NICE advice

PredictSure-IBD for inflammatory bowel disease prognosis

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is PredictSure-IBD. It is used as a prognostic tool to identify patients who will go on to have severe, relapsing Crohn's disease and ulcerative colitis and who might benefit from early aggressive (biological) therapy.
- The **innovative aspect** is that it is designed to predict clinical prognosis when Crohn's disease or ulcerative colitis are diagnosed, using a combination of existing assays based on polymerase chain reaction technology.
- The intended **place in therapy** would be to help the gastroenterologist's choice of treatment for people who have been recently diagnosed with Crohn's disease or ulcerative colitis.
- The **main points from the evidence** summarised in this briefing are from 2 biochemical studies and 1 prospective cohort study with 248 adult patients in a UK NHS secondary care outpatient setting. They show that PredictSure-IBD can accurately show which patients are likely to have severe relapsing disease. Evidence suggests an improved disease response when treatment with tumour necrosis factor (TNF) inhibitors is started early.
- **Key uncertainties** around the evidence or technology are that the test has only been validated in biochemical studies.
- The **cost** of PredictSure-IBD is £1,250 per unit (exclusive of VAT). The **resource impact** could be much lower than the current standard of care if starting anti-TNF therapy early leads to disease remission and prevents disease flare-ups but this is uncertain because it depends on

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- the positive predictive value of the test, which is not yet determined.

The technology

PredictSure-IBD (PredictImmune Limited) is a prognostic assay which predicts long-term disease outcomes in immune-mediated diseases such as Crohn's disease and ulcerative colitis. This can help to personalise medical treatment. The assay reports the risk of severe, relapsing disease in patients recently diagnosed with Crohn's disease or ulcerative colitis. This allows anti-tumour necrosis factor (TNF) treatment to be offered to those who will benefit the most and to be given early in the disease course when it is most effective. The assay needs 2.5 ml of whole blood which is processed in a reverse transcriptase polymerase chain reaction (RT-PCR). This gives a result within 48 hours. The test is run on a Roche LightCycler PCR platform. After measuring the expression of 17 genes, the company's algorithm produces a clinical outcome prediction (high or low risk) for severe, relapsing Crohn's disease or ulcerative colitis.

Innovations

PredictSure-IBD is an assay designed to predict the prognosis for people recently diagnosed with Crohn's disease or ulcerative colitis. By identifying those whose disease is more likely to progress to severe and relapsing, PredictSure-IBD can allow more personalised and effective anti-TNF treatment to start sooner.

Current care pathway

After initial diagnostic investigations and tests for inflammatory bowel disease (IBD), drug treatment is prescribed in a stepped approach. This depends on the efficacy of the treatment, tolerability of the side effects and the severity of the disease.

Severe, active Crohn's disease is defined as very poor general health and 1 or more of: weight loss, fever, severe pain in the abdomen, frequent bouts (3 or more per day) of diarrhoea. If this does not respond to steroids and immunosuppressive drugs, the biological TNF inhibitors infliximab or adalimumab can be offered. Surgery can also be considered. Infliximab is an option for adults, children and young people aged 6 and over, but adalimumab is an option for adults only. Both drugs can be used with an immunosuppressive drug. NICE guidance also recommends vedolizumab after TNF inhibitors have not responded.

Severe ulcerative colitis is defined as 6 or more bowel movements a day with visible blood, high temperature and heart rate and anaemia. It is treated first with intravenous corticosteroids or intravenous ciclosporin for people who cannot tolerate, or decline, corticosteroids. Some people

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might also need surgery. If there is no improvement after 72 hours, corticosteroids and ciclosporin can be given together or surgery can be reconsidered. Infliximab can also be prescribed to people who cannot tolerate ciclosporin.

The PredictSure-IBD test would identify people for early treatment with TNF inhibitors. However, TNF inhibitors are not currently recommended by NICE for first-line treatment of Crohn's disease.

Population, setting and intended user

PredictSure-IBD is for use in people with Crohn's disease or ulcerative colitis before drug therapy has been started. The test would usually be done in an outpatient gastroenterology clinic and could also be used during a flare of disease for inpatients. It needs a 2.5 ml whole blood sample to be taken by a trained professional (such as a phlebotomist, nurse or doctor). The sample is then processed by a centralised laboratory facility in Cambridge, and the result returned to a specialist gastroenterologist within 7 days.

No additional staff training is needed to do the test, which is on an industry standard LightCycler RT-PCR system.

Costs

Technology costs

PredictSure-IBD was launched in April 2019 with a price of around £1,250.

Costs of standard care

Currently in the NHS, no testing is offered to personalise the treatment of IBD. Current practice involves titrating and increasing drug treatment from steroids to immunosuppressives. Biological therapies are used on a 'step-up' and trial and error basis. In 2012, NICE estimated this to cost £31,000 per person over 5 years because of the costs of treatment, maintenance therapies, and managing complications associated with the disease and treatment.

Resource consequences

The cost of introducing PredictSure-IBD to the treatment pathway could lead to substantial cost savings overall. This is if starting anti-TNF treatment earlier leads to reductions in disease flare-ups, use of maintenance therapy, surgery, disease complications and treatment complications.

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The resource consequences of introducing the technology are low because the test uses existing technology and takes 2.5 days to return a result. It is expected that a batch of tests will be done once a week, meaning results will be returned in 7 to 10 days. This fits within the current NHS approach to treatment.

The company have done market research with 50 NHS consultants to find out their views on using different treatments and approaches. Of the consultants questioned, 98% agreed there was a need for an assay to predict clinical outcome, and all consultants said they would be likely to use such a test. These consultants were treating at least 15 patients with Crohn's disease per week.

Regulatory information

PredictSure-IBD is a CE-marked in vitro diagnostic.

No manufacturer field safety notices or medical device alerts for this technology have been identified.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

No equality issues directly associated with the use of this test were identified. People with inflammatory bowel disease may be protected under the disability provision of the Equality Act.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

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Published evidence

Two published cohort studies and 1 prospective cohort study (currently under review) are summarised in this briefing. The studies provide biochemical 'proof of concept' evidence for the signature underlying PredictSure-IBD. They also provide evidence that the assay can predict severe relapsing Crohn's disease and severe ulcerative colitis in patients with inflammatory bowel disease (IBD). Both of the studies use the underlying signature for PredictSure-IBD but do not use the actual test. The prospective study looks at the use of PredictSure-IBD in clinical practice and follows up patients for around 5 years. These studies are summarised in table 1.

Overall assessment of the evidence

One cohort study used existing assays together to detect patterns of gene expression related to T-cell exhaustion. This showed some specific signatures in several infectious and autoimmune diseases, including IBD. A specific transcriptional signature can identify patients with active, untreated Crohn's disease who could have beneficial long-term outcomes if anti-tumour necrosis factor (TNF) therapy is started early. The company used this algorithm to do further applications of the assay in different cohorts. They present data for the test used in 350 patients with any type of autoimmune disease, but this is limited to 210 patients with Crohn's disease and ulcerative colitis.

Most of the evidence is retrospective analyses of cohorts of blood samples from patients recruited to the study when first diagnosed. They have been followed through to development of Crohn's disease from first presentation with IBD. There are few demographics or other details of the patients available.

The prospective cohort study recruited patients with IBD for testing with PredictSure-IBD. These patients were followed-up for around 5 years. PredictSure-IBD identified 2 patient subgroups with different severity of disease. Further research is being done by recruiting patients to have the test and then have treatment based on the results.

Table 1 Summary of selected studies

McKinney et al. (2015)	
Study size, design and location	Observational cohort study of 58 people with Crohn's disease. Location: UK.

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Intervention and comparator(s)	Polymerase chain reaction analysis of blood samples to detect CD8 T-cell transcriptional signature. No comparator.
Key outcomes	Results showed a transcriptional signature of the expression of surrogate markers of co-stimulation/exhaustion signatures in independent data sets. This confirmed an association with poor outcome in autoimmune and inflammatory disease. The results are based on a retrospective analysis of a relatively small group of 58 patients. The study also looked at other immune-related disorders (type 1 diabetes, adeno-associated virus, systemic lupus erythematosus, idiopathic pulmonary fibrosis and dengue haemorrhagic fever) as well as association of signatures with good clinical outcome or response to therapy in infections (hepatitis C virus) and vaccination (yellow fever, malaria, influenza).
Strengths and limitations	This is a high-quality biochemical study looking at markers in blood samples characteristic of immune response in terms of up and down gene regulation in response to various infectious and autoimmune diseases. It showed there was a clear signature in the blood of untreated people with Crohn's disease at the point they presented as patients with IBD, which was associated with poor outcome. This is the same underlying signature as that in the PredictSure-IBD test but not identical to that used in the test.
Lee et al. (2011)	
Study size, design and location	Observational prospective study of 35 people with Crohn's disease and 32 people with ulcerative colitis. Location: UK.
Intervention and comparator(s)	Standard care step-up strategy given by doctors blinded to the PredictSure-IBD signature test results (note – this study did not use the actual test but did use the same signature that is used in PredictSure-IBD). No comparator.

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Key outcomes	The study used statistical techniques to identify 2 subgroups of patients, IBD1 and IBD2. This showed CD8+ T-cell transcriptional signatures that identified 2 subgroups that had very different disease courses. Patients in the subgroup with elevated expression of genes involved in antigen-dependent T-cell responses had substantially higher incidence of frequently relapsing disease. The authors comment that this suggests that the course of otherwise distinct autoimmune and inflammatory conditions may be influenced by common pathways and identifies the first biomarker that can predict prognosis in Crohn's disease at first diagnosis. This is a step toward personalised therapy.
Strengths and limitations	This study presents a data analysis of results from the PredictSure-IBD signature in a cohort of Crohn's disease patients, 66% of whom were previously undiagnosed. The patients were recruited specifically for this study and all treatment was blinded to the test results. The study is relatively small and gives basic demographic information for the patients. Very detailed descriptions of the treatment course and outcomes are presented in the supplementary information as are details of the complex statistical methods used in the analysis.
Biasci et al. (2019)	
Study size, design and location	Prospective cohort study of 66 people with Crohn's disease and 57 people with ulcerative colitis. Location: UK.
Intervention and comparator(s)	People with previously untreated Crohn's and ulcerative colitis were tested with PredictSure-IBD. Clinicians were blinded to the test result.
Key outcomes	There were 33 people with Crohn's disease and 24 people with ulcerative colitis classified as IBD1 phenotype. These people had more aggressive disease and needed earlier and more frequent escalations in treatment in comparison to people identified as having the IBD2 phenotype over a median follow up of 5.3 years.

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Strengths and limitations	People included in the study were treated according to national guidelines at the discretion of their clinician rather than following a formal protocol. This may have led to some differences in the way individuals were treated but is representative of clinical practice in the NHS. The study results show that people with IBD1 phenotype have more severe disease but does not show how basing therapy choices on this might improve outcomes (this is being assessed in the PROFILE trial).
Abbreviations: CD8, cluster of differentiation 8; IBD, inflammatory bowel disease.	

Recent and ongoing studies

- PROFILE – personalised medicine in Crohn's disease. Status: recruiting, publication expected 2022. Indication: Crohn's disease. Devices: PredictSure-IBD (funded by a Wellcome Trust Translational Award).

Specialist commentator comments

Comments on this technology were invited from clinical specialists working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

All specialists were familiar with this technology or other similar methods.

Level of innovation

Two specialists stated that PredictSure-IBD is a novel technology. One specialist stated that there was not enough evidence to determine how innovative PredictSure-IBD is.

Potential patient impact

The 3 experts agreed that PredictSure-IBD could offer benefits to people with Crohn's disease. The experts stated that PredictSure-IBD might be a helpful test to determine the most appropriate biologic therapy. One expert noted that this could be particularly important to people with severe inflammation and may help avoid surgery and long-term complications. One expert noted that PredictSure-IBD could help patients with good outcomes avoid taking unnecessary biologics.

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Potential system impact

All experts agreed that PredictSure-IBD could provide information to allow clinicians to prescribe more appropriate therapy. One expert noted that there was potential for this to reduce the length of hospital stays, surgery and long-term complications. However this is highly dependent on the positive predictive value of the test, which has not yet been determined. Two experts stated that the use of PredictSure-IBD is likely to lead to cost savings if it performs as expected, but one expert noted that the cost of drug treatment will reduce as biosimilars to treat Crohn's disease will be available for December 2018.

General comments

One expert noted that the current evidence suggests that the test is successful in predicting disease outcome in the early stages. However, the value of the test is dependent on the effectiveness of early intervention and how good the test is at discrimination between good and poor outcomes. Two experts noted that people with Crohn's disease and ulcerative colitis may benefit from this test.

Patient organisation comments

A spokesperson for Crohn's and Colitis UK, a UK health charity that supports people affected by Crohn's disease, thought the test could change the way patients with Crohn's disease are treated by identifying the most effective treatment as early as possible. The test might also reduce the need to experiment with other drug treatment options that have potentially harmful side effects. They noted diagnostics of this type do not currently exist and they could reduce the need for surgery. There are limited treatment options for those with Crohn's disease and a lot of unmet need.

Specialist commentators

The following clinicians contributed to this briefing:

- Prof Mohammad Ilyas, professor of pathology, Faculty of Medicine and Health Sciences, University of Nottingham. Did not declare any interests.
- Dr Anjan Dhar, consultant gastroenterologist, County Durham and Darlington NHS Foundation Trust. Dr Dhar is a lead investigator for the PROFILE trial.
- Dr Robert Logan, consultant gastroeneterologist, Kings College Hospital NHS Foundation Trust. Did not declare any interests.

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Representatives from the following patient organisations contributed to this briefing:

- Crohn's and Colitis UK.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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