NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

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

Final scope

June 2019

1 Introduction

The PredictSURE-IBD test is manufactured by PredictImmune. The medical technologies topic oversight group identified PredictSURE-IBD as suitable for evaluation by the Diagnostics Assessment Programme on the basis of a briefing note. The final scope was informed by discussions at the scoping workshop on 30 April 2019 and the assessment subgroup meeting on 15 May 2019.

A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technologies

This section describes the properties of the diagnostic technologies based on information provided to NICE from the manufacturer and on information available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technologies

PredictSURE-IBD and IBDX are laboratory-based tests that may help to identify people with Crohn's disease who are at a higher risk of severe disease course. PredictSURE-IBD was reported to identify people at a higher risk of a frequently relapsing course of the disease, while IBDX was shown to identify people at a higher risk of first complication and abdominal surgery.

People who are at a higher risk of a severe disease course may benefit from early treatment with biological therapies such as tumour necrosis factor (TNF)-alpha inhibitors ('top down' approach, see section 3.2.4 for details). Early adequate control of disease activity may: lead to reduction in disease flare-ups; prevent bowel damage; and limit the need for surgery. Currently, there is no method to predict long-term disease course and facilitate personalised treatment. Instead, people with Crohn's disease typically follow a 'step-up' therapy (see section 3.2.3), which involves titrating and escalating drug use through steroids to immunosuppressives

and biological therapies in response to refractory or relapsing disease, on a trial and error basis.

In addition, PredictSURE-IBD and IBDX risk prediction could help gastroenterologists plan the frequency of follow-up appointments. People at a higher risk of a severe disease course could benefit from close monitoring, while those at a lower risk of a severe disease course could have the burden of more frequent clinic visits removed, and the healthcare system could benefit from more efficient clinic use.

2.2 Product properties

2.2.1 PredictSURE-IBD

PredictSURE-IBD is a whole blood-based biomarker prognostic test combined with a proprietary algorithm to produce a risk categorisation (high- or low risk). PredictSURE-IBD testing would be provided as a testing service by a centralised laboratory facility (Clinical Genetics Laboratory, Addenbrooke's Treatment Centre, Cambridge University Hospitals NHS Foundation Trust), using the PredictSURE-IBD test kit. In the future, testing could be expanded to other laboratories.

PredictSURE-IBD testing requires a 2.5 ml whole blood sample to be taken by a trained professional (such as a phlebotomist, nurse or doctor) in a PAXgene Blood RNA tube (QIAGEN), which protects the intracellular RNA in blood samples. The blood sample is then sent to the centralised laboratory for testing. The blood sample is stable for up to 3 days at ambient temperature, over 5 days when refrigerated (2-8°C), over 7 days when frozen (-25 to -15°C), or at ambient temperature for 3 days followed by 4 days frozen.

The PredictSURE-IBD test involves isolation of mRNA from the whole blood sample using the PAXgene Blood RNA kit (QIAGEN), followed by quantitative polymerase chain reaction with reverse transcription (RT-qPCR) to assesses expression of 15 target genes and 2 controls. The RT-qPCR is carried out as a 2-step process: cDNA synthesis in the reverse transcription reaction, and then a qPCR on a 384-well plate. A maximum of 4 samples may be analysed per plate as cDNA derived from each RNA sample is run in triplicate (a total of 12 rows). A quality control RNA (supplied as part of the PredictSURE-IBD kit; run in triplicate) and a no-RNA control (run singularly) are tested with each batch of patient RNA samples to validate the run. The RT-qPCR is run on a Roche LightCycler 480/480 II platform, which is a standard platform. No additional staff training is required to undertake the test in the central laboratory in Cambridge, which is already providing testing services as part of an ongoing study (PROFILE; see section 7 for details). If other laboratories were to undertake testing, PredictImmune would support staff training which would take 2-3 days.

The RT-qPCR results are fed into a proprietary algorithm which calculates a continuous risk score, and based on this score, classifies patients as being at high or low risk of following a frequently relapsing form of the disease. A confidence level associated with the result is also indicated, presented as a percentage from 0% to 100%.

The results are returned to the referring gastroenterologist within 7-10 days.

2.2.1.1 Underlying principle of PredictSURE-IBD: CD8+ T-cell exhaustion

PredictSURE-IBD detects a genomic signature of CD8+ T cell exhaustion. CD8+ T cells are part of the immune system involved in the regulation of immune response. T cell exhaustion is a state characterized by T-cell dysfunction, which lowers T-cell-related immune response. CD8+T cell exhaustion has been reported to predict better prognosis in multiple autoimmune diseases, including inflammatory bowel disease; people with a 'non-exhausted' CD8+ T cell signature were linked to a higher risk of frequently relapsing disease course than people with an 'exhausted' signature (Lee et al. 2011; McKinney et al. 2015). A frequently relapsing disease course was defined as early need for treatment escalation (start of immunomodulators, biologics or surgery) as well as an increase in the total number of treatment escalations required over the course of 12 months from blood sample draw.

The CD8+T cell exhaustion signature was first identified by whole-genome transcriptional analysis of isolated T cells in a prospective cohort of patients with Crohn's disease and ulcerative colitis (Lee et al. 2011; McKinney et al. 2015). A blood-based prognostic test suitable for routine clinical use was subsequently developed to identify the high- and low-risk subgroups without the need for cell separation (Biasci et al. 2019).

2.2.2 IBDX

The IBDX is a panel of 6 indirect solid phase enzyme-linked immunosorbent assay (ELISA) kits measuring levels of anti-glycan antibodies in human serum:

- IBDX anti-Saccharomyces cerevisiae (gASCA) IgG ELISA kit
- IBDX anti-laminaribioside (ALCA) IgG ELISA Kit
- IBDX anti-chitobioside (ACCA) IgA ELISA Kit
- IBDX anti-mannobioside (AMCA) IgG ELISA Kit
- IBDX anti-chitin (anti-C) IgA ELISA Kit
- IBDX anti-laminarin (anti-L) IgA ELISA Kit

Anti-glycan antibodies are markers of seroreactivity to microbial antigens, which were reported to be linked to Crohn's Disease prognosis (Rieder et al. 2010a; Rieder et al. 2010b). People who are positive for 2 or more anti-glycan antibodies were reported to be at a higher risk for first complication and abdominal surgery. Among

people with prior Crohn's disease-related surgery or complication (fistula, stenosis), positivity for 3 or more anti-glycan antibodies was associated with higher risk for future additional Crohn's disease-related surgery and complications.

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.

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*	45-50	55-60	80-90	90-100	45-50	45-50
Positive	>50	>60	>90	>100	>50	>50

* Repeating the sample assay is recommended

3 Target conditions

3.1 Crohn's disease

Crohn's disease is a relapsing-remitting form of inflammatory bowel disease (IBD). There are currently at least 115,000 people in the UK with Crohn's disease (Crohn's & Colitis UK), with incidence (newly diagnosed disease) of about 8 per 100,000 people annually (Rubin et al. 2000; Garcia Rodriguez et al. 2005). The causes of Crohn's disease are widely debated. Smoking and genetic predisposition are two important factors that are likely to play a role.

Some people with Crohn's disease experience frequent flares and relapses and often do not respond to standard drug therapy, despite multiple treatment escalations (dose escalations and add-on therapies, including immunosuppressives and biologics). These people are at a high risk of severe complications (such as intestinal obstruction, fistulae or perianal disease), progressive disability and surgery. In contrast, other people with Crohn's disease achieve prolonged remission without any treatment escalations, and have excellent long-term outcomes. What determines disease course and prognosis in Crohn's disease is poorly understood.

In addition to the significant impact on clinical outcomes and quality-of-life, Crohn's disease poses high economic burden due to disability, loss of work productivity, surgery and hospitalisation. Five years after onset, 15% to 20% of people are disabled by their disease to some degree, and between 50% and 80% of people with Crohn's disease will eventually need surgery (NICE CG152). The main indications for this are strictures causing symptoms of obstruction, other complications such as fistula formation, perforation or failure of medical therapy.

3.2 Diagnostic and care pathway

3.2.1 Diagnosis and classification

A single reference standard for the diagnosis of Crohn's disease does not exist (ECCO-ESGAR 2019). The diagnosis is based on a combination of clinical, biochemical, stool, endoscopic, cross-sectional imaging, and histological investigations. The diagnostic workup also helps to assess the disease severity, inflammatory burden, disease subtype and risk factors for poor prognosis.

Crohn's disease severity is based on the assessment of overall patient well-being, frequency of diarrhoeal stools, intensity of abdominal pain, presence of extraintestinal symptoms and presence of complications. The Harvey-Bradshaw Index (HBI) or Crohn's Disease Activity Index (CDAI) tools are often used to assess disease severity in clinical trials but CDAI is impractical for use in routine clinical practice. Instead, HBI or quality of life instruments are typically used in routine clinical practice, but there is variability between trusts.

Inflammatory burden can be assessed from endoscopic and cross-sectional imaging and the use of biomarkers such as C-reactive protein (CRP) or faecal calprotectin. The utility of these biomarkers is increasingly being recognised, despite the lack of consensus on the optimal thresholds to interpret the results.

Disease subtyping (phenotyping) usually takes into account age at diagnosis, disease location and disease behaviour (ECCO 2016). Young age at diagnosis, extensive disease and perianal involvement are linked to worse prognosis. Other risk factors include smoking, severe disease at presentation, the need for surgery at presentation, and fistula formation. However, there is no consensus or algorithm on how these risk factors should be combined to predict long-term disease course, and their predictive value is limited. Subject to clinical judgement, people with complex perianal disease, significant fistulising disease or those with multiple risk factors may be considered at a high risk of poor prognosis and may be offered 'top-down' treatment (early treatment with biologics; see section 3.2.2 and 3.2.4 for details). Furthermore, there is no standard definition of 'poor prognosis' or 'severe disease course'. It is usually defined as refractory or relapsing disease necessitating multiple treatment escalations (dose increases and/or add-on treatment), development of

significant complications (for example, irreversible penetrating or stricturing lesions), need for more than 1 surgery, need for hospitalisation, or as a combination of these factors.

There is a high unmet need for methods to better predict disease course and guide personalised therapy in Crohn's disease. Such methods would help offer adequate treatment (avoid undertreatment) and monitoring to people with Crohn's disease likely to experience a severe disease course, while avoiding overtreatment and over-monitoring of those likely to experience a mild disease course. The need for such methods was emphasized by the British Society of Gastroenterology (BSG) in their Clinical Research Strategy 2018 document. The top 2 of 5 research priorities for IBD described the need for optimal markers or combinations of markers to:

- decide the optimal treatment strategy
- stratify patients with regards to disease course, monitoring disease activity, and disease prognosis.

3.2.2 Treatment overview

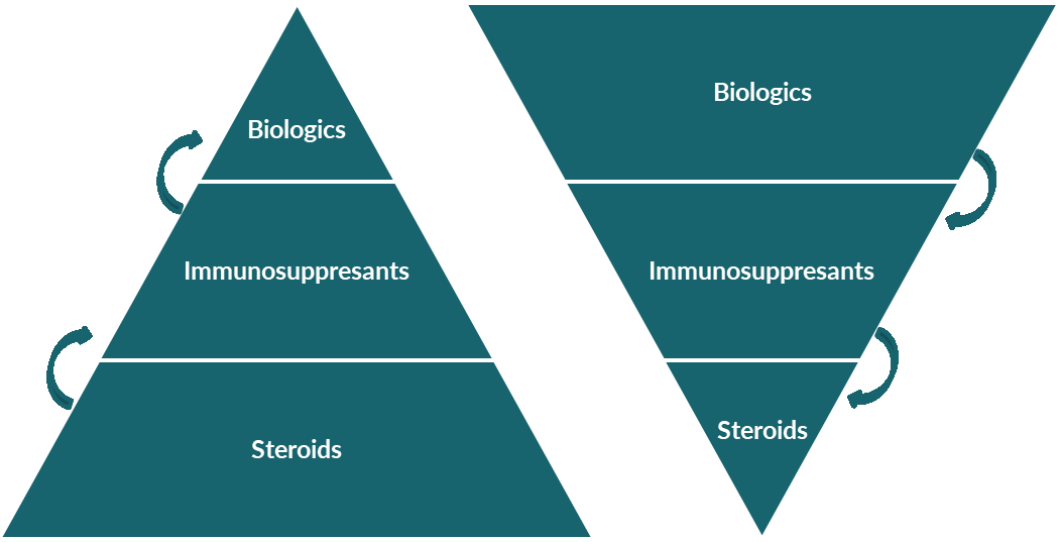
NICE's guideline on Crohn's disease states that the treatment goal in Crohn's disease is to induce and maintain clinical remission. The goal of reaching mucosal healing is gaining acceptance but is not yet part of standard care in the UK.

Currently, people with Crohn's disease usually follow an accelerated 'step-up' therapy (often referred to simply as a 'step-up' therapy; see Figure 1 and section 3.2.3). It involves titrating and escalating drug use from corticosteroids to immunosuppressants and then to biological therapies when disease does not respond or losses response to treatment, on a trial and error basis. In contrast to the historical approach to 'step-up' therapy, which could have involved multiple courses of steroids before stepping up the treatment, accelerated 'step-up' therapy involves a rapid acceleration of therapeutic strategies if no adequate response is seen within the expected time frame. Adequate response can be defined either as absence of clinical symptoms and/or no signs of ongoing inflammation.

'Step-up' therapy is not suitable for all people with Crohn's disease. With this strategy, people with refractory or relapsing course of disease may experience long delays in reaching adequate control of their disease. This puts them at increased risk of irreversible bowel damage, serious complications and the need for surgery. It has been advocated that these people could benefit from the 'top-down' approach, that is early treatment with biological therapies such as tumour necrosis factor (TNF)-alpha inhibitors (see section 3.2.4). This early treatment could achieve a faster and higher rate of mucosal healing and has the potential of modifying the natural course of disease. Thus, early adequate control of disease activity could lead to reduction in disease flare-ups, prevent bowel damage and limit the need for surgery in patients with severe course of disease.

Clinical experts indicated that Crohn's disease is currently undertreated, but indiscriminate use of the 'top-down' approach in all people with newly diagnosed Crohn's disease would expose people with a 'mild' disease course to unnecessary risks of adverse events, and may be prohibitively expensive. Therefore, there is a high need for predictive tools indicating which patients could benefit most from early biologic treatment.

Figure 1 'Step-up' (standard care) versus 'top-down' (alternative treatment option) treatment strategies in Crohn's disease



Note: Medications at the top are considered more potent but present greater risk.
Note: enteral nutrition can be an alternative to a conventional steroid in children in whom there is concern about growth or side effect, or in young people in whom there is concern about growth.

3.2.3 Current standard care: 'step-up' therapy

The existing NICE guidelines on management of Crohn's disease and technology appraisals guidance for infliximab and adalimumab, vedolizumab, and ustekinumab recommend a 'step-up' approach to induce remission of Crohn's disease (Appendix D):

- **Steroids:** Treatment is typically started as monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone). Except for severe presentation, budesonide may be offered instead of conventional steroids (see NICE NG129 for details[1]). Budesonide is less effective than a conventional glucocorticosteroid, but may have fewer side effects. Enteral nutrition can be considered as an alternative to a conventional steroid to induce remission for:

[1] Clinical experts commented that 5 aminosalicylic acid (5-ASA, mesalazine) is no longer used in Crohn's disease.

- children in whom there is concern about growth or side effects and
- young people in whom there is concern about growth.

A course of steroids can also be repeated in people who have a single inflammatory exacerbation of Crohn's disease in a 12-month period.

- **Immunosuppressants:** For people who have 2 or more inflammatory exacerbations in a 12-month period, or for whom the glucocorticosteroid dose cannot be tapered, azathioprine, mercaptopurine or methotrexate can be added to a conventional glucocorticosteroid or budesonide therapy (see NICE NG129 for details). Immunosuppressants should not be offered as monotherapy to induce remission.
- **TNF-alpha inhibitors**: Infliximab and adalimumab are treatment options 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. They can be offered either as monotherapy or combined therapy with an immunosuppressant.[2] Treatment with TNF-alpha inhibitors should be regularly reviewed (see NICE NG129 for details); however, there is no consensus about the optimal duration of treatment with TNF-alpha inhibitors.
- **Other biologics:** Vedolizumab is a treatment option for treating moderately to severely active Crohn's disease only if a TNF-alpha inhibitor has failed (that is, the disease has responded inadequately or has lost response to treatment) or a TNF-alpha inhibitor cannot be tolerated or is contraindicated. Ustekinumab is a treatment option for moderately to severely active Crohn's disease in adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-alpha inhibitor, or have medical contraindications to such therapies.

In people who reach remission, maintenance treatment may be considered, as described in NICE's guideline on the management of Crohn's disease.

ECCO 2016 guidelines provide further information on diagnosis and management of Crohn's disease according to the site of disease and disease activity. BSG guidelines are currently in development and are expected to be published shortly. Other relevant clinical guidelines include:

- European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/ECCO consensus guidelines (2014) on the medical

[2] SONIC (Colombel et al. 2010) and DIAMOND (Matsumoto et al. 2016) studies showed that TNF-alpha inhibitor (infliximab or adalimumab) plus azathioprine produced significantly better outcomes than TNF-alpha inhibitor or azathioprine alone.

management of paediatric Crohn's disease, and position paper (2018) on nutrition in inflammatory bowel disease

- American Gastroenterological Association (AGA) Institute guideline (2013) on drug therapy for Crohn's disease
- American College of Gastroenterology (ACG) guideline (2018) on management of Crohn's disease in adults
- North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) statement (2012) on the use of enteral nutrition in paediatric Crohn's disease

3.2.4 Alternative treatment strategy: 'top-down' therapy

The 'top-down' approach, that is, early treatment with biological therapies such as TNF-alpha inhibitors, is not routinely used in the UK. However, in specialist centres, it may be offered to people with Crohn's disease who have complex perianal disease, significant fistulising disease or have multiple risk factors (see section 3.2.1). NICE guidelines on management of Crohn's disease do not cover the 'top-down' approach, and it is also not clearly defined in the ECCO 2016 guidelines. In particular, there is no guidance on the optimal duration of early treatment with biologics.

A study by d'Haens et al. 2008 suggested that a 'top down' approach of early combined immunosuppression (infliximab plus azathioprine) is more effective than conventional 'step-up' therapy in inducing remission and reducing corticosteroid use in people who had been recently diagnosed with Crohn's disease. In this study, patients in the 'top-down' group received induction treatment with infliximab (5 mg/kg bodyweight at weeks 0, 2, and 6, in combination with azathioprine), followed by azathioprine maintenance therapy (no infliximab maintenance but patients could receive additional infusions of infliximab if their symptoms worsened). 'Top down' treatment was associated with significantly higher rates of steroid-free remission at weeks 26 and 52, and higher rates of mucosal healing at week 104, compared with conventional 'step-up' therapy. Long-term follow-up from this study (Hoekman et al. 2018; median follow-up of 8 years) showed limited impact of 'top-down' therapy on long-term outcomes (clinical remission, endoscopic remission, hospitalization, surgery or new fistulas) compared with 'step-up' therapy. However, lower relapse rates and reduced use of TNF-alpha inhibitors and corticosteroids were observed with 'top-down' therapy.

A systematic literature review done by Tsui and Huynh (2018) suggested that 'top-down' therapy showed inconsistent results. While some studies showed increased efficacy of this treatment strategy compared with 'step-up' therapy, some did not show any benefit. Authors note this could be related to differences in the 'top-down'

therapy used (medication type, dosage, combination and timing), patient population, outcomes definitions, trial duration, and other methodological aspects. This may highlight the need for appropriate patient selection, timely start of biologic treatment and optimisation of 'top-down' therapy protocols.

3.2.5 Potential place of PredictSURE-IBD and IBDX in the care pathway

Testing would be ordered once a diagnosis of Crohn's disease is confirmed. Clinical experts noted that test results could be used in one of the following scenarios:

- The test is ordered during the appointment in which a diagnosis of Crohn's disease is confirmed and discussed with the patient. Test results could then be reviewed:
    - During routine follow-up appointment (usually 4 weeks after initial diagnosis) to adjust initial treatment and plan future treatment based on the PredictSURE-IBD or IBDX test result.
    - By referring clinician as soon as the results are available to start or adjust initial treatment and plan monitoring frequency. The 2 possible test results (high or low risk of severe disease course) and consequent treatment plans would have to be discussed during the initial appointment.
- The test is ordered before the appointment with the patient, based on an early review of imaging or histopathology results confirming a diagnosis of Crohn's disease by the treating clinician. Test results could then be reviewed and discussed during the same appointment in which a diagnosis of Crohn's disease is confirmed and discussed with the patient. However, an early review of diagnostic assessment results is not routinely performed in the NHS.

3.3 Patient issues and preferences

The blood sample for the PredictSURE-IBD and IBDX test would be taken in a routine phlebotomy appointment - no additional appointment would be needed and no preparations for the test are needed. No additional appointment with the gastroenterologist should be needed as the test results can be discussed during a routine follow-up appointment to tailor treatment.

The test result could help personalise treatment for people with Crohn's disease. Information on future disease course could help patients to plan their lives and remove some uncertainty related to living with a chronic disease. For example, it could provide reassurance to people who are at a low risk of a severe course of disease. It could potentially improve outcomes and quality of life for those at a high risk of a severe course of disease by guiding the choice of a 'top-down' approach.

4 Target population

The target population for this assessment is people[3] with Crohn's disease[4] who have active disease and are currently not receiving any concomitant steroids, immunomodulators or biologic therapies. The patient population who could benefit most from a prognostic test for disease course in Crohn's disease, is people who:

- Have newly or recently diagnosed disease (although people with longer duration of disease could potentially benefit from testing, the benefits are expected to be diminishing with time, as the course of disease becomes more obvious, and some patients might already have had irreversible bowel damage, complications and/or surgery)

- Have moderate-severe active disease (people with mild symptomatic disease and low inflammatory burden would be expected to be at lower risk of a severe disease course and are unlikely to be offered 'top-down' therapy)

- Would not receive 'top-down' therapy as part of current standard care in the NHS (for example, people who have complex perianal fistulising Crohn's disease would be offered 'top-down' therapy regardless of test results, so testing would be redundant).

5 Comparator

The comparator is current standard care in the NHS in which most people are offered 'step-up' therapy or 'accelerated step-up therapy' (see section 3.2.3).

Currently, no validated test or algorithm is used to stratify people with Crohn's disease into low- and high-risk groups for following a severe course of disease. The presence of known risk factors (described in section 3.2.1) may be used to help guide treatment, but their predictive value is low, and there is no consensus on how different risk factors should be combined for determining prognosis.

[3] The clinical course of Crohn's disease can be different in children (for example, these patients often have more aggressive disease and have higher use of biologics). IBDX has been tested in both adult and paediatric populations. PredictSURE-IBD has not yet been validated in children (17 years or younger) but these data are currently being processed and are expected to be available in mid- to late 2019. The data on use of the tests in children and on comparison of 'step-up'/'top-down' treatment strategies in children may be limited.

[4] The scope of this assessment focuses on the potential benefits of prognostic tests in Crohn's disease; however, NICE is aware that PredictSURE-IBD could also help predict the course of disease in people with ulcerative colitis. The 2 diseases have different natural courses of disease, treatment pathways and clinical outcomes, and thus would require 2 separate assessments and economic models.

6 Scope of the assessment

Table 2 Scope of the assessment

Decision question	Does testing with PredictSURE-IBD or IBDX in people with active Crohn's disease represent a clinically and cost-effective use of NHS resources?
Populations	People with active Crohn's disease who are: • Currently not receiving any concomitant steroids, immunomodulators or biologic therapies. • Have newly or recently diagnosed disease • Have moderate-severe active disease • Would not receive 'top-down' therapy with current standard care in the NHS
Interventions	PredictSURE-IBD and IBDX
Comparator	Current clinical practice in the NHS - most people with Crohn's disease are offered an 'accelerated step-up' treatment (also referred to simply as 'step-up' therapy). No test or algorithm is currently used to predict disease course.
Healthcare setting	Secondary and tertiary care
Outcomes	Intermediate measures for consideration may include: • Time to result • Number of test failures • Number of inconclusive test results • % of patients classified as high and low risk of frequently relapsing disease course • % of patients for whom 'top-down' therapy was offered • Test accuracy (sensitivity, specificity, positive predictive value, negative predictive value and hazard ratios for predicting severe disease course)
	Clinical outcomes for consideration may include: • Rates and duration of response and remission • Rates and duration of flare-ups and/or relapses • Rates and duration of remission free from steroids and/or surgery • Cumulative steroid exposure • Measures of mucosal healing • Rates of and time to treatment escalation • Rates of and time to hospitalisation • Rates of and time to surgical intervention

	• Rates of and time to serious complication • Composite outcomes such as major adverse outcomes (hospitalisation, surgery or serious complication) • Adverse effects of treatment
	Patient-reported outcomes for consideration may include: • Health-related quality of life
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Cost of testing (including the cost of sample collection, processing, transport, and the testing service) • Cost of treatment (including biologics) • Costs of other resource use (e.g. associated with managing active disease states, flare-ups or complications) - outpatient appointments - hospitalisation - additional tests - surgery
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

7 Other issues for consideration

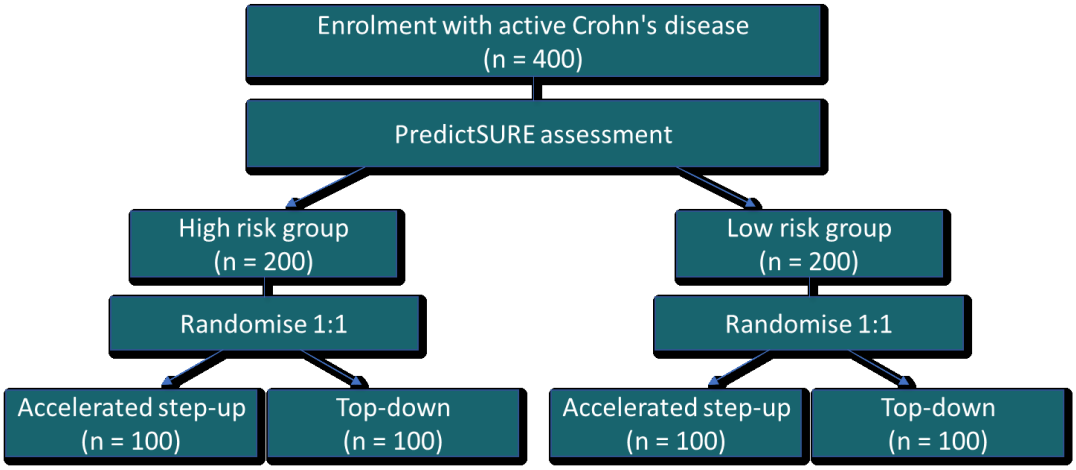
Ongoing study

PredictSure-IBD is currently being evaluated in a multicentre, randomised, biomarker-stratified trial (PROFILE). The trial will compare the relative efficacy of 'top-down' and 'accelerated step-up' treatment strategies in patients with newly diagnosed (within 3 months) active[5] Crohn's disease classified as high-risk or low-risk for frequently relapsing disease course. The trial is currently recruiting, with publication expected in 2022 (Parkes et al. 2018). Trial design is presented in Figure 2; following PredictSURE-IBD risk stratification, patients will be randomised in a 1:1 fashion to either 'top-down' or 'accelerated step-up' treatment arms. The primary

[5] Defined as clinical evidence of active Crohn's disease (corresponding to HBI score above 7), endoscopic evidence of at least moderately active Crohn's disease (corresponding to Simplified Endoscopic Score in Crohn's disease above 6 or above 4 if limited to the terminal ileum), and C reactive protein above the upper limit of normal on local assay or faecal calprotectin above 200 microgram/g.

outcome will be the incidence of sustained surgery and steroid-free remission from the completion of induction treatment through to week 48.

Figure 2 Trial design of the PROFILE study (Parkes et al. 2018)



Modelling approach

The PROFILE study is currently ongoing and there may be no published studies for PredictSURE-IBD or IBDX showing the impact of these test on treatment choices or patient outcomes; therefore, a linked-evidence approach to modelling is likely to be needed. Studies suggest that PredictSURE-IBD and IBDX can identify patients at a higher risk of a severe course of disease, who may benefit from the 'top-down' approach (early treatment with biologics). Benefits of 'top-down' treatment have previously been reported in an unselected population of people with Crohn's disease, but it is not clear how these benefits would translate to the 'high-risk' group of patients identified by PredictSURE-IBD or IBDX.

'Top-down' approach

'Top-down' therapy refers to a treatment strategy where people with newly diagnosed Crohn's disease are offered a more potent biological therapy, usually TNF-alpha inhibitors. This therapy can also be referred to as an early treatment with biologics. However, this therapy may be associated with higher risk of adverse events.

Usually, 'top-down' strategy refers to a first-line treatment with biologics but some 'top-down' studies allow an initial course of steroids before the start of biological therapy. However, studies enrolling people who had more than 1 course of steroids and/or other therapies, or have long-lasting disease (usually, longer than 3-6 months) would not generally be considered a 'top-down' approach. Clinical experts commented that in clinical practice, there may be no clear distinction between 'top-down' and 'very accelerated step-up' strategies.

Population

Evidence on the use of the 2 tests in children and on the comparison of 'step-up'/ 'top-down' treatment approaches in children may be limited. An economic model developed for adults with Crohn's disease may not be generalizable to a paediatric population given the differences in natural history and treatment pathways between adults and children with Crohn's disease.

Crohn's disease is a heterogenous disease. The performance of the 2 tests and potential clinical utility across all disease subtypes may need to be explored. Furthermore, people with Crohn's disease often present with comorbid conditions; the impact of comorbidities on analytical and clinical utility of PredictSURE-IBD and IBDX may need to be explored.

8 Potential equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

PredictSURE-IBD has not yet been validated in children (17 years or younger); therefore, prognostic accuracy of PredictSURE-IBD in children is unknown. However, evidence on children may become available while the guidance is in development. IBDX has been studied in both adults and children.

Crohn's disease can have a substantial and long-term adverse effect on a person's ability to carry out normal day-to-day activities. Therefore, people with Crohn's disease may be covered under the disability provision of the Equality Act (2010).

9 Potential implementation issues

Evidence of clinical utility

The clinical utility of PredictSURE-IBD and IBDX to inform treatment and monitoring decisions that improve outcomes compared with standard care is uncertain. Clinical experts indicated that this is the biggest barrier to adoption.

Cost and commissioning

It is currently unclear who within the NHS would pay for the PredictSURE or IBDX tests. For example, the test could be included in the relevant outpatient tariff, or paid for by the Clinical Commissioning Groups on a case by case basis.

Sample collection and transport

Blood samples for PredictSURE-IBD test must be collected into a PAXgene Blood RNA tubes, which are not routinely used in the NHS. The manufacturer indicated they would initially provide the tubes free of charge. However, in the long run, the referring centres will have to buy the tubes themselves. The tubes may expire if not used in high volume, creating wastage. Sending samples from referring trusts to central laboratories is well established in the NHS.

IBDX tests require a small amount of the standard serum sample (no special tubes or sample preparation are needed).

Testing service

PredictSURE-IBD testing will initially be done by a single central laboratory. This laboratory is already providing a PredictSURE-IBD testing service as part of the PROFILE study. Currently, the testing is being done weekly, with the test result turnaround time of 7-10 days. However, if the demand is high, the test could be run daily, with an expected turnaround time of approximately 3 days. Experts expressed concern about possible delays if the central laboratory does not have the capacity to meet national demand for testing. However, the manufacturer indicated that if demand is high, testing can be extended to other NHS centre of excellence laboratories in the UK. The manufacturer will support staff training. Adequate quality assurance systems would have to be in place at the testing laboratories. At the moment, there is no nationally recognised quality assurance system.

In countries other than the UK, IBDX testing is available via national laboratories, using kits purchased from Glycominds. Adequate quality assurance systems would have to be in place at the testing laboratories providing the service.

Reporting test results

The results will be available, via a secure link, to download from the PredictSURE-IBD server. The link will be sent by the central laboratory to the referring clinician or the main contact at the referring laboratory. The central laboratory can also issue PredictSURE-IBD test results to the referring trust through their existing reporting mechanisms. PredictImmune will hold patient results (with no personal identifiable information) for 365 days on their secure server.

Clinical experts indicated that the 7-10 days turnaround time is an acceptable timeframe for clinical decision making.

Reporting test results for IBDX is likely to follow standard procedures.

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Appendix A Glossary of terms

Adalimumab: A recombinant human anti-TNF-alpha IgG1 monoclonal antibody

Anti-glycan antibodies: antibodies directed against microbial cell wall surface components

CD8+ cytotoxic T cells: cells of the immune system that are involved in the regulation of immune response

CD8+T cell exhaustion: a state characterized by the stepwise and progressive loss of T-cell functions

Immunosuppressants: A class of drugs used to supress of prevent an immune response

Inflammatory bowel disease: A group of inflammatory conditions of the colon and small intestine, the two most common being Crohn's disease and ulcerative colitis

Infliximab: A chimeric (human-murine) anti-TNF-alpha IgG1 monoclonal antibody

Seroreactivity - The reactivity of the blood serum, that is, the presence of specific antibodies (for example, against an infectious or non-infectious microorganism), in the serum of a patient

TNF-alpha inhibitors: Biological therapies which target the TNF-α protein with the aim of modifying the inflammatory disease process

Ustekinumab: A fully human monoclonal antibody that targets interleukin-12 (IL-12) and IL-23

Vedolizumab: a humanised IgG1 monoclonal antibody that targets α4β7 integrin

Appendix B Abbreviations

BSG	British Society of Gastroenterology
CDAI	Crohn's Disease Activity Index
ECCO	European Crohn´s and Colitis Organisation
HBI	Harvey Bradshaw Index
RT-qPCR	Quantitative polymerase chain reaction with reverse transcription
TNF-alpha	Tumour necrosis factor alpha
TPMT	thiopurine methyltransferase

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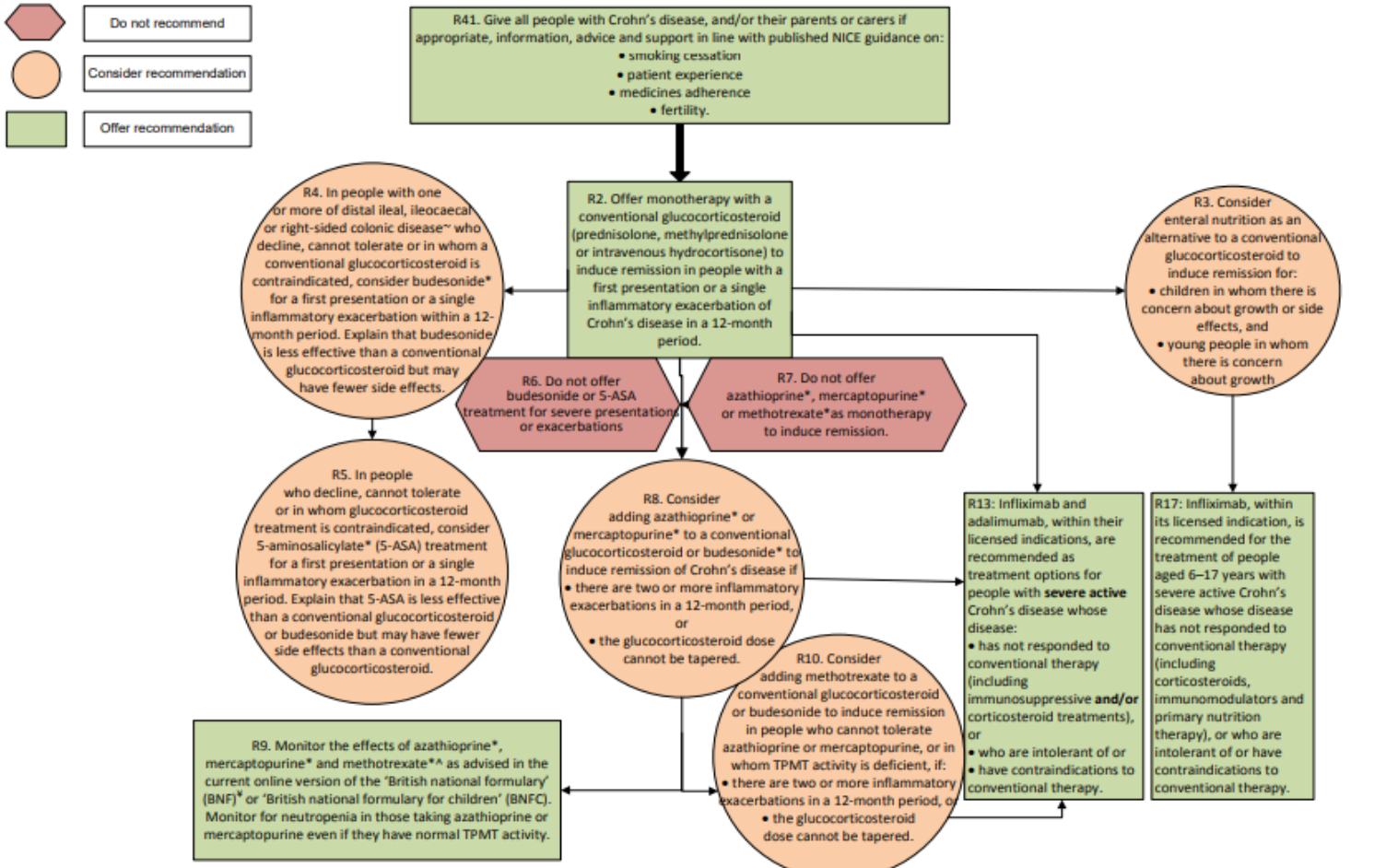
Appendix D NICE guidance on ‘step-up’ therapy in Crohn’s disease



~See recommendation 31 and 32 for when to consider surgery early in the course of the disease for people whose disease is limited to the distal ileum *Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine, mercaptopurine, methotrexate, mesalazine, olsalazine and balsalazide did not have UK marketing authorisation for inducing remission in Crohn's disease and budesonide did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council’s Good practice in prescribing medicines – guidance for doctors for further information. ^ Follow BNF/BNFC cautions on prescribing methotrexate. [¥]Advice on monitoring of immunosuppressives can be found in the BNF/BNFC. The gastroenterology chapter and other relevant sections should be consulted.