PredictSURE-IBD and IBDX to guide personalised treatment of Crohn's disease in adults

DAR PROTOCOL

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Title: PredictSURE-IBD and IBDX to guide personalised treatment of Crohn's disease in adults

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TABLE OF ABBREVIATIONS

Abbreviation	In full
CASP	Critical Appraisal Skills Programme
CDAI	Crohn's Disease Activity Index
CDSR	Cochrane Database of Systematic Reviews
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
DARE	Database of Abstracts and Reviews of Effects
EAG	Evidence assessment group
FCP	Faecal calprotectin
HBI	Harvey–Bradshaw Index
HSUV	Health state utility values
HTA	Health technology assessment
IBD	Inflammatory bowel disease
ICER	Incremental cost-effectiveness ratio
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
PCR	Polymerase chain reaction
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies tool – 2
RCT	Randomised controlled trial
ROBINS-I	Risk Of Bias In Non-randomised Studies – of Interventions
RT	Reverse transcriptase
SLR	Systematic literature review
TNF	Tumour necrosis factor
UK	United Kingdom

1 PLAIN ENGLISH SUMMARY

Crohn's disease is a type of inflammatory bowel disease that can affect any part of the digestive tract, and the section and size of the inflamed part of the intestine vary from person to person. The areas of inflammation are often irregular, with sections of healthy intestine between affected parts. The cause of Crohn's disease is not known. Environmental factors, such as smoking and certain medications (e.g., antibiotics), genes, and the immune system are thought to have a part in the development of and course of Crohn's disease.

Symptoms of the disease include pain in the abdomen, severe diarrhoea, tiredness, and weight loss. Crohn's disease can also cause problems outside the gastrointestinal tract, which are known as extraintestinal manifestations. People with Crohn's disease might also develop arthritis, and skin and eye problems. In severe cases, Crohn's disease can lead to life-threatening complications. Symptoms of Crohn's disease can be different from person to person, and there is no one test to identify the condition so diagnosing the disease is difficult.

Although there is no cure for Crohn's disease at this time, treatments are available that can manage the symptoms, and, in some cases, can lead to someone having no symptoms for a long time (remission). Drugs are given to reduce the inflammation, with a corticosteroid usually the first treatment. If symptoms do not improve with a corticosteroid, the next option is a drug that blocks the response of the immune system (immunosuppressant), which can be given on its own or with a corticosteroid. Some immunosuppressants are known as biologics (e.g., infliximab), and, although these therapies are more effective at improving symptoms, they can have side effects and are often used when symptoms are severe and do not respond to other treatments.

Some people with Crohn's disease have symptoms (known as a flare) much more often than others, and, as a result, are at a higher risk of complications of their disease. Symptoms can vary from mild cramping and diarrhoea to severe abdominal pain or blockages of the bowel. Identifying who will have flares more often is difficult, because there is no test available that can accurately predict long-term disease course. Using clinical judgement and a person's history, clinicians try to identify a person as being at risk of having a severe course of disease and decide to treat these people earlier with biologics. However, because of the possibility of side effects, there are concerns about giving biological therapies to people if symptoms could be managed with corticosteroids and immunosuppressants. Various biomarkers have been identified that are linked with having a higher risk of severe course of Crohn's disease, and diagnostic tools have been developed to identify people who have the characteristic biomarkers. Predicting which people are at risk of long-term complications of their Crohn's disease could lead to improved clinical outcomes because clinicians might be able to personalise treatment.

The aim of this project is to review the clinical scientific evidence, and to assess the costs and benefits associated with the use of two prognostic tools — the PredictSURE-IBD™ and the IBDX — to identify those with Crohn's disease at a high risk of having a severe course of disease.

2 DECISION PROBLEM

2.1 Aim of the assessment

The aim of this diagnostic assessment review is to assess the test accuracy and clinical and cost-effectiveness of two molecular diagnostic tools for inflammatory bowel disease (IBD) in identifying those at a high-risk of severe course of disease, with a restriction to Crohn's disease for this project. The tools assessed in the review reported here are PredictSURE-IBD™ and the Crohn's disease Prognosis Test (IBDX). At the time of writing, no validated test or algorithm is available to stratify people with Crohn's disease by risk of developing complications of disease. Presence of known risk factors for flare and for complications in Crohn's disease could influence the treating clinician's management of the condition, but consensus on use of risk factors to determine prognosis of disease has yet to be achieved and treatment can vary. The accuracy, clinical and cost-effectiveness of the diagnostic tools will be evaluated against standard clinical care in the National Health Service (NHS), based on input from clinical advisors, when assessing the likely course of Crohn's disease.

2.2 Population and target condition

2.2.1 Population: High risk of severe course of Crohn's disease

IBD is characterised by chronic inflammation of the gastrointestinal tract and primarily comprises two subtypes of disorder – Crohn's disease and ulcerative colitis.[1-3] The symptoms of Crohn's disease and ulcerative colitis are similar, and both types of IBD affect men and women equally.[1-3] Crohn's disease and ulcerative colitis are lifelong conditions for which there is no cure, the courses of which are characterised by recurring cycles of exacerbation (also referred to as flare) and remission. The key differences between the conditions are the section of the intestine affected, and the extent of inflammation. Ulcerative colitis is limited to the colon, whereas Crohn's disease can occur anywhere between the mouth and the anus. Additionally, whereas ulcerative colitis affects only the inner most lining of the colon, Crohn's disease can penetrate into all layers of the bowel wall.

Flares of IBD indicate a return to active disease and, potentially, symptoms for an individual. Several factors have been proposed as triggers for flare, including poor adherence to treatment, certain medications (e.g., antibiotics and non-steroidal anti-inflammatory drugs), infection, smoking, and emotional stress.[4, 5] As has been noted in other immune-mediated diseases, the course of Crohn's disease and ulcerative colitis varies widely among affected individuals, making it challenging to predict the severity or frequency of occurrence of flare.

Endoscopic assessment and biopsies provide data on level of disease activity in IBD but do not give an insight into factors for relapse and course of disease. Evaluating blood and stool-based biomarkers of inflammation, such as C-reactive protein (CRP) and faecal calprotectin (FCP), is less invasive than

endoscopy and such laboratory tests provide reproducible, quantitative results that, together with clinical assessment, can aid clinicians in the diagnosis and management of IBD. However, serum and faecal biomarkers have limited application in the prediction of the severity of the course of IBD in the longer term.[6] With no validated prognostic marker available, clinicians and patients use their judgement and experience to determine an individual's risk of developing a severe course of disease, with the goal of reducing or preventing future exacerbations of disease.

2.2.2 Target condition: Crohn's disease

Crohn's disease can affect any segment of the gastrointestinal tract, but the most commonly affected areas are the end of the ileum (the last part of the small intestine) and the colon.[7] Diseased segments are frequently separated by intervening areas of healthy bowel tissue.[2, 8] The size of the inflamed area may be limited to a few centimetres, or could affect an extensive part of the bowel.[2, 8] As well as affecting the lining of the gastrointestinal tract, Crohn's disease may also penetrate the wall of the bowel.

As Crohn's disease can affect any part of the gastrointestinal tract, and to different extents, there is considerable variation in the symptoms experienced at the individual level by people with the disease, making recognition and diagnosis difficult.[2, 8] Moreover, symptoms and severity of disease can change over time. People with Crohn's disease most commonly present with:[2, 8, 9]

- abdominal pain;
- altered bowel pattern, including diarrhoea (mucus, pus or blood may be mixed with the diarrhoea);
- tiredness and fatigue;
- loss of appetite and weight loss;
- anaemia.

Neither the underlying aetiology of Crohn's disease nor the factors that determine the course and prognosis of the disease are fully understood. Environmental factors (e.g., smoking), genes, and the immune system are thought to have a part in the development of and course of Crohn's disease.[2, 8] Those who develop Crohn's disease that follows a non-severe course might achieve prolonged remission with no treatment. With medical treatment, and with or without surgery:[10]

- about 50% of patients will be in remission or have mild disease over the subsequent 5 years;
- 45% of those in remission will remain relapse-free over the next year;

- 35% will have one or two relapses;
- 11% will have chronically active disease.

For those in remission with Crohn's disease after treatment, relapse rates at 1, 2, 5, and 10 years are estimated at 20%, 40%, 67%, and 76%, respectively.[11] In contrast to a non-complicated course of Crohn's disease, cases characterised as following a severe course are likely to experience more frequent flares, and typically require early aggressive treatment strategies, including multiple treatment escalations and augmentation. People with severe forms of Crohn's disease are at high risk of complications of disease, including intestinal obstruction, fistulae and perianal disease, and progressive disability and need for surgery.[2, 8, 9]

Crohn's disease can also cause problems outside the gastrointestinal tract, which are known as extraintestinal manifestations.[9] Associated conditions typically occur during flare, but can also manifest during remission or before development of any signs of IBD. Conditions developing as a result of Crohn's disease include:[9]

- arthritis (more commonly of the large joints of the arms and legs, including the elbows, wrists, knees and ankles);
- skin problems, most commonly erythema nodosum;
- eye problems (episcleritis, scleritis and uveitis).

Crohn's disease is a debilitating disease, having a marked impact on physical and emotional health, as well as quality of life. Additionally, Crohn's disease is associated with high economic burden due to disability, loss of work productivity, surgery and hospitalisation.[12] In 2015, a UK study estimated the annual cost of care for a person with Crohn's disease to be £6,156 (£1,800 for those in remission compared with £10,513 for those experiencing relapse),[13] which translates to a total annual cost of ~£700 million. Five years after onset, 15% to 20% of people are affected to some degree by their disease, and between 50% and 80% of people with Crohn's disease will eventually need surgery as a result of, for example, development of strictures, perforation of the bowel, or failure of drug therapy.[14]

2.2.3 Epidemiology

Crohn's disease can appear at any age, but more than 90% of people will develop symptoms before the age of 40.[15] In the UK, it is estimated that Crohn's disease affects one in every 650 people[9] and that there are at least 115,000 people with the condition.[8] Incidence and prevalence of Crohn's disease have been rising since the mid-1970s, with highest rates observed in Northern Europe and North America.[16]

Incidence of Crohn's disease in the UK is reported to be about 8 per 100,000 people per year,[17, 18] with an age–sex adjusted point prevalence of 144.8 per 100,000 people.[18]

2.2.4 Current diagnostic and treatment pathways

2.2.4.1 Diagnosis of Crohn's disease

The symptoms of Crohn's disease are common to various conditions, which makes diagnosis of the condition challenging. Furthermore, there is no single test to diagnose definitively Crohn's disease, and diagnosis is reached through a combination of clinical examination, laboratory tests, imaging assessment, and endoscopy.[19]

On diagnosis of Crohn's disease, guidelines recommend that subsequent investigations focus on assessing level of activity of disease, as well as risk of complications in the longer term.[20] Three key areas are assessed when determining the severity of Crohn's disease: impact of the disease on the individual (e.g., clinical symptoms, quality of life, fatigue, and disability); burden of disease (e.g., C-reactive protein, mucosal lesions, upper gastrointestinal involvement, and disease extent); and course of disease (e.g., structural damage, perianal disease, number of flares, and extraintestinal manifestations).[21]

Two clinical tools available to assess level of disease activity are the Crohn's Disease Activity Index (CDAI)[22] and the Harvey–Bradshaw Index (HBI).[23] The HBI is a simple derivative of the CDAI, and the two tools are correlated, with a change in the CDAI of 100 points corresponding to a 3-point change in the HBI.[24] Clinical experts commented that, in clinical practice, their preference is for the HBI tool, as the CDAI is impractical for routine clinical assessment and its use is typically limited to clinical trials. Severity of disease activity is categorised as:[25]

- clinical remission: CDAI score of ≤150, which corresponds to a HBI score of ≤4;
- mild: CDAI score of 150–220, which corresponds to a HBI score of 4–8;
- moderate–severe: CDAI score of 220–450, which corresponds to a HBI score of ≥8;
- severe fulminant disease: CDAI score of ≥450, which corresponds to a HBI score of ≥15.

IBD activity and severity could be considered a continuum, and some people might not easily be categorised based on their symptoms. Moreover, the CDAI and HBI are based on subjective measures, and there is a move to using more objective parameters and the presence or absence of bowel destruction to assess severity.[20] Using patient-reported outcomes to assess disease activity in Crohn's disease is also becoming more common. Often used to guide treatment recommendations, the CDAI and HBI scores

represent status of activity at a point in time and do not account for long-term prognosis or course of disease.[26]

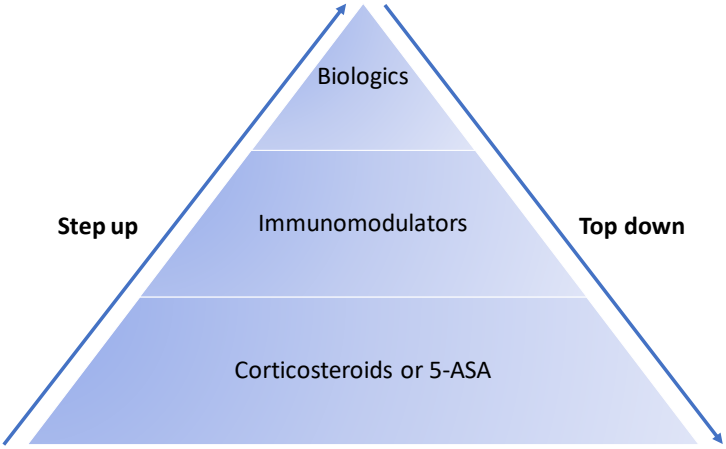
As well as assessing clinical parameters, clinicians might use physical characteristics, symptoms and results from imaging and laboratory to gauge a person's risk of experiencing a severe course of disease, and identify those who could benefit most from early use of aggressive treatments (immunosuppressors and biological therapies).[25] Prognostic factors associated with a more complicated disease course include bowel damage, extraintestinal manifestations of disease, number of flares, need for glucocorticoids, and resultant hospitalisations.[26] Other risk factors for a worse course of disease include smoking, and fistula formation. Factors at diagnosis of disease that were found to be associated with a worse prognosis were young age (<40 years), presence of perianal disease, and initial need for corticosteroid treatment.[25] A person's Crohn's disease may be considered to be following a severe course if they have refractory or relapsing disease necessitating multiple treatment escalations (dose increases and/or add-on treatment), development of significant complications (e.g., irreversible penetrating or stricturing lesions), need for more than one surgery, need for hospitalisation, or a combination of the listed factors. There is no consensus or algorithm available outlining how to combine known risk factors to determine long-term course of disease, and estimation of prognosis is based on subjective clinical judgement.

Being able to better predict the course of Crohn's disease would help clinicians and people with the condition to decide on the most appropriate treatment to manage symptoms. Tools such as the PredictSURE-IBD™ and IBDX could potentially help achieve the goal of personalising treatment in Crohn's disease.

2.2.4.2 Management of Crohn's disease

As noted earlier, there is no cure for Crohn's disease and, at the time of writing, the goal of treatment is to initially control or reduce symptoms to induce remission.[12] Once symptoms are under control, maintenance treatment might be given to prolong remission and prevent relapse.[12] Globally, there are two treatment algorithms followed in the management of Crohn's disease – the "step up" and "top down" approaches (Figure 1) – both of which involve several tiers of medication, and, as the names suggest, are the inverse of each other.[27]

Figure 1. “Step up” versus “top down” treatment algorithms for Crohn’s disease



Abbreviation: 5-ASA, 5-aminosalicylate.
Note: In the treatment hierarchy, the more potent drug therapies are placed at the top of the pyramid.

Currently, the NICE guideline (NG129[12]) recommends a “step up” approach for the management of Crohn’s disease (Figure 1), which involves starting treatment with the least clinically effective of the options available and, in cases where disease does not respond to treatment as desired, escalating therapy in stages, with the strategy determined by clinical judgement and patient preference. If an adequate response is not apparent in the expected time frame, the “step up” plan can be accelerated.[19] The Evidence Assessment Group’s (EAG’s) clinical expert advised that, for those people judged likely to benefit from the “step up” approach, most clinicians would prefer to accelerate treatment rather than follow the conventional “step up” algorithm.

The “top down” approach is currently not recommended by NICE.[12] The strategy involves treatment earlier in the pathway with those therapies that are more clinically effective, but that are also potentially associated with a greater risk of adverse effects. Early use of biological therapies in a “top down” approach is thought to modify the course of Crohn’s disease, to increase the possibility of mucosal healing (prevents structural damage of the bowel), and to be more effective than the “step up” approach at inducing and prolonging remission.[27]

The focus of treatment in Crohn's disease is to induce and maintain remission, to improve patient symptoms and quality of life, with a move towards personalising treatment. The goal of achieving mucosal healing during treatment is gaining acceptance but is not yet part of standard care in the UK. Neither the “step up” nor “top down” approach is suitable for all people with Crohn’s disease. Considering the risk–benefit profile of the “top down” approach, some clinicians could be reticent to expose those with mild activity of Crohn’s disease at time of assessment, or those thought to be at low risk of experiencing a relapse, to the unnecessary risk of an adverse effect. Conversely, those assessed as potentially being at risk of having a severe course of disease are at risk of undertreatment if the step up approach is followed, with consequent prolonging of symptoms and of inadequate control of disease

activity, and the associated long-term risks. Another consideration is cost of treatment, with the “top down” approach typically more expensive compared with the “step up” approach.[28]

Ability to easily stratify those with Crohn’s disease by risk of course of disease could help identify the most appropriate treatment strategy for the patient.

2.2.4.2.1.1 “Step up” approach

NICE NG129[12] advises starting treatment with a corticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) for those with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period. Alternative treatments for those who cannot tolerate, or who are contraindicated to, the recommended corticosteroids, are another corticosteroid, budesonide, and 5-aminosalicylate, both of which are less effective, but might be associated with fewer adverse effects, than preferred initial treatment:[14] clinical experts advised that 5-aminosalicylate is no longer used in clinical practice in the UK. Budesonide should not be considered for those presenting with severe disease activity or exacerbations.

Should disease not respond to initial treatment with a corticosteroid, a subsequent treatment option is addition of an immunosuppressant (azathioprine or mercaptopurine) to a conventional glucocorticosteroid or budesonide if:[12]

- there are 2 or more inflammatory exacerbations in a 12-month period; or
- the glucocorticosteroid dose cannot be tapered.

Alternatively, if it is thought that the person would be unable to tolerate mercaptopurine or azathioprine, addition of methotrexate could be considered.

For adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy, recommended treatment is escalation to a tumour necrosis factor (TNF)-alpha inhibitor (infliximab or adalimumab) given as a monotherapy or in combination with an immunosuppressant.[12]

For those with moderately to severely active Crohn's disease and who have failed treatment with a TNF-alpha inhibitor (i.e., disease has responded inadequately or lost response to treatment) or who are intolerant to conventional therapies, other biologics, such as vedolizumab and ustekinumab, are additional treatment options.[12]

Options for maintenance of remission are:[12]

- azathioprine or mercaptopurine as monotherapy after corticosteroids (including budesonide) to induce remission and for those who have not previously received these drugs;

- methotrexate:

    - For those who required methotrexate to induce remission;

    - For those who tried but could not tolerate azathioprine or mercaptopurine for maintenance;

    - For those are contraindicated to azathioprine or mercaptopurine.

- continued treatment with biologic, if appropriate.

2.2.4.2.2 "Top-down" approach

Although the "top-down" approach is not recommended by NICE, clinicians in specialist centres might choose to offer the strategy as an option to those they consider to have a poor prognosis in terms of outcomes, for example, those with complex perianal disease, significant fistulising disease or those with multiple risk factors. No accepted treatment strategy is available for the "top down" approach, with disparity across studies in the definition of "aggressive" therapy.[28] Additionally, evidence in support of the effectiveness of the "top down" approach is inconsistent, with some studies finding a benefit of early treatment with biologics and some reporting no benefit.[28] Variation in results across studies could be related to differences in, for example, the definition of 'early' intervention and of outcomes measured, population, and trial duration.

2.3 Interventions

2.3.1 PredictSURE-IBD™

PredictSURE-IBD™ is proposed for use in adults (16 years or older) with IBD, including Crohn's disease, who have active disease and are not receiving concomitant steroids, immunomodulators or biological therapies. PredictSURE-IBD™ could be particularly beneficial for people with:

- newly or recently diagnosed IBD;

- moderate or severe active IBD (people with mild disease are unlikely to have early aggressive treatment with biologics);

- disease that would not require early aggressive treatment with biologics ('top-down' approach) with current standard care in the NHS (e.g., people who do not have fistulising and/or complex perianal Crohn's disease, or have multiple risk factors).

PredictSURE-IBD™ facilitates stratification of people with IBD into high and low risk of frequently relapsing course of disease through detection of a gene sequence associated with CD8+ T cell exhaustion. Gene expression profiling of peripheral blood CD8+ T cells identified a signature gene sequence that was associated with CD8+ T cell exhaustion,[29-31] a state that is reached through the stepwise and progressive loss of T-cell function and that inhibits the immune response.[32] Level of expression of the genes indicating CD8+ T cell exhaustion was found to be linked with course of disease in multiple autoimmune diseases, including IBD.[29-31] People with a CD8+ T cell signature not associated with T cell exhaustion were shown to be at higher risk of a frequently relapsing disease course than those with the signature for T cell exhaustion.[29-31] Early identification of those at high risk of recurrent course of Crohn's disease may lead to improved clinical outcomes through facilitation of personalised treatment, particularly in those with newly diagnosed disease.

The PredictSURE-IBD™ test determines the presence or absence of the signature gene sequence (15 target genes and 2 control genes) indicating CD8+ T cell exhaustion through *in vitro* quantitative reverse transcription-polymerase chain reaction (RT-qPCR) of messenger RNA (mRNA) isolated from a whole blood sample (2.5 ml). The blood sample must be taken by a trained professional and stored in a sample tube (PAXgene Blood RNA tube): the vessel for the blood sample is not supplied as a component of the PredictSURE-IBD™ test kit and must be purchased separately. Isolation of mRNA and subsequent RT-qPCR is carried out in a centralised laboratory (Clinical Genetics Laboratory, Addenbrooke's Treatment Centre, Cambridge University Hospitals NHS Foundation Trust).

In RT-qPCR, because the starting genetic material is RNA rather than DNA, the first step in the process requires transcription of mRNA into complementary DNA (cDNA) using reverse transcriptase (RT). Next, the cDNA acts as the template for qPCR for DNA amplification. qPCR is carried out in a 384-well plate (16 x 24 wells). Given the requirements for quality control of the assay, a maximum of 4 samples can be analysed per plate. Each sample of cDNA is amplified in triplicate, which requires 12 rows of the plate. A quality control RNA (supplied as part of the PredictSURE-IBD™ kit and run in triplicate [3 rows]) and a no-RNA control (run singularly [1 row]) are tested with each batch of mRNA samples to validate the run. The centralised laboratory uses a Roche LightCycler 480/480 II platform, which is a standard platform, to carry out RT-PCR. Staff training to process the PredictSURE-IBD™ kits will not be required at the centralised laboratory as the site is already providing testing services as part of an ongoing study (PROFILE). If required, PredictImmune would support staff training at additional laboratories to facilitate expansion of testing, with training thought require 2–3 days at each centre (draft scope from NICE).

Results from RT-qPCR are fed into a proprietary algorithm that calculates a continuous risk score, and based on this score, patients are categorised as high- or low-risk of following a frequently relapsing

form of IBD. A confidence level associated with the result is also reported and presented as a percentage. Turnaround time for the test is 7–10 days.

2.3.2 Crohn's disease Prognosis Test

The Crohn's disease Prognosis Test (IBDX) developed by Glycominds uses serological markers to identify those at risk of a more complicated course of Crohn's disease (development of strictures and fistulae, and need for surgery).

The abnormal interaction of environmental, genetic and microbial factors with the immune system leads to the dysregulated immune response that is responsible for the intestinal inflammation typical of Crohn's disease. Those with Crohn's disease have an atypical immune response to the normal bacteria found in the gut that leads to the production of antibodies against microbial components.[33] Examples include anti-Saccharomyces cerevisiae antibodies (ASCA), antibodies against Pseudomonas-associated sequence I2 (anti-I2), and against the bacterial flagellin cBir1 (Anti-cBir1).[33]

A set of biomarkers that has been reported to be highly specific for Crohn's disease, with potential predictive value for prediction of complicated course of disease, are the anti-glycan-antibodies.[34] Glycans are saccharides that can be attached to various biological molecules through an enzymatic process called glycosylation. Glycans are usually found on the exterior of cell walls, and they form the main components of the cell wall surface in many microbes, including fungi, yeast, and bacteria.[34] Anti-glycan antibodies comprise anti-Saccharomyces cerevisiae antibodies (gASCA), anti-mannobioside antibodies (AMCA), anti-laminaribioside antibodies (ALCA), anti-chitobioside antibodies (ACCA), anti-laminarin antibody (Anti-L) and anti-chitin antibody (Anti-C).

The IBDX tool detects antibodies including:[35]

- ACCA;
- ALCA;
- AMCA;
- gASCA;
- Anti-L;
- Anti-C.

The IBDX antibodies are detected in patient serum or plasma by an indirect solid-phase enzyme-linked immunosorbent assay (ELISA). Each kit (sold individually) contains the relevant anti-glycan 96-well

microwell plate (12 X 8 well strips), ELISA reagents, negative control, positive control, and calibrators. The microwell plates, conjugates and controls are specific for each kit, but all other reagents are the same. All kits follow the same procedure (including incubation times), so they can easily be processed at the same time, if desired. For each biomarker, positivity is assessed based on the cut-off values presented in Table 1.

Those with Crohn's disease are considered to be at greater risk for disease complication (stricturing or penetrating) or surgery intervention if they are positive for two or more serological markers.

Table 1. Cut-off values for individual IBDX ELISA kits

	gASCA IgG	ALCA IgG	ACCA IgA	AMCA IgG	anti-C IgA	anti-L IgA
Negative	<45	<55	<80	<90	<45	<45
Equivocal[a]	45–50	55–60	80–90	90–100	45–50	45–50
Positive	>50	>60	>90	>100	>50	>50
a Repetition of sample assay is recommended.						

2.4 Place of the interventions in the treatment pathway

The proposed placement of PredictSURE-IBD™ and IBDX in the treatment pathway is in the stratification of those with a diagnosis Crohn's disease as high versus low risk of severe course of disease, thereby facilitating personalised treatment.

2.5 Relevant comparators

As no validated tool or algorithm is available to determine course of Crohn's disease, the relevant comparator is standard clinical care in the NHS.

2.6 Reference standard

As there is no test or algorithm available to determine long-term course of disease or an individual's risk of developing severe course of disease, estimation of prognosis is based on subjective clinical judgement of presenting signs and symptoms, together with potential risk factors for severe course of disease. Thus, there is no reference standard for the tools under evaluation.

3 REPORT METHODS FOR ASSESSING THE OUTCOMES ARISING FROM THE USE OF THE INTERVENTIONS

A systematic literature review will be carried out to evaluate the clinical effectiveness, cost-effectiveness and diagnostic test accuracy of the PredictSURE-IBD™ and Crohn's disease Prognosis Test (IBDX) tools for the identification of those at high risk versus at low risk of developing a severe course of Crohn's disease.

A review of the evidence for clinical effectiveness will be undertaken systematically following the general principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in healthcare,[36] NICE's Diagnostics Assessment Programme manual[37] and the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[38]

3.1 Review eligibility criteria

The eligibility criteria required for inclusion of a study in the review of the clinical effectiveness evidence are described in the subsections that follow.

3.1.1 Population

Study population eligible for inclusion will be those with a confirmed diagnosis of active Crohn's disease, and a diagnosis of disease.

3.1.2 Interventions

The PredictSURE-IBD™ and IBDX diagnostic tools.

3.1.3 Comparators

No studies will be excluded based on type of comparator or lack of comparator.

3.1.4 Reference standard

As there is no test or algorithm available to determine long-term course of disease or an individual's risk of experiencing severe course of disease, estimation of prognosis is based on subjective clinical judgement. Thus, there is no reference standard for the tools under evaluation.

3.1.5 Outcomes

Evidence permitting, the outcomes listed below will be considered:

- diagnostic accuracy (e.g. sensitivity and specificity, and/ or if raw data are available, the numbers of true positive, true negative, false positive and false negative test results for predicting course of disease);
- diagnostic yield (number of diagnoses of severe versus non-severe course of Crohn's disease);
- time to test result;
- number of test failures;
- number of inconclusive test results;
- percentage of people for whom early treatment with biologics was offered ('top-down') by subgroup of severe versus non-severe course of disease;
- rates and duration of response and remission by subgroup of severe versus non-severe course of disease;
- rates and duration of flare-ups and/or relapses by subgroup of severe versus non-severe course of disease;
- rates and duration of corticosteroid-free remission by subgroup of severe versus non-severe course of disease;
- cumulative corticosteroid exposure by subgroup of severe versus non-severe course of disease;
- measures of mucosal healing by subgroup of severe versus non-severe course of disease;
- rates of and time to treatment escalation by subgroup of severe versus non-severe course of disease;
- rates of and time to hospitalisation by subgroup of severe versus non-severe course of disease;
- rates of and time to surgical intervention by subgroup of severe versus non-severe course of disease;
- rates of and time to serious complication (e.g., obstruction, intestinal ulcers, fistula, anal fissure) by subgroup of severe versus non-severe course of disease;

- composite outcomes formed of hospitalisation, surgery or serious complication (obstruction, intestinal ulcers, fistula, anal fissure) by subgroup of severe versus non-severe course of disease;

- adverse effects of treatment;

- health-related quality of life by subgroup of severe versus non-severe course of disease.

3.1.6 Study design

The highest level of evidence for assessment of the clinical effectiveness of the prognostic tool that is the focus of the systematic review outlined in this protocol would be a randomised controlled trial (or systematic review of such studies) that allocated those with Crohn's disease to treatment guided by assessment using the tool or to treatment based on clinical judgement. However, based on scoping searches, and given that the interventions are prognostic tools, retrieval of relevant RCTs is unlikely. Thus, to ensure that all relevant studies are captured, no limit relating to study design will be applied, with the exception that studies must be carried out in humans. Studies analysing the clinical validity (the ability of the test to reliably and accurately identify the biomarkers of interest or determine the risk of developing severe versus non-severe course of Crohn's disease) or clinical utility (the ability of the test to improve measurable clinical outcomes, and its usefulness and added value to patient management) of the prognostic tool will be eligible for inclusion. Studies evaluating analytical validity will be included where applicable, where analytical validity denotes the ability of the tool to accurately and reliably measure the biomarker of interest as assessed using laboratory tests on samples that are representative of those with Crohn's disease. Studies not published in English language will be included if sufficient relevant data can be extracted from the full-text publication in non-English language, or from an English language abstract. Studies excluded on the basis of language will be listed separately. Non-peer-reviewed reports or abstracts will only be included if the data are presented in a succinct and accessible manner (e.g. a manuscript prepared for submission to a journal), if sufficient methodological details are reported to allow critical appraisal of the study quality, and if results are reported in sufficient detail.

3.2 Search strategy

Search terms will be a combination of Medical Subject Headings (MeSH) and free text terms for the population of Crohn's disease and for relevant biomarkers. Terms for the interventions of interest and relevant alternative terms are included in consideration of future updates but it is noted that, based on scoping searches, inclusion of intervention names retrieves zero relevant records and terms must be combined with "or" to avoid omission of known potentially relevant studies. A flow diagram illustrating

the flow of information through the systematic review process will be presented according to the PRISMA reporting guidelines.

The systematic literature search will comprise the following main elements:

- Searching of electronic bibliographic databases;
- Contact with clinical experts in the field;
- Review of the reference lists of retrieved papers.

Electronic databases will be searched from inception until the latest available version. The electronic databases that will be searched are:

- MEDLINE (draft search strategy provided in Appendix 9.1);
- EMBASE;
- The Cochrane Central Register of Controlled Trials (CENTRAL).

Clinical trial registers will also be searched to identify relevant ongoing clinical trials that when completed may have an impact on the results of this review. Registers to be searched include:

- WHO International Clinical Trials Registry Platform;
- ClinicalTrials.gov (http://clinicaltrials.gov/).

The website of the US Food and Drug Administration (FDA) will also be searched to identify unpublished data.

Relevant reviews and guidelines will be identified through consultation with clinical experts and searching the National Institute for Health and Care Excellence (NICE) website to identify additional potentially relevant studies.

Reference lists of included papers will be assessed. If necessary and if time allows, the authors of eligible studies will be contacted for further information (e.g. full text of citations listed ahead of print).

The abstracts from key conference proceedings from the past 2 years, of conferences identified in consultation with clinical experts, will be screened, where possible, for additional potentially relevant studies.

3.3 Study selection

The titles and abstracts of studies retrieved from the electronic database searches will be independently assessed for potential relevance by two reviewers according to the prespecified eligibility criteria. In cases in which consensus cannot be achieved, the full texts of potentially relevant studies will be ordered. Full-text copies of potentially relevant studies will be obtained and assessed independently by two reviewers for inclusion against the prespecified eligibility criteria. Any disagreements will be resolved by discussion, or, a third reviewer will be consulted, if necessary.

3.4 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction form, and independently checked for accuracy by a second reviewer. Information extracted will include details of the study's design and methodology, intervention and comparator tests, reference standard, baseline characteristics of participants, and outcome measures, including clinical outcome efficacy and any adverse events. Where there is incomplete information, if time allows, attempts will be made to contact authors with a request for further details. Discrepancies will be resolved by discussion, with involvement of a third reviewer if necessary.

3.5 Quality assessment strategy

The quality of diagnostic test accuracy studies will be assessed using the PROBAST (Prediction model Risk Of Bias ASsessment Tool) tool.[39, 40] The quality of clinical effectiveness studies will be assessed based on their study design: randomised controlled trials will be assessed as per recommendations by the CRD[36] and the Cochrane Handbook for Systematic Reviews of Interventions[41] and recorded using the Cochrane Risk of Bias Tool;[41] non-randomised studies will be assessed using the Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I) tool;[42] and qualitative studies will be assessed using the Critical Appraisal Skills Programme (CASP) tool.[43] All quality appraisal assessments will be carried out by one reviewer and verified by another independently, with disagreements resolved by discussion or the involvement of a third reviewer, if necessary.

The results of the quality assessments might be used to inform sensitivity analyses to investigate the impact of study quality on the findings of the review through sensitivity analyses (where evidence permits).

3.6 Methods of analysis/synthesis

Details of results on clinical effectiveness and quality assessment for each included study will be presented in structured tables and as a narrative summary. Should clinically and methodologically homogenous studies be identified, data will be synthesised using appropriate meta-analytic techniques. Clinical, methodological and statistical heterogeneity will be investigated.

For test accuracy data, absolute numbers of true positive, false negative, false positive and true negative test results, as well as sensitivity and specificity values, with 95% confidence intervals will be presented for each study. Other measures of test accuracy data will be presented if reported.

3.6.1 Potential subgroup analyses

Subgroups of interest are:

- children versus adults with a diagnosis of Crohn's disease;
- newly diagnosed Crohn's disease versus established diagnosis of Crohn's disease;
- mild versus moderate-severe activity of disease;
- presence versus absence of fistulising or complex perianal disease.

3.6.2 Sensitivity analyses

Sensitivity analyses will be carried out including studies deemed to be high risk of bias (excluded from primary analyses).

4 REPORT METHODS FOR SYNTHESISING EVIDENCE OF COST EFFECTIVENESS

The economic evaluation will assess the cost-effectiveness of PredictSURE-IBD™ and Crohn's disease Prognosis Test (IBDX), compared with standard care in the NHS. The population to be included in the economic analysis consists of adults (aged 16 years and older) who have been newly diagnosed with moderate to severe Crohn's disease, and who have not been offered biologics under current standard care. A systematic literature review (SLR) of existing economic evaluations will be undertaken to inform the need, (and if necessary) the conceptualisation and development of a *de novo* economic model.

4.1 Identifying and systematically reviewing published cost-effectiveness studies

A SLR will be undertaken to identify published full economic evaluations of the PredictSURE-IBD™ and IBDX tools for the identification of those at high risk of developing a severe course of Crohn's disease, as well as economic evaluations of treatments for Crohn's disease. It is anticipated that searches conducted to retrieve records on the treatment of Crohn's disease will capture the relevant treatment strategies, including the "top-down" and "step-up" (standard and accelerated) approaches. In case such approaches are not identified through the SLR, a targeted search on "top-down" and "step-up" treatment strategies in the NHS will be conducted. A search filter to identify economic evaluations will be applied to the search strategies and the electronic databases will be searched from inception until the latest available version. The methodological quality of the full economic evaluations identified in the review will be assessed using the Drummond checklist.[44]

The following databases will be searched for relevant studies:

- Ovid MEDLINE® In-Process & Other Non-Indexed Citations (Ovid);
- Ovid MEDLINE® ePub Ahead of Print (Ovid);
- Embase (Ovid);
- NHS Economic Evaluation Database (NHS EED) (Centre for Reviews and Dissemination, CRD);
- Cochrane Database of Systematic Reviews (CDSR) (Cochrane);
- Cochrane Central Database of Controlled Trials (CENTRAL) (Cochrane);
- Database of Abstracts of Reviews of Effects (DARE) (CRD);

- Health Technology Assessment Database (HTA) (CRD).

Separate searches will be carried out for supporting information on utility data. To identify cost and resource use evidence, the Evidence Assessment Group (EAG) will search the same sources identified for the economic evidence and treatment of Crohn's disease, together with NHS reference costs, the Unit Costs of Health and Social Care (Personal Social Services Research Unit [PSSRU]), the Electronic Marketing Information Tool (eMIT) and the British National Formulary (BNF). If the latter do not provide sufficient data to populate the economic model, a separate targeted search on costs and resource use will be conducted. Study selection and data extraction will be carried out as described in Sections 3.3 and 3.4, respectively.

The search strategies will combine terms capturing the interventions or comparators (Sections 3.1.2 and 3.1.3) of interest and the target economic population aforementioned in Section 4. Health economic and quality of life search terms will be applied to capture the study designs of interest (cost-effectiveness, cost and quality of life, health state utility values [HSUVs]). Searches will be restricted to studies published in the English language; however, no restriction by setting or geographical location will be applied to the search strategy. If sufficient data are available from a UK setting, data from non-UK based studies will not be extracted. Moreover, if sufficient EQ-5D data are found during the searches for utility data, the EAG will restrict the data extraction to EQ-5D data.

In addition, clinical experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, identified systematic reviews and submissions from companies will be searched for additional references.

Main findings from the studies identified from the SLR will be presented with a narrative synthesis and structured tables.

4.2 Development of a health economic model

Following the completion of the SLR, if a *de novo* economic model is deemed necessary, the EAG will develop the model in an appropriate software package (e.g., Microsoft® Excel) and using clinical expert opinion. The model will assess the cost-effectiveness of PredictSURE-IBD™ and IBDX, compared with standard care in the NHS, in adults (16 years and over) with a newly diagnosis of moderate to severe Crohn's disease, who have not been offered biologics under standard care. The cost-effectiveness analysis will assess the clinical and economic impact of early categorisation of patients' disease's risk (with the use of PredictSURE-IBD™ and IBDX) on disease management and clinical outcomes.

Model parameters (e.g., utilities, cost data) will be populated from the results of the economic and outcome searches and combined with unit costs from NHS reference costs and other relevant

publications of UK health care costs as appropriate. The EAG will elicit expert opinion if published data are not available to inform all model parameters. All evidence will be evaluated according to the recommendations of the NICE Diagnostics Assessment Programme manual.[37]

4.2.1 Model structure

The structure of the model will take into consideration any identified economic models in the area of Crohn's disease's treatment. The model structure will be dependent on the data that are identified through both the clinical and economic SLR.

Event pathways will be modelled to estimate long-term costs and benefits. The economic model will incorporate the pathways of care that individuals follow under standard practice in the UK NHS and for which credible evidence is available. The EAG will review previous economic models and seek expert clinical advice to help structure the diagnostic and care pathways.

The economic assessment will be undertaken from the perspective of the NHS and Personal Social Services. The model time horizon will be set to patient lifetime and both costs and benefits will be discounted at 3.5% per annum.

The output of the economic model will be incremental cost effectiveness ratios (ICERs), using quality-adjusted life-years (QALYs) as the measure of effectiveness. Various sensitivity analyses will be conducted to test the robustness of the model to changes in parameter assumptions and potentially also to alternative data sources. To assess the overall uncertainty in the model estimates, a probabilistic sensitivity analysis (PSA) will be conducted using appropriately sampled values for all relevant parameters in the model.

5 HANDLING INFORMATION FROM THE COMPANIES

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 15th July 2019. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by a manufacturer and specified as such will be highlighted in blue and underlined in the assessment report (followed by company name in brackets). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. An executable model will be supplied, with any confidential data used in the cost effectiveness model replaced with dummy data.

6 COMPETING INTERESTS OF AUTHORS

None of the authors has any relevant competing interests to declare.

7 TIMETABLE/MILESTONES

Milestone	Date to be completed
Draft protocol	07/05/2019
Final protocol	03/06/2019
Progress report	30/08/2019
Draft assessment report	25/10/2019
Final assessment report	22/11/2019

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9 APPENDICES

9.1 Appendix 1. Draft search strategy (MEDLINE)

9.1.1 Strategy relating to the prognostic tools

1 Crohn Disease/ (37,127)

2 Crohn*.mp (53,078)

3 ((Crohn$ adj2 (disease or syndrome)) or regional enteritis).tw. (42,922)

4 Inflammatory bowel diseases/ (20,088)

5 IBD.mp. (22,385)

6 Inflammatory bowel disease*.mp. (48,006)

7 or/1-6 (84,427)

8 CD8-Positive T-Lymphocytes/ (34,740)

9 CD8+ T cells.mp. (34,151)

10 CD8 Antigens/ (8,663)

11 CD8 antigens.mp. (8,789)

12 CD8*.mp. (107,146)

13 CD 8*.mp. (1,182)

14 T-Lymphocytes, Regulatory/ (29,156)

15 Regulatory t cells.mp. (20,552)

16 (PredictSure or PredictImmune).mp. (0)

17 or/8-16 (139,264)

18 Antibodies/ (97,137)

19 antibod*.mp. (1,120,457)

20 glycan.mp. (15,592)

21 (antichitobioside carbohydrate antibod* or ACCA or chitobioside).mp. (379)

22 (antilaminaribioside carbohydrate antibod* or ALCA or laminaribioside).mp. (291)

23 (antimannobioside carbohydrate antibod* or AMCA or mannobioside).mp. (321)

24 (anti-Saccharomyces cerevisiae antibod* or ASCA or gASCA or mannan).mp. (4,622)

25 (anti-laminarin carbohydrate antibod* or anti-L or laminarin).mp. (1,458)

26 (neutrophil elastase degraded elastin or EL-NE).mp. (7)

27 glycominds.mp. (4)

28 (Crohn's disease prognosis test or IBDX).mp. (1)

29 or/18-19 (1,120,457)

30 or/20-28 (22,330)

31 29 and 30 (4,874)

32 7 and 17 (1,665)

33 7 and 31 (421)

34 32 or 33 (2,076)

9.1.2 Strategy relating to interventions used to treat Crohn's disease

1 Crohn Disease/ (37,127)

2 Crohn*.mp (53,078)

3 ((Crohn$ adj2 (disease or syndrome)) or regional enteritis).tw. (42,922)

4 Inflammatory bowel diseases/ (20,088)

5 IBD.mp. (22,385)

6 Inflammatory bowel disease*.mp. (48,006)

7 or/1-6 (84,427)

8 prednisolone/ (32,042)

9 prednisone/ (38,447)

10 cortisone/ (19,547)

11 methylprednisolone/ (18,295)

12 hydrocortisone/ (70,241)

13 (corticosteroid or prednisolone or prednisone or methylprednisolone or hydrocortisone or budesonide).ti,ab. (120,262)

14 mesalamine/ (3,342)

15 sulfasalazine/ (4,014)

16 (mesalamine or sulfasalazine or "5-aminosalicylic*" or "5-aminosalicylate*" or "5-asa" or 5aminosalicylic* or 5aminosalicyclate* or 5asa or pentasa or mesalazine or mesalamine or asacol or sulfasalazine* or salazopyrin* or salazosulfapyridine* or asulfidine* or azulfadine* or azulfidine*).ti,ab. (7,653)

17 6-mercaptopurine/ (6,143)

18 azathioprine/ (14,342)

19 methotrexate/ (36,634)

20 (immunosuppressant or immunomodulator or mercaptopurine or methotrexate or amethopterin or Otrexup or Rasuvo or Rheumatrex or Trexall or Maxtrex or Nordimet or Zlatal or Methofill or Metoject or Jylamvo or azathioprine or Imuran or Azapress or thiopurine).ti,ab (67,727)

21 (biologic or biologics or tumour necrosis factor alpha or TNF adj2 (inhibitor*)).ti,ab (4,152)

22 (infliximab or Remicade or Remsima or Inflectra or Zessly or Flixabi or adalimumab or Humira or Imraldi or Amgevita or Hulio or vedolizumab or Entyvio or ustekinumab or Stelara).ti,ab (15,541)

23 (top-down or top down or step-up or step up).ti,ab. (15,728)

24 or/8-23 (344,143)

25 7 and 24 (13,367)