widespread disease, higher need for more aggressive treatment and have increased risk of cancer and mortality compared with patients diagnosed as adults.

Furthermore, up to 50% of patients with IBD experience extraintestinal manifestations (EIMs) of IBD or immune-mediated inflammatory diseases (IMIDs) before or during the disease course of IBD. Most commonly, EIMs occur in the musculoskeletal, dermatological, hepatopancreaticobiliary and ocular organ systems. Some EIMs, IMIDs (such as spondyloarthritis or psoriasis) and IBD share common inflammatory mechanisms and environmental factors that are associated with increased morbidity and mortality. In addition, oral health status (ie, presence/absence of periodontitis, caries, periapical lesions) including the composition of the oral microbiome has been frequently discussed in the last decade as a potentially relevant factor for IBD development, severity and progression. Based on the results of a recent questionnaire-based, case–control study performed in Denmark a significant association between diagnosis and severity of IBD, periodontitis and tooth loss rate was confirmed. Exploration of the pathogenesis of EIMs, including their overlap with IBD, might help clarify whether EIMs are systemic manifestations directly related to the intestinal disruptions of IBD, or whether these clinical conditions represent an abnormal, genetically mediated immunological response to complex environmental stimuli. Such efforts could facilitate the identification of novel pathogenic pathways that can be targeted by individually tailored treatments.

Changes in the disease course of IBD are believed to be determined by factors within the first few years following diagnosis. Therefore, it is important to identify patients at an early stage who might later develop aggressive disease to offer these patients closer follow-up and individually tailored therapy. Currently, physicians rely on relatively poor predictors of the disease course of UC and CD when managing patients with these diseases. In UC, current predictors include young age at diagnosis and extensive disease, which have been shown to be associated with an increased risk of acute severe UC. Accordingly, specific phenotypic appearances of CD, including perianal and upper GI involvement, have been shown to be predictive of disabling disease. Second, environmental risk factors, such as smoking, are associated with increased risk of medical refractoriness in patients with CD. Third, intestinal ultrasonography (IUS), a non-invasive modality for the assessment of disease activity and complications, has shown potential in predicting therapeutic response and risk of surgery.

Gut microbiomes may fluctuate with IBD activity, and cytokine profiles in patients with IBD likewise seem to change over time. Changes in these measures might therefore predict the disease course of IBD and the response to IBD medications. Similarly, interactions between host and gut microbiota might play a role in IBD pathogenesis and thus warrant further research in representative cohorts. For example, it has been very recently reported that the gut microbiome of patients with IBD—in contrast to the gut microbiome of IBD-free controls—is significantly more alike to the oral microbiome. Recent preclinical trials investigating different mechanisms of the potential interplay between periodontitis and IBD have quite consistently shown the potential devastating effect of the oral microbiome on IBD pathogenesis and course, and a potentially positive effect of periodontal treatment on gut microbiome. A prospective investigation of the changes over time in all biological and environmental exposure patterns is necessary to assess their interactions and associations with the disease course which might ultimately facilitate development and implementation of precision medicine in the care of patients with IBD.

STUDY AIMS

IBD Prognosis Study aims to establish a prospective population-based cohort with an organised biobank system, from the time of diagnosis and added to throughout follow-up in order to characterise and predict the individual disease courses and treatment responses in patients with IBD. The primary and secondary aims are listed in table 1.
Methods
Study design overview

The IBD Prognosis Study is a population-based inception cohort study of newly diagnosed paediatric, adolescent and adult patients with IBD according to current diagnostic criteria (ie, Porto diagnostic criteria or Copenhagen diagnostic criteria within the 2-year period between 1 May 2021 and 30 April 2023). Patients will be followed prospectively with regular clinical examinations, imaging assessments and collection of biological samples, as described below. While the study aims to follow all patients for 20 years after their diagnosis of IBD, samples for the biobank will be collected during the first 5 years of follow-up. The study will be conducted at the Department of Gastroenterology and Hepatology, Herlev University Hospital and at the Gastrounit and Department of Paediatrics, Hvidovre University Hospital. The Department of Paediatrics, Hvidovre University Hospital covers the paediatric uptake area of both Hospitals. Together, these two hospitals cover an uptake area of approximately 1 050 000 inhabitants in the Copenhagen area (~20% of the total Danish population).

Follow-up

Follow-up visits will be scheduled according to the study timelines presented in tables 2 and 3. Additional follow-ups will take place at the treating physician’s discretion in case of significant disease events, which are defined as IBD-related hospitalisation or disease progression necessitating intensification of treatment. The follow-up period is 20 years from diagnosis until 30 April 2043. During years 6–20, patients will only be followed through their medical records.

Data collection and management

Tables 2 and 3 provide the timeline for adult and paediatric patients, respectively. The study outcome definitions and measures are listed in table 4. At each visit, all IBD-related clinical data will be prospectively collected, including patient demographics, disease activity, phenotypical disease presentation, results

Table 1 Primary and secondary aims of the IBD Prognosis Study

<table>
<thead>
<tr>
<th>Primary aims</th>
<th>To identify differences in microbial (mucosal and luminal), serological, environmental and genetic profiles (collectively called ‘biological profiles’) between phenotypes of patients with IBD of all ages at the time of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>To determine associations between changes in the biological profiles and disease outcomes, including changes in phenotype, hospital admissions, surgeries and treatment responses</td>
</tr>
<tr>
<td></td>
<td>To determine associations between biological profiles and disease activity and severity in terms of endoscopic severity, intestinal damage as determined by imaging assessment and objective markers of inflammation</td>
</tr>
<tr>
<td></td>
<td>To identify novel biological markers that can predict the disease course of IBD</td>
</tr>
<tr>
<td></td>
<td>To determine the distribution of inflammatory (and structural) lesions in axial and peripheral joints and entheses of patients with IBD</td>
</tr>
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<td></td>
<td>To investigate and compare the musculoskeletal imaging findings with the musculoskeletal clinical examination and the imaging and clinical factors associated with IBD activity in musculoskeletal symptomatic and asymptomatic patients with IBD</td>
</tr>
<tr>
<td>Secondary aims</td>
<td>To describe the occurrence of IBD in a population-based cohort of both adult-onset and paediatric-onset patients</td>
</tr>
<tr>
<td></td>
<td>To describe the natural history of IBD, including disease progression and prognosis</td>
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<td></td>
<td>To identify clinical markers associated with the prognosis and disease progression of IBD</td>
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<tr>
<td></td>
<td>To describe the occurrence, pattern of involvement, and natural history of IMIDs and EIMs in patients with IBD</td>
</tr>
<tr>
<td></td>
<td>To identify food purchase patterns, and novel biological and clinical markers, that can predict the disease course of IBD</td>
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<tr>
<td></td>
<td>To assess the ability of IUS to predict clinical and objective disease course</td>
</tr>
<tr>
<td></td>
<td>To validate the IBUS-SAS against objective measures of inflammation</td>
</tr>
<tr>
<td></td>
<td>To assess changes in the oral microbiome and microbial proteome over time and in dependence of the disease course of IBD</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel diseases; EIM, extra-intestinal manifestation; IMID, immune-mediated inflammatory disease; IUS, intestinal ultrasound; IBUS-SAS, International Bowel Ultrasound Segmental Activity Score
<table>
<thead>
<tr>
<th>Time point</th>
<th>Time of diagnosis</th>
<th>During the first year after diagnosis</th>
<th>At 12 months of follow-up</th>
<th>During the second year after diagnosis</th>
<th>At 24 months of follow-up</th>
<th>During years 3–5 after diagnosis</th>
<th>At 60 months of follow-up</th>
<th>Years 6–20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of visit</td>
<td>Minimum every third month and at events</td>
<td>Minimum every 6 months and at events</td>
<td>Minimum annually and at events</td>
<td>Minimum annually and at events</td>
<td>Minimum annually and at events</td>
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<tr>
<td>Screening for inclusion</td>
<td>X</td>
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<tr>
<td>Participant information and written informed consent</td>
<td>X</td>
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<tr>
<td>Collection of information from medical record including any medical adverse events</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Detailed environmental questionnaire</td>
<td>X</td>
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<tr>
<td>Collection of purchase data</td>
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<tr>
<td>Clinical disease activity score</td>
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<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Collection of faecal sample and rectal swab</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Collection of blood sample</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Collection of saliva sample</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Collection of biopsies at endoscopy</td>
<td>X</td>
<td>(X)</td>
<td>X</td>
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<tr>
<td>MR cholangio-pancreatography</td>
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<td>Rheumatological assessment</td>
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<tr>
<td>MRI of spine and sacroiliac joints</td>
<td>X</td>
<td></td>
<td>(X)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>US of peripheral joints end entheses</td>
<td>X</td>
<td></td>
<td>(X)</td>
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<tr>
<td>Dermatological assessment</td>
<td>(X)</td>
<td>(X)</td>
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<tr>
<td>DXA scan</td>
<td>X</td>
<td></td>
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<tr>
<td>IUS</td>
<td>X</td>
<td>(X)</td>
<td>X</td>
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<tr>
<td>Fibroscan</td>
<td>At sign of liver disease</td>
<td>At sign of liver disease</td>
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<tr>
<td>Dental assessment</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Panoramic radiograph</td>
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</tbody>
</table>

Continued
of blood and stool samples, current medical therapy, surgery, hospitalisation and occurrence of cancers.

In addition, all medical adverse reactions will be recorded prospectively. During each follow-up time point, patients are systematically asked about any medical adverse events which are categorised according to the medical dictionary of regulatory activities (MedDRA) 18.1 (or newer) terminology (table 1). Severity of adverse events, which will be graded based on clinical examination, and its implications for clinical management will be monitored as well.

Study data will be collected and managed using electronic case report forms (eCRFs) in the Research Electronic Data Capture system.46

### Imaging assessments

MR enterography will be performed in all patients at the time of diagnosis as part of their diagnostic workup. Additionally, patients with CD or an unclassified type of IBD will undergo MR enterography 12 months after diagnosis, and CD patients will also undergo it 5 years from diagnosis (tables 2 and 3). Results and images from any scheduled or unscheduled endoscopic assessments will be recorded. The images will be scored as specified in table 4. Paediatric patients younger than 16 with CD will receive an X-ray examination of the left hand and wrist to investigate growth impairment at the time of diagnosis, and repeatedly if indicated by their disease phenotype (table 3).

### Intestinal ultrasound

The infrastructure of the IBD Prognosis Study will be used to conduct substudies of the use of IUS in assessing disease burden and of its use as an early detector of disease progression. As such, IUS is planned at diagnosis, and again at 3, 6 (if FC-calprotectin is higher than 250 µg/g), and 12 months of follow-up, and annually thereafter. In case of IBD-related surgery, IUS will be performed preoperatively and as part of the postoperative assessment 6–12 months after surgery. Sonographic disease activity will be assessed in terms of bowel wall thickness, colour Doppler signal, inflammatory fat (i-fat) and bowel wall stratification. The IBUS-SAS score, which integrates these four items, will be calculated as well.47 Scans will be performed systematically of the entire bowel, including the sigmoid colon, descending colon, transverse colon, ascending colon, cecum, terminal ileum and the proximal small bowel. Image acquisition, grading of parameters and documentation will follow the recommendations by Novak et al.47 Additional details for the IUS substudies are described in online supplemental file 1.

### Patient-reported outcomes

As specified in table 5, validated patient-reported outcomes (PROs) of clinical disease activity, environmental factors, disability and health-related quality of life will be collected throughout the study.

<table>
<thead>
<tr>
<th>Time point</th>
<th>Collection of dental treatment needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after diagnosis</td>
<td>X</td>
</tr>
<tr>
<td>At 12 months of follow-up</td>
<td>X</td>
</tr>
<tr>
<td>Time after diagnosis</td>
<td>X</td>
</tr>
<tr>
<td>During the first year after diagnosis</td>
<td>X</td>
</tr>
<tr>
<td>During the second year after diagnosis</td>
<td>X</td>
</tr>
<tr>
<td>During years 6-20</td>
<td>X</td>
</tr>
</tbody>
</table>

**Table 2 Continued**

<table>
<thead>
<tr>
<th>Time point</th>
<th>Collection of dental treatment needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>X (X) indicates that the investigation will be performed if clinically relevant. MR enterography will be performed after 5 years in patients with CD. FIB4 will be calculated if a FIB4 calculation is greater than 1.45. MR, magnetic resonance; IUS, intestinal ultrasound.</td>
<td></td>
</tr>
</tbody>
</table>
Extra-intestinal assessments

MR cholangiopancreatography (MRCP) will be performed at the time of diagnosis and after 5 years in all adult patients with IBD to assess the occurrence and phenotype of co-occurring hepatobiliary diseases associated with IBD. An MRCP will only be performed in paediatric patients older than 6 years with two consecutive abnormal (more than two times the reference value) plasma alanine aminotransferase or Gamma-glutamyl transferase measurements. The imaging protocols are presented in online supplemental file 3.

Adult patients recruited during the first year of study will be examined by experienced rheumatologists, including a systematic clinical evaluation, MR of the spine and sacroiliac joints, as well as ultrasonographic evaluation of peripheral joints and entheses at the time of diagnosis and repeated after 5 years. The patients will also have a systematic analysis for Human Leucocyte Antigen B27 (HLA-B27) positivity, and will be asked to answer several PROs relating to rheumatological EIMs (online supplemental file 2). In addition, The Toronto Axial Spondyloarthritis Questionnaire on IBD (TASQ-IBD), which is a validated screening tool for extra-intestinal musculoskeletal symptoms will, along with the first examination and newly occurring rheumatological symptoms after 1 year, determine whether a patient will be offered an additional assessment 1 year after the diagnosis of IBD.

All adult patients recruited during the second year of study will be examined by experienced dentists, including a systematic clinical evaluation at the time of diagnosis and again after 12, 24 and 60 months. In addition, patients will be asked general questions on dental visit patterns, treatment needs, oral hygiene habits and occurrence of oral lesions, as well as questions on oral health-related quality of life (OHIP-5). Questions previously recommended for self-reported surveillance of periodontitis will also be asked to calculate the Periodontal Screening Score. Panoramic radiographs of the jaws will be recorded at baseline and after 5 years. The type and amount of dental treatment performed will be extracted annually from the Danish Health Insurance Registry (SSSY register).

All adolescent and paediatric patients included during the 2-year inclusion period will be offered an assessment by a paediatric rheumatologist including a systematic clinical evaluation and systematic ultrasonographic assessment of peripheral joints and entheses at the time of diagnosis and after 5 years.

### Table 3 Study timeline for paediatric and adolescent patients with inflammatory bowel diseases

<table>
<thead>
<tr>
<th>Time point</th>
<th>Time of diagnosis</th>
<th>During years 1–2 after diagnosis: Follow-up minimum every third month and at events</th>
<th>At 12 months of follow-up</th>
<th>During years 3–5 year after diagnosis: Follow-up minimum every 6 months and at events</th>
<th>60 months of follow-up</th>
<th>Years 6–20 Follow-up minimum annually and at events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening for inclusion</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant information and written informed consent (repeated at age 18)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of information from medical record including any medical adverse events</td>
<td>X X X X</td>
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<td>X X X X X X</td>
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<tr>
<td>Impact III questionnaire</td>
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<tr>
<td>Detailed environmental questionnaire</td>
<td>X</td>
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<tr>
<td>Clinical disease activity</td>
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<tr>
<td>Collection of faecal samples</td>
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<tr>
<td>Collection of blood sample</td>
<td>X</td>
<td></td>
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<tr>
<td>Collection of biopsies at endoscopy</td>
<td>X (X)</td>
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<td>(X)</td>
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<tr>
<td>Collection of saliva sample</td>
<td>X</td>
<td></td>
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<td>X X X X X X</td>
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<tr>
<td>MR cholangio-pancreatography</td>
<td>(X) (X)</td>
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<tr>
<td>MR enterography</td>
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<td></td>
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</tr>
<tr>
<td>Rheumatological assessment</td>
<td>X (X) (X)</td>
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<tr>
<td>Dermatological assessment</td>
<td>(X) (X) (X)</td>
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<tr>
<td>Left-hand radiograph for bone age</td>
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<tr>
<td>DXA scan</td>
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<tr>
<td>IUS</td>
<td>X (X)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Collection of dental treatment needs</td>
<td>X X X X X X</td>
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</tbody>
</table>

(X) indicates that the investigation will be performed if clinically relevant.

DXA, dual-energy X-ray absorptiometry; IUS, intestinal ultrasound.
Disease activity will be evaluated according to the Juvenile Arthritis Disease Score with the same frequency of examinations as adults.\textsuperscript{50} In addition, measurements of HLA-B27, antinuclear antibodies and rheumatoid factor will be performed in all adolescent and paediatric patients at the time of diagnosis of IBD.

Table 4  Study outcome measures and definitions

<table>
<thead>
<tr>
<th>Study outcome measures</th>
<th>Study outcome definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity in the adult population: Harvey-Bradshaw Index\textsuperscript{54} (HBI) for CD and Simple Clinical Colitis Activity Index\textsuperscript{55} (SCCAI) for UC and IBD-U</td>
<td>Abdominal surgery: IBD-related surgery including resection, colectomies, balloon dilatation, stoma surgery and perianal surgery</td>
</tr>
<tr>
<td>Disease activity in the paediatric population: abbreviated Paediatric CD Activity Index for CD\textsuperscript{56} (abbPCDAI) and Paediatric UC Activity Index\textsuperscript{57} for UC and IBD-U (PUCAI)</td>
<td>Perianal surgery: any perianal procedure related to fistula or abscesses in the perianal area</td>
</tr>
</tbody>
</table>
| Endoscopic activity: Mayo Endoscopic Score\textsuperscript{58} in UC and SES-CD\textsuperscript{59,60} in CD patients | Clinical disease activity, defined as follows:

- Adult CD: HBI (scores ≤4: clinical remission; scores 5–7: mild disease; scores 8–16: moderate disease; scores >16: severe disease)\textsuperscript{54,64}
- Paediatric CD: abbPCDAI (scores 0–9: inactive disease; scores 10–15: mild disease; scores 16–25: moderate disease; scores >25: severe disease)
- Perianal disease in CD: Perianal Disease Activity Index (scores ≤4: clinical remission; scores >4: active disease)\textsuperscript{65}
- Adult UC: SCCAI (scores ≤2: clinical remission; scores 3–5: mild disease; scores 6–11: moderate disease; scores ≥12: severe disease)
- Paediatric UC: PUCAI (scores 0–9: inactive disease; scores 10–34: mild disease; scores 35–64: moderate disease; scores 65–85: severe disease)

Endoscopic disease activity, defined as follows:

- CD: SES-CD (scores <2: endoscopic remission; scores 3–6: mild endoscopic activity; scores 7–15: moderate endoscopic activity; scores >15: severe endoscopic activity)\textsuperscript{59,60}
- UC: Mayo Endoscopic Score (scores >1: active disease)\textsuperscript{58}

Non-response/loss of response to medical treatment: either no change or an increase in disease activity following treatment initiation

Malignancy: Any malignancies will be registered

Mortality: All-cause mortality will be registered

Biological treatment including time to this end-point and indicated hereof: Treatment of IBD or IMIDs with biological therapies, including antibodies against TNF-\(\alpha\), integrin \(\alpha_4\beta_7\), IL12/23, JAK inhibitors and future anti-IBD targets and small molecules

In paediatric IBD: Growth impairment, as defined by the Paris classification\textsuperscript{63}

In paediatric IBD: Delayed onset of puberty defined as no breast development at age 13 in girls or a bilateral testis volume of less than 3mL at age 14 in boys

Occurrence of gingivitis or periodontitis according to the current classification system,\textsuperscript{66,67} occurrence of caries, occurrence of endodontic lesions, and occurrence and reason for tooth loss, occurrence of peri-implantitis\textsuperscript{58}

CD, Crohn’s disease; EIMs, extra-intestinal manifestations; IBD, inflammatory bowel disease; IMIDs, immune-mediated inflammatory diseases; IUS, intestinal ultrasonography; PROs, patient-reported outcomes; SES-CD, Simple Endoscopic Score for Crohn Disease; UC, ulcerative colitis.

However, in contrast to adult patients, adolescent and paediatric patients will only receive an MR scan of the spine and sacroiliac joints at the diagnosis of IBD if it is considered clinically relevant.

Adolescent and paediatric patients recruited during the second year of study will not be examined by dentist; however, dental radiographs will be requested annually from the national paediatric dental system (‘Skoletandpleje’). Additionally, the number and type of periodontal treatments, fillings and endodontic treatments will be collected annually via the Danish Health Insurance Registry (SSY register).

All patients who present dermatological manifestations will have these abnormalities photodocumented and evaluated by a dermatologist. If determined to be clinically relevant, the patient will be invited to a physical examination by a dermatologist, who will focus on IBD-associated EIMs and IMIDs, for example, hidradenitis suppurativa, pyoderma gangrenosum, erythema nodosum and psoriasis, which will be recorded in detail. Furthermore, all patients will undergo a regular screening by questionnaires for abscesses that could indicate hidradenitis suppurativa.\(^\text{34}\) In such cases, an experienced hospital dermatologist will make an assessment and any instances of hidradenitis suppurativa will be scored according to the recommended scoring indices (online supplemental file 2). When considering dermatological adverse events with difficulty in distinguishing these from new-onset distinct dermatological diseases, we will refer these patients to dermatologists as described above.

Finally, all adult, adolescent and paediatric patients are offered examination with a dual-energy X-ray scan at the time of diagnosis and after 5 years of follow-up to explore the occurrence and course of osteopenia and osteoporosis. Fibroscans are performed whenever patients present biochemical and clinical signs of chronic liver diseases.

### Food purchase data

Adult patients are invited to participate in a substudy focusing on consumer data. Purchase data are to be automatically logged and collected throughout the study period using a mobile app, Storebox, which records all payment receipts made with credit cards, from participants using the digital receipt provider Storebox.\(^\text{32}\) The aim of the substudy is to assess the purchase behaviour and its association and interplay with the disease course of IBD. Currently, more than one million Danes use the digital receipts provider, which covers three out of the six largest supermarket chains in Denmark. This method allows for in-depth and large-scale description of food intake pattern over time, without the need for participants to invest their time in the sub study actively. Unfortunately, this method cannot distinguish food bought for the patients from those bought for offspring or partners.

### Biological samples

Biological samples, including blood samples, rectal swabs, stool samples, saliva samples and swabs of the oral cavity, will be collected at the time of diagnosis and prospectively during each scheduled and unscheduled follow-up visit, as well as at the time of disease events in all participants. The biobanking of blood samples includes plasma, serum, and saliva samples and swabs of the oral cavity.

At the time of diagnosis, four intestinal tissue biopsies (two snap-frozen and two held in RNAlater) or two intestinal tissue biopsies (one snap-frozen and one held in RNAlater) will be collected from five predefined intestinal segments, according to presence or absence of macroscopic inflammation, respectively. The five segments include the terminal ileum, cecum, transverse colon, sigmoid colon and rectum. Following diagnosis, two samples (one snap-frozen and one held in RNAlater) will be collected from each segment and will be handled as described in Table 6. Additional biopsies will be collected from other segments in the presence of inflammation.

### Patient and public involvement statement

No patients were involved in formulating the research question or the outcome measures, nor in planning the study design.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Questionnaires and patient-reported outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult cohort</td>
</tr>
<tr>
<td>Disease-specific</td>
<td>For Crohn’s disease</td>
</tr>
<tr>
<td></td>
<td>HBI(^\text{54})</td>
</tr>
<tr>
<td></td>
<td>SCCAI(^\text{56})</td>
</tr>
<tr>
<td>Quality of life</td>
<td>EQ-5D(^\text{69})</td>
</tr>
<tr>
<td>Evaluation of musculoskeletal and dermatological symptoms</td>
<td>Section 3.3.4 and online supplemental file 2</td>
</tr>
<tr>
<td>Environmental factors</td>
<td>Revised version of environmental factors scheme by IOIBD(^\text{74})</td>
</tr>
<tr>
<td></td>
<td>Dietary questionnaire (‘Hjertekost’)(^\text{75})</td>
</tr>
</tbody>
</table>

AbbvCDAI, Abbreviated Paediatric CD Activity Index; EQ-5D, European Quality of life - 5 Dimensions; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HBI, Harvey-Bradshaw Index; IBD-DI, Inflammatory Bowel Disease-Disability Index; IOIBD, International Organisation of Inflammatory Bowel Disease; JADAS, Juvenile Disease Activity Score; PDAI, Perianal Disease Activity Index; SCCAI, Simple Clinical Colitis Activity Index; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.
Analysis plan for biological samples
Microbiota analysis and microbiota DNA sequencing

Stool and saliva samples will be analysed for microbiota, which will undergo 16S and 18S PCR (examining bacteria, fungi and parasites), Illumina sequencing and annotation of DNA sequences to the species level. These data will be analysed with in-house R-scripts or equivalent current standard platforms that will identify both quantitative and qualitative differences in microbiota between specific groups of patients.

Human metagenomic analysis

After removing the human sequences from the computer set by aligning the reads against the human reference genome, the remainder will then be compared with databases containing reads from previously identified pathogens and our own WGS database using the software MGmapper (https://cge.cbs.dtu.dk/services/MGmapper/) or the equivalent current standard analysis platforms. To confirm that the microorganisms we find can be identified in the metagenomics analyses, we will perform single-nucleotide polymorphism analysis of the corresponding sequences found in the microbiome.

RNA and protein extraction and analysis in both adult and paediatric populations

Buffy coat, intestinal biopsies and saliva samples will be analysed using a multiomics approach. RNA will be extracted from the standard punch biopsies of the intestine collected in RNAlater. Biopsies will then be transferred to a lysis buffer, homogenised and total RNA extracted simultaneously with protein and DNA fractions.

Global gene expression is to be analysed by RNA sequencing (Illumina PE150 system, Illumina, San Diego, California, USA) or the available platform at the time of analysis. Furthermore, gene analysis will focus on genes

---

**Table 6  Biobank of the IBD prognosis study**

<table>
<thead>
<tr>
<th>Biological sample</th>
<th>Medium/vial</th>
<th>Processing</th>
<th>Aliquoting</th>
<th>Storage</th>
<th>No of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>9mL EDTA tube</td>
<td>Centrifugation at 3500 rpm at room temperature for 10 min</td>
<td>3x EDTA plasma for protein analysis</td>
<td>−80°C</td>
<td>2x 1x 2x</td>
</tr>
<tr>
<td>9mL serum tube</td>
<td>Sedimentation at room temperature for 30 min. Thereafter, centrifugation at 3500 rpm at room temperature for 10 min</td>
<td>4x serum for protein analysis</td>
<td>−80°C</td>
<td>2x 1x 1x</td>
<td></td>
</tr>
<tr>
<td>2.5mL PAX-gene RNA blood tube</td>
<td>21°C: 2 hour → −20°C: 24 hours → −80°C</td>
<td>1x blood for RNA analysis</td>
<td>−80°C</td>
<td>2x 1x 1x</td>
<td></td>
</tr>
<tr>
<td>4mL EDTA tube</td>
<td>Direct storage</td>
<td>Whole blood storage</td>
<td>−80°C</td>
<td>2x</td>
<td></td>
</tr>
<tr>
<td>Swab</td>
<td>Faecal swab</td>
<td>Direct storage</td>
<td>1x faecal sample for DNA analysis</td>
<td>−80°C</td>
<td>2x 1x 1x</td>
</tr>
<tr>
<td>Stool</td>
<td>Faecal tube with 96% ethanol</td>
<td>Direct storage</td>
<td>4x faecal sample for DNA analysis</td>
<td>−80°C</td>
<td>2x 2x 2x</td>
</tr>
<tr>
<td>Intestinal biopsy</td>
<td>RNA later stabilisation solution</td>
<td>Storage at room temperature for 24 hours</td>
<td>1x biopsy for RNA analysis</td>
<td>−80°C</td>
<td>2x per segment 1x per segment 1x per segment</td>
</tr>
<tr>
<td>Liquid nitrogen</td>
<td>Direct storage</td>
<td>1x biopsy for backup</td>
<td>−80°C</td>
<td>2x per segment 1x per segment 1x per segment</td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>Unstimulated saliva sample</td>
<td>Direct storage (dry ice and in transport medium)</td>
<td>1x</td>
<td>−80°C</td>
<td>1x 1x 1x</td>
</tr>
<tr>
<td>Swab</td>
<td>Direct storage (dry ice and in transport medium)</td>
<td>2x</td>
<td>−80°C</td>
<td>2x 2x 2x</td>
<td></td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel diseases.
related to IBD pathogenesis, EIM pathogenesis and pharmacodynamics and kinetics of IBD-related medicine. PCR analysis, Western blotting and immunohistochemistry will subsequently be used on the same subgroup of patients to confirm expression patterns of interest.

Live peripheral blood mononuclear cells derived fromuffy coat from blood samples will be archived in a subset of the patients and handled in order to perform single-cell characterisation, including single-cell sequencing and multiparameter cytometry, to characterise the composition and activation status of innate and adaptive cell populations.

For the assessment of proteome profiles, the isolated protein fraction will be investigated with antibody-based multiplex analyses detecting proteins related to inflammation, barrier function, tissue degeneration, regeneration and fibrosis.

Blood samples will be centrifuged to obtain plasma and stored at −80°C until needed for characterisation of preselected plasma proteins using inflammation assays.

Finally, metabolomics will be applied for the analysis of gut microbial metabolism as well as metabolic changes in patients with IBD using proton nuclear MR (1H-NMR) spectroscopy or mass spectrometry (MS).

**Statistical analysis**

Statistics will be computed using IBM SPSS software V.28.0.1 or R V.4.1.0 or newer. Descriptive analysis of the baseline characteristics of the overall population and by gender will be conducted. Continuous variables will be presented as mean±SD or median with IQRs and counting data will be presented as number and percentage (n, %). Comparison of groups will be conducted using t-test or Wilcoxon rank-sum test based on the type of distribution of data and homogeneity of variance. $\chi^2$ test or Fisher’s exact probability method will be used for counting data as appropriate.

The incidence rate of UC and CD and their disease events, as previously defined, will be estimated as the number of new cases of UC/CD or events divided by the total person-time at risk. The person-time at risk for each individual will be estimated as the time each participant remains free of events during the 20 years follow-up period. Survival analysis will be conducted using Kaplan-Meier curves and Cox proportional hazards method to calculate HRs with 95% CIs. In addition, multiple linear and logistical regression analysis will be used to evaluate the association between outcomes and potential risk factors. All models will be adjusted for potential confounding factors. In these regression analyses, missing data will be handled by the multiple imputation method. Participants lost to follow-up will be treated as right-censored data. A two-sided significance level of 0.05 will be used for all primary and secondary analyses unless stated otherwise.

Comparison of adult and paediatric data is not preprotocolled but might be conducted based on the findings.

**ETHICS AND DISSEMINATION**

The protocol has been approved by the Ethics Committee of the Capital Region of Denmark (H-20065831) and the Danish Data Protection Agency (P-2020-1065). The study will be conducted in accordance with the ethical principles outlined in the current version of the Declaration of Helsinki and all applicable local regulatory requirements. Study results will be published according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

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**Competing interests** HRS: HRS has received honoraria as speaker from Sanofi Genzyme, Denmark and Novartis, Denmark, as consultant from Sanofi Genzyme, Denmark, Lophora, Denmark, and Lundbeck AS, Denmark, and as...
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**REFERENCES**

Supplementary File 1: Intestinal ultrasonography studies

Validation of IBUS-SAS

**Aims:** To validate the Intestinal Bowel Ultrasound Group Segmental Activity Score (IBUS-SAS) against objective measures of inflammatory activity in Crohn’s Disease (CD).

**Methods:** Intestinal ultrasonography (IUS) will be performed on all patients from the cohort. Acquisition and documentation of all scans will include a minimum of three cine loops (one cross-sectional, one longitudinal, and one with colour Doppler imaging) for all pathological segments\(^1,2\). In non-pathological segments, one still image will be recorded. The sonographer will assess IBUS-SAS from the worst segment and will assess all segments for the presence of transmural remission (defined as BWT of 3 mm or less without colour Doppler signal)\(^3\). The baseline and one-year follow-up scans of CD patients recruited within the first year of study will be centrally read (blinded to other measures of inflammation) by two experts in IUS and used for subsequent analyses.

**Statistics:** IBUS-SAS scores will be correlated to SES-CD\(^4\) and MARIAs\(^5\) for each patient and segment using Spearman’s coefficient test. The accuracy of IBUS-SAS for predicting active disease (including subclassifications, as described in Table 4) will be evaluated by the receiver operator characteristic area under the curve. Kappa statistics will be used to assess agreement between SES-CD, MARIAs, and faecal calprotectin (FC) for binary classification of active and severe disease. Responsiveness: Changes in IBUS-SAS scores will be examined on a segmental basis and compared to changes in SES-CD and MARIAs. IBUS-SAS from ulcerated segments at baseline will be compared with one-year follow-up IBUS-SAS for those in endoscopic remission and those not in endoscopic remission.

**The predictive value of IUS**

**Aims:**
To determine which IUS parameters at diagnosis and at three months, as well as the absolute and relative changes between the two timepoints, most accurately predict objective signs of response/remission one year after diagnosis.

**Methods:**
Patients in the cohort are scanned with IUS at diagnosis and after three months of follow-up. The sonographer will assess the IBUS-SAS score on the most affected segment and will assess all segments for the presence of transmural remission (defined as BWT of 3 mm or less without colour Doppler signal)\(^3\). As specified in the study protocol, all patients are expected to undergo ileocolonoscopy 12 months after diagnosis with endoscopic assessment using the Simple Endoscopic Score in CD (SES-CD)\(^4\) for patients with CD and the Mayo Endoscopic Score\(^6\) for patients with ulcerative colitis (UC) or unclassified inflammatory bowel disease (IBD-U).

**Statistics**
The distinct parameters within the IBUS-SAS score measured at diagnosis and after three months of follow-up, as well as any absolute and relative changes between the two timepoints, will be correlated to the primary and secondary outcomes defined below. Prospective IUS response is defined as a reduction of bowel wall thickness (continuous measurements) of more than 25%, or more than 2.0 mm, or of more than 1 mm in combination with one colour Doppler signal reduction.

**Primary outcome:**
Endoscopic response/remission in CD and UC/IBD-U at 12 months.
For patients with CD, endoscopic remission is defined as a SES-CD score less than 2 and endoscopic response as a reduction in SES-CD of more than 50% for CD. For patients with UC/IBD-U, endoscopic remission is defined as a Mayo Endoscopic Score of 0 and endoscopic response is defined as a 50% reduction.

Secondary outcomes within one year of follow-up:
Abdominal surgery for IBD, including resection, balloon dilatation, strictureplasty, stoma surgery and perianal surgery
Hospital admission for IBD
Treatment intensification, including initiation, change or dose escalation of biological treatment for IBD
Biochemical remission, defined as a FC less than 250 μg/g or C-reactive protein less than 5 mg/L
Clinical remission, defined as HBI of 4 or less in CD and a SCCAI score of 2 or less in UC

References
Supplementary File 2: Questionnaires and Clinical Assessments of Extra-Intestinal Manifestations in The IBD Prognosis Study

Rheumatological assessments

Clinical evaluation and composite indices

- Ankylosing Spondylitis Disease Activity Score (ASDAS) CRP
- The Bath Ankylosing Spondylitis Metrology Index (BASMI)
- Disease Activity Index (DAS28/DAS44) CRP
- Clinical Disease Activity Index (CDAI)
- Thorax expansion
- Swollen and tender joint count
- SPARCC Enthesitis Index
- Leeds Enthesitis Index
- Symptomatic SpA features
- Physician global assessment (VAS 0-100)

Patient-reported outcomes

- Pain VAS
- Back pain VAS
- Patient global assessment of disease activity
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- The Bath Ankylosing Spondylitis Functional Index (BASFI)
- Health Assessment Questionnaire (HAQ)
- Patient Acceptable Symptom State (PASS)
- The musculoskeletal disease status as assessed by the patient at the current visit, with the last visit as an anchor
- Evaluation of central sensitization of the pain
- Widespread Pain Index (WPI)
- Symptom Severity Scale (SSS)
- Tender points

Dermatological assessment

- Photo documentation of any skin changes or abnormalities, to be evaluated by an experienced dermatologist. If deemed relevant, patients will be invited to a physical examination by a dermatologist
- Systematic screening for the presence of hidradenitis suppurativa using a questionnaire
- Systematic screening for the presence of pyoderma gangrenosum with HBI, SCCAI, and general questioning about wounds and ulcers
- Assessment of hidradenitis suppurativa with:
  - Hurley stages
  - Hidradenitis Suppurativa Score (HSS)
• Dermatology Quality of Life Index

• Assessment of pyoderma gangrenosum: PARACELSUS score

**Dental assessment**

• Clinical and radiographic full-mouth examination to assess:
  - number of lost teeth
  - periodontitis grade and stage
  - number of endodontically treated teeth
  - number of periapical lesions
  - number of decayed teeth/number of filled teeth
  - number and type of prosthetic reconstructions/number of dental implants
  - number of dental implants with peri-implantitis

• Register-based assessment of dental treatment needs

• General questions on dental visits, treatment needs, oral hygiene habits, and occurrence of oral lesions

• Oral Health Impact Profile (OHIP)-5
  - Periodontal Screening Score (PESS)

**References**


Supplementary File 3: MR Protocol for The IBD Prognosis Study

Procedures prior to, and during, the scans:

1) **Fasting**: 4 hours
2) **MRCP**: Duration: 30 minutes
3) **MR total spine**: Duration: 30 minutes
4) **MR of sacroiliac joints**: Duration: 10 minutes
5) **Contrast**: 2 x 450 ml bariumsulfat contrast (Neulumex) over 40 minutes. The next scan will be conducted 20 minutes later.
6) **MR Enterography**: Duration: 30 minutes.

Technical setup for MR scans:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Plane</th>
<th>Slice thickness (mm)</th>
<th>Distance (mm)</th>
<th>In-plane resolution (mm)</th>
<th>Contrast agent (oral/i.v.)</th>
<th>Motion artifact reduction (bh/trig/bus)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MRCP</strong></td>
<td>T2w</td>
<td>axial</td>
<td>7</td>
<td>0.7</td>
<td>1.5x1.5</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>T1w</td>
<td>in/out</td>
<td>5</td>
<td>0.5</td>
<td>1.3x1.7</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>T2w</td>
<td>radial</td>
<td>40</td>
<td>-</td>
<td>1x1.2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>T2w 3D</td>
<td>axial obl.</td>
<td>1.6</td>
<td>0</td>
<td>1x1.3</td>
<td>-</td>
</tr>
<tr>
<td><strong>SPINE</strong></td>
<td>STIR</td>
<td>sagittal</td>
<td>4</td>
<td>0.8</td>
<td>1x1.2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>T1w</td>
<td>sagittal</td>
<td>4</td>
<td>0.8</td>
<td>1x1.2</td>
<td>-</td>
</tr>
<tr>
<td><strong>Sacro iliac joints</strong></td>
<td>STIR</td>
<td>axial obl.</td>
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<td>0.8</td>
<td>1x1.2</td>
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<tr>
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<td>T1w</td>
<td>axial obl.</td>
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<td>0.8</td>
<td>1x1.2</td>
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<tr>
<td><strong>Enterography</strong></td>
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<td>coronal</td>
<td>4</td>
<td>-</td>
<td>2x2</td>
<td>oral</td>
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<tr>
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<td>-</td>
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<td>oral - i.v.</td>
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<td>2x3</td>
<td>oral - i.v.</td>
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<td>1.5x1.5</td>
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<td>1.4x1.6</td>
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<td>Balanced GRE</td>
<td>axial</td>
<td>5</td>
<td>-1</td>
<td>1.9x2.1</td>
<td>oral - i.v.</td>
</tr>
<tr>
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<td>Balanced GRE</td>
<td>axial</td>
<td>5</td>
<td>-1</td>
<td>1.9x2.1</td>
<td>oral - i.v.</td>
</tr>
</tbody>
</table>

Contrast agents, oral - barium sulfate suspension, 0.1% w/v (Neulumex) 2x450 ml in 40 minutes. Finished 20 min before scan start; i.v., gadolinium-based contrast agent 0.1 mmol pr kg body weight; motion artifact reduction, bh – breath hold; trig, respiratory triggering; bus, Hyoscinbutylbromid (Buscopan) 20 mg i.v.; "e-thrive / VIBE; Balanced GRE, balanced FFE / True FISP.