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Diagnostics Assessment Programme

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

The following documents are made available to stakeholders:

1. **Stakeholder comments on the Diagnostics Consultation Document (DCD) and NICE's response**
2. **Outcome of the resolution panel meeting held on 19 July 2021**
3. **Additional scenario analysis prepared by BMJ-TAG**
4. **Stakeholder comments on the additional analysis and response by BMJ-TAG**
5. **Appendix to response to stakeholder comments prepared by BMJ-TAG**
6. **Erratum to Appendix to response to stakeholder comments prepared by BMJ-TAG**

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 7 October 2020

THEME: General

Comment number	Name and organisation	Section number	Comment	NICE response
1	British Society of Gastroenterology		No comment	No response required
2	Crohn's & Colitis UK		**Statement** In 2009, Crohn's and Colitis UK (formerly known as National Association of Crohn's and Colitis) awarded a research grant to Dr [redacted] at the Cambridge Institute for Medical Research. The research aimed to assess whether genes expressed by white blood cell subsets, isolated from patients with IBD, correlated to IBD activity. Title: The application of gene expression profiling in Inflammatory Bowel Disease to predict disease behaviour Grant Holding Institution: University of Cambridge Lead Investigator: Dr [redacted] Grant Amount: £81,981 Duration: 24 months As part of the standard terms and conditions of Crohn's & Colitis UK research grants, we reserve the right to a share in the revenue arising from Intellectual Property. In January 2017 we were informed by the grant holder that a single biomarker identified through our funding would form a minor part of the diagnostic test, which was to be commercialised by a spin-out company called PredictImmune Ltd. In February 2017, Crohn's & Colitis UK agreed to a revenue share of 8.5% of the value of the single biomarker arising from the research we had funded. We understand that numerous biomarkers make up the diagnostic test to which we do not have rights and we will not receive a revenue.	Thank you for your comment, which the committee has considered.

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			To date, no revenue has been received. End of statement	
3	Crohn's & Colitis UK		**Crohn's & Colitis UK** Crohn's & Colitis UK is the major UK charity for everyone in the UK affected by these conditions. Established in 1979, we provide a wide range of information and support, work to improve treatment and care, raise awareness and fund research.	Thank you for your comment, which the committee has considered.
4	Crohn's & Colitis UK	1.1 and 1.2	In light of the stated current absence of sufficient robust evidence on which these prognostic tests could be recommended for use in the NHS, Crohn's & Colitis UK wishes to highlight two primary issues. This response is grounded in the experiences of people with Crohn's Disease and Inflammatory Bowel Disease more generally, our knowledge of current treatment options and diagnostic technology, plus recently published research. 1. Given that these prognostic tests have not been recommended at this point due to the stated current absence of sufficient robust information, **we would seek a commitment from NICE to review this decision as soon as such evidence becomes available.** It is our understanding that the current PROFILE trial has recruited well across many of the sites involved and that the results should be available by 2022. This would appear to be an appropriate time to revisit these recommendations unless additional evidence is available sooner. 2. We would seek to remind the Committee that, as mentioned by the patient expert, many people with Crohn's Disease cycle through various treatment options, often for extended periods. These treatments, including steroids, immunosuppressants and surgery, are associated with a range of side	Thank you for your comment, which the committee has considered. NICE reviews the evidence 3 years after publication of guidance to ensure that any relevant new evidence is identified. However, NICE may review and update the guidance at any time if significant new evidence becomes available. NICE is keen to hear about any new evidence that becomes available before the review date (please send information to diagnostics@nice.org.uk). NICE will assess the likely impact of the new evidence on the recommendations and will propose an update to the published guidance if required.

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			effects and potential complications with additional significant impact on quality of life. Therefore, a reliable prognostic test which then allows a much greater personalised and targeted approach to treatment would be widely welcomed by people with Crohn's Disease	
5	Crohn's & Colitis UK	7	We would reiterate the request made in relation to Pt. 1.1 – that NICE commits to reviewing this Guidance in the light of any new relevant research becoming available, notably the PROFILE study which is due to report in 2022.	Thank you for your comment, which the committee has considered. NICE reviews the evidence 3 years after publication of guidance to ensure that any relevant new evidence is identified. However, NICE may review and update the guidance at any time if significant new evidence becomes available. NICE is keen to hear about any new evidence that becomes available before the review date (please send information to diagnostics@nice.org.uk). NICE will assess the likely impact of the new evidence on the recommendations and will propose an update to the published guidance if required.
6	Crohn's & Colitis UK	5.1.	We would support the need for further research in the areas identified to enable confidence in the tests, reflecting relevant differences between treatment pathways for paediatric and adult patients, and to support effective shared decision-making about treatment options.	Thank you for your comment, which the committee has considered.
7	PredictImmune Ltd		**References**	Thank you for your comment, which the committee has considered.

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THEME: General

Comment number	Name and organisation	Section number	Comment	NICE response
			1. D. C. Massey, F. Bredin, M. Parkes, Use of sirolimus (rapamycin) to treat refractory Crohn's disease. *Gut* **57**, 1294-1296 (2008). 2. M. Lazzerini *et al.*, Effect of thalidomide on clinical remission in children and adolescents with refractory Crohn disease: a randomized clinical trial. *JAMA* **310**, 2164-2173 (2013). 3. G. D'Haens *et al.*, Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* **371**, 660-667 (2008). 4. D. R. Hoekman *et al.*, Long-term Outcome of Early Combined Immunosuppression Versus Conventional Management in Newly Diagnosed Crohn's Disease. *J Crohns Colitis* **12**, 517-524 (2018). 5. M. Marchetti, N. L. Liberato, A. Di Sabatino, G. R. Corazza, Cost-effectiveness analysis of top-down versus step-up strategies in patients with newly diagnosed active luminal Crohn's disease. *Eur J Health Econ* **14**, 853-861 (2013). 6. J. F. Colombel *et al.*, Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* **362**, 1383-1395 (2010). 7. F. Baert *et al.*, Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology* **138**, 463-468; quiz e410-461 (2010). 8. D. R. Berg, J. F. Colombel, R. Ungaro, The Role of Early Biologic Therapy in Inflammatory Bowel Disease. *Inflamm Bowel Dis* **25**, 1896-1905 (2019).	

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THEME: Clinical need

Comment number	Name and organisation	Section number	Comment	NICE response
8	Crohn's & Colitis UK	2.1	**Clinical need and practice** We would like to make the Committee aware of recent research from the SAIL Databank (Inflammatory Bowel Disease in Numbers: Understanding the Scale of Crohn's and Colitis in Wales, 2020, SAIL Databank and Crohn's & Colitis UK), which suggests that the lifetime prevalence is substantially higher than stated at 1:271. This reflects the findings of similar research in South West England and Lothian (Hamilton et al, Prevalence and phenotype of IBD across primary and secondary care: implications for colorectal cancer surveillance. *Gut* 2018; Jones et al, Multi-parameter datasets are required to identify the true prevalence of IBD: the Lothian IBD registry, *Journal of Crohn's and Colitis,* 2019). Crohn's Disease can start at any age, but usually appears for the first time between the ages of 10 and 40, although there is a small peak in the number of people diagnosed over the age of 60. The research highlighted above indicated that the highest incidence of Crohn's disease in the Welsh primary care population was in the 18-29 age group with the overall median and mean age being 33 years. The description of the condition and its impact within the consultation document is highly simplified and we would like to see the description extended to reflect this more fully. This is a complex, lifelong condition in which the intestines become swollen, inflamed and ulcerated. Symptoms include abdominal pain, weight loss, tenesmus (constant urge to have a bowel movement), diarrhoea and profound fatigue (which can still be experienced by a proportion of people during remission). Symptoms vary in severity from person to person and flare up or improve, often unpredictably. Additionally, there are a wide range of extraintestinal manifestations, which can affect the joints, skin, bones, eyes, kidneys and liver and an associated psychological impact.	Thank you for your comment, which the committee has considered. The committee considered the impact and description of the condition further at the second committee meeting. Section 4.1 of the diagnostics guidance has been updated to extend the description and impact of the condition.

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			People living with the conditions often face a lifetime of medication and, in many cases, repeated and major surgery. The impact of the condition and its treatment on all aspects of a person's life can be highly debilitating, affecting relationships and emotional wellbeing, education and employment. Given the often relatively early age of diagnosis, the adverse effects associated with living with the condition may be experienced for decades. Further information can be found at https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis	
9	Crohn's & Colitis UK	4.1	Recent research from University of London and St George's University Hospitals NHS Foundation Trust (see below) analysed 97,000 IBD diagnoses made during the period 1998 – 2016. It identified that almost 10% of people waited over 5 years for a diagnosis of Crohn's disease from the onset of their symptoms. This delay in initial diagnosis, when added to the time taken later cycling through treatment regimes, means that people with Crohn's disease can often spend many years where their life is being adversely affected by the disease as outlined below. An effective prognostic test could significantly reduce the adverse effects which people report during this extended period	Thank you for your comment, which the committee has considered. The committee considered the potential benefits of a prognostic test further at the second committee meeting. Section 4.1 of the diagnostics guidance has been updated to include more of these potential benefits.

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			Conclusions There is an excess of GI symptoms 5 years before diagnosis of IBD compared to the background population, probably attributable to undiagnosed disease. Previous diagnoses of IBS and depression are associated with delays in specialist review. Enhanced pathways are needed to accelerate specialist referral and timely IBD diagnosis. **Prevalence and Duration of Gastrointestinal Symptoms Before Diagnosis of Inflammatory Bowel Disease and Predictors of Timely Specialist Review: A Population-Based Study** J Blackwell, S Saxena, N Jayasooriya, A Bottle, I Petersen, M Hotopf, C Alexakis, R C Pollok POP-IBD study group In addition to the effects rightly highlighted by the patient expert on the Committee, Crohn's Disease can often have other serious adverse effects, both on the person with the condition and on those around them. Therefore, the potential benefits of an effective prognostic test could include: • **Increased quality of life outcomes and a reduction in physical symptoms** when prescribers are able to treat those with more severe, relapsing disease more effectively from the outset. This will **result in a reduced need to treat with both unncessary and less effective first line drug treatments** during the 'step-up' stage • a **reduction in potential side effects** from first line drug treatment options. These can include: opportunistic infections, steroid-induced psychosis, dependence, diabetes and osteoporosis from the use of corticosteroids; risk of	

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			non-Hodgkin's lymphoma; early hypersensitivity reactions such as fever and pancreatitis; bone marrow suppression and hepatotoxicity associated with azathioprine, mercaptopurine or methotrexate. • A **reduction in physical symptoms -** being able to identify more effective drug treatment at an earlier stage could **reduce symptoms** such as frequent bloody and painful diarrhoea, anaemia, cramping pains in the abdomen, joint pain, weight loss and profound fatigue. It also has the potential to reduce secondary symptoms such as bone thinning, liver complications, inflammation of the joints, skin conditions, eye problems and blood clots. • **Increased quality of life outcomes -** more effective and earlier drug treatment can enable patients to **resume a more normal life and daily routines**; continue with education, employment and training opportunities; have a family; maintain and form new personal relationships; travel and enjoy an active social life and interests. • From a **psychological perspective**, an effective prognostic test has the potential to **reduce the anger, embarrassment, frustration, sadness and fear** (for example, of surgery or complications) associated with living with this condition through earlier and more effective treatment. Rates of anxiety and depression are higher in people with Inflammatory Bowel Disease. The frequent and urgent need for the toilet, together with loss of sleep and the invisible symptoms of pain and continual or profound fatigue, can severely affect self-esteem and social functioning. • **Effective prognostic tests** have the potential to **reduce**, **prevent or delay the need for surgery.**	

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			• Some people living with Crohn's Disease **may require significant support from their carers and families**. This may include support with cleaning themselves, or washing clothes, floors, bedding and/or toilets following involuntary evacuation of the bowel and support with dressing and remaking beds. **The impact of Crohn's Disease on every aspect of an individual's life, and the lives of those around them, highlights the need for timely and effective treament.** All the above benefits stemming from the early identification of an effective treatment regime to the person with Crohn's Disease have a concomitant benefit to NHS services. A person experiencing a controlled disease makes many fewer demands on healthcare services than a person with an uncontrolled or flaring condition. Each year, Crohn's Disease care costs: • £1,800 for patients in remission • £10,513 for patients in relapse (Ghosh N, Premchand P. UK cost of care model for inflammatory bowel disease, Frontline Gastroenterology, 2015)	

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THEME: Treatment pathway

Comment number	Name and organisation	Section number	Comment	NICE response
10	Crohn's & Colitis UK	2.3	**Use of steroids, when to introduce biologics and appropriate response measures** The consultation document suggests that "step-up treatment involves multiple courses of steroids before changing to a stronger treatment". We would strongly urge the Committee to reference the BSG consensus guidelines on the management of children and adults (Lamb et al, Gut, 2020) which "recommend that corticosteroid therapy is harmful and should be minimised by specialist intervention and involvement with the multidisciplinary team to explore other treatment options (GRADE: strong recommendation, moderate-quality evidence. Agreement: 97.8%)" [Statement 98] The guidelines further "recommend that systemic or locally acting corticosteroids should be avoided as maintenance therapy in Crohn's Disease due to toxicity and lack of efficacy (GRADE: strong recommendation, high-quality evidence. Agreement: 100%)" [Statement 38] Additionally, "that moderate to severely active uncomplicated luminal Crohn's Disease should be treated initialy with systemic corticosteroids", with the suggestion "that those with extensive disease or other poor prognostic features should be considered for early introduction of biological therapy". The BSG guidelines state that the decision to start biological therapy should also consider factors such as stage of life, work absence and availability of other treatment options and encourage discussion in a multidisciplinary team meeting. Patients should be fully involved in decisions and supported to understand the benefits and risks of different treatment options.	Thank you for your comment, which the committee has considered. The committee considered the use of steroids in the treatment pathway at the second committee meeting. It noted that corticosteroids continue to be used as first line treatment in adults with moderate to severe Crohn's disease except where contraindicated. In a top down treatment strategy, a shorter period of corticosteroids, or sometimes no corticosteroids, may be used before starting treatment on biologics. This detail has been added to section 4.7 of the diagnostics guidance.

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			We would urge the Committee to reflect the importance of quality of life and patient-reported measures, as well as shared decision-making in the definition of "adequate response" to treatment. Currently, this is focused in the consultation document on "no clinical symptoms, no signs of ongoing inflammation, or both." The BSG guidelines refer to both endoscopic and quality of life measures, presenting a more complete picture to inform decision-making, including measures that are important to the patient and should be considered.	
11	PredictImmune Ltd	4.2.2	We note that the treatment sequence proposed by the EAG does not reflect either UK clinical practice or current NICE guidance for the treatment of Crohn's disease (NC129, https://www.nice.org.uk/guidance/ng129). The EAG model assumes that steroid therapy given in step-up regimen 'cancels out' that given in a top-down regimen as 100% of step-up patients are assumed to progress directly to an immunomodulator from steroid (hence the only difference in the regimens is assumed to be inclusion of an immunomodulator treatment in step-up therapy). The EAG chose to deviate from the current NICE guidelines as clinical experts advised that 100% patients would progress to an immunomodulator. We note that NICE guidance is recent (published May 2019) and are not aware of more recent evidence supporting the novel treatment sequence included by the EAG. We also provide here two pieces of evidence suggesting that the EAG treatment regimen is not reflected in current UK clinical practice. First, we have queried the UK NIHR IBD BioResource (https://www.ibdbioresource.nihr.ac.uk/) a collection of almost 35,000 IBD patients from 125 participating centres in the UK. This analysis (available to anyone approaching the BioResource, including the EAG and provided here) demonstrated that, of CD patients recently recruited to the IBD Bioresource within 3 years of their diagnosis, 43.7% had not received an immunomodulator or biologic at time of	Thank you for your comment, which the committee has considered. The committee heard from the EAG that the assumption of not including corticosteroids as the first treatment step in the top down and the step up arms is based on a model simplification. The decision to exclude this step in the model was based on the assumption that including corticosteroids would not impact model results given that 100% of high-risk patients (in both the top down and the step up arms) would receive an initial induction treatment with corticosteroids and move to the next treatment steps. This assumption is based on the following: 1) In top down, steroids are provided as initial treatment, while the logistics of arranging anti-TNFα take place. 2) In step up, 100% of patients need to be escalated to an immunomodulator because

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			recruitment (474/1083, avg time from diagnosis to recruitment = 1.2 years). Of patients recruited within 5 years of their diagnosis, 33.5% had not received an immunomodulator or biologic by time of recruitment (969/2889, avg time from diagnosis to recruitment = 1.6 years). Of patients recruited within 10 years of their diagnosis, 23.7%% had not received an immunomodulator or biologic by time of recruitment (1585/6700, avg time from diagnosis to recruitment = 3.5 years). Secondly, The PROFILE trial clinical protocol (https://bmjopen.bmj.com/content/8/12/e026767) includes both a step-up and top down arm, and has been agreed by 45 participating UK centres who have signed up to use of the protocol. In PROFILE, the protocolized step-up arm does not include progression directly from a course of induction corticosteroid to immunomodulator treatment. We also note that this assumption by the EAG has knock-on consequences that have impacted upon the conclusions drawn: • exclusion of individual patient data with exclusion of patients deemed not to follow the UK clinical treatment sequence (section 4.2.4.1). Patients receiving steroid therapy and not progressing to an immunomodulator are inappropriately excluded from consideration (representing over 50% of available patient data in the Biasci et al. study). • exclusion of published clinical evidence (section 4.1.1.2) on relative efficacy of early TD therapy, because this evidence does not conform to what they incorrectly consider to be the current UK treatment sequence.	it is assumed the modelled population cannot be managed with corticosteroids alone. The committee heard further from the EAG that: 1) Without knowing the disease severity of patients in the NIHR IBD BioResource, it is difficult to draw comparisons to the modelled population. 2) If the BioResource data set demonstrates that a proportion of high-risk patients do not need to be escalated from corticosteroids to the next treatment step (an immunomodulator or an anti-TNF) then the classification of these patients into high or low risk patients does not appear to lead to treatment differentiation (i.e. top down versus step up) as it is not beneficial for this group of patients. Therefore, making the use of any diagnostic tool on these patients unnecessary. Specialist committee members raised a concern about the potential risk of additional complications associated with the step up strategy given the delay for initiating treatment with biologics. The committee

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				heard that Hoekman *et al.* concluded that in the long-term (10 year follow up) there was no difference found in complications, such as new fistulas or surgery, across the top down and step up arms. Finally, the EAG notes that: 1) If the model were to include a proportion of patients who respond to initial treatment with corticosteroids in the top down and step up arms, the rate of response to corticosteroids between the top down and step up arms is expected to be the same; 2) If the model were to include a proportion of patients who respond to initial treatment with corticosteroids in the step arm alone, the benefit associated with the step up in the economic analysis would be even greater, as a proportion of patients could be successfully managed with a very inexpensive treatment in the step up arm compared with the top down arm. Nonetheless, the EAG appreciates that excluding the corticosteroid step from the model may result in a minor discrepancy in the costs associated with the two pathways, i.e. step up patients may receive a

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				full course of corticosteroids and top down patients are likely to only receive a partial course of corticosteroids. However, given the uncertainty around length of treatment and the low cost of corticosteroids, the EAG considers this assumption would have a minimal impact on the results. The committee's consideration is described in section 4.7 of the diagnostics guidance.

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THEME: Model structure

Comment number	Name and organisation	Section number	Comment	NICE response
12	PredictImmune Ltd	4.12	The EAG notes two key differences between their model and that submitted by PredictImmune: 1) the treatment sequence modelled by PredictImmune had an immunomodulator as a last treatment step in the top-down arm 2) PredictImmune's model assumed a constant relative treatment effect, whereas the EAG's model assumed a diminishing relative treatment effect Regarding point 1, the PredictImmune model deliberately included an immunomodulator as a last treatment step, which was missing in the EAG model. A longer sequence in the step-up arm vs. top-down means that patients always have an additional treatment step from which to derive QALY gain before they reach the end up the sequence, where quality of life is poor. The availability of an additional treatment in the step-up arm means that the EAG model is inherently biased against top-down treatment before any treatment effects are even incorporated. The EAG model allows a longer treatment sequence in step up arm, giving that arm an unreasonable advantage in terms of accruing QALY gain. It is important to consider that in practice patients may receive further immunomodulators after they fail multiple lines of biologic. For example, Crohn's disease patients have been successfully treated using other immunomodulators such as sirolimus(1), and thalidomide(2). The cessation of active treatment at the end of a set number of sequences is therefore artificial, and actual number of treatments will depend more on individual patient characteristics and clinician decision. This is an important consideration when length of sequence is such a critical determinant of QALY gain. In order to reduce bias due to unequal sequence lengths, immunomodulator was	Thank you for your comment, which the committee has considered. The committee heard from the EAG that its three clinical experts said that immunomodulators would not be given to patients after biologics. Therefore, the EAG's model does not include this as the last step at the end of top down treatment. The EAG undertook an additional scenario analysis where the immunomodulator step was included as the last treatment option in the top down treatment sequence. When this option is implemented in the model, the EAG's deterministic base case ICER (dominated against top down) changes to £105,148 per QALY gained, with top down (via the use of PredictSURE IBD) generating 0.07 additional QALYs compared to step up (15.93 top down versus 15.86 step up), at an additional cost of £7,502 (£209,427 top down versus £201,925 step up). This scenario results in an increase in the total QALYs associated with top down and a decrease in total costs compared with the EAG's base case ICER, while the costs and QALYs associated with standard care remain unchanged. The overall increase in QALYs and decrease in costs associated with top down is due to the immunomodulator treatment costs being lower than the costs associated with patients staying in the alternative moderate to severe health state after

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included at the end of the top-down sequence in the PredictImmune model in order to maintain sequences of similar lengths in the two arms.

Addressing point 2, the EAG's statement is incorrect. Although the treatment effect on escalations was kept constant over time, the effect was capped at 10 years (given a period of approximately 10 years of follow up from the d'Haens RCT(3) and the longer-term follow-up study by Hoekman(4)). Treatment effect was calculated from the median time to treatment escalation, as after this point the treatment effect is underpinned by very few patients at risk in the d'Haens Kaplan-Meier plot. The cap of 10 years was applied from model entry to all patients. The PredictImmune model does not therefore assume a constant treatment effect as suggested.

Most importantly, the EAG fails to describe the key difference between the EAG model and the PredictImmune and Marchetti models: the lack of any effect of earlier biologic on quality of life from higher remission rates. In line with the available literature (d'Haens et al., 2008; Colombel et al., 2010, Baert et al., 2010; Berg et al., 2019), both the PredictImmune and Marchetti models(5) assume that patients treated with earlier biologic experience higher mucosal healing and remission rates(3, 6-8). In contrast, the differences included in extended scenario modelling by the EAG are only marginal (Tables 1 and 2).

Table 1: Clinical remission rates at 1 year in key RCTs

Study	Conventional/accelerated step-up	Anti-TNF + immunomodulator arm
D'Haens et al., 2008	42.2%	61.5%
Colombel et al., 2010	54.7%	74.1%

Table 2: Clinical remission rates (maintenance phase) EAG model (Table 4 of EAG addendum)

they relapsed on second line biologics. Similarly, the immunomodulator state is associated with a probability of remission and mild disease and both health states yield a higher utility value than the moderate to severe states.

The committee heard from the EAG that the company assumed a constant relative risk of treatment escalation of 0.4 (for the first 10 years) for top down versus step up, whereas the EAG's modelling implies that the relative effect diminishes over time (that is, the relative risk gets closer to 1 and top down becomes as effective as step up as time goes by in the model). The relative risk in the EAG's model starts below 0.4 but rises above that after less than 3 months. After one year the relative risk in the EAG's model is at 0.7 and continues increasing after that. Therefore, the company's effectiveness estimates are potentially overestimating the effect of top down versus step up for the first 10 years of the model compared to the EAG's estimate.

As noted in the diagnostics assessment report and in the addendum, there is no available evidence to suggest that top down is more effective than step up as an entire treatment sequence. The only literature identified by the EAG with the only treatment effect available in literature being the D'Haens et al. estimate for a proxy of the anti-TNF versus immunomodulator step. This is the only step in the

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THEME: Model structure

<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><th>Intervention</th><th>Step-up</th><th>Top-down</th></tr>
<tr><td>Immunomodulator</td><td>25%</td><td>-</td></tr>
<tr><td>Anti-TNF</td><td>33%</td><td>33%</td></tr>
</table>
In both models, greater time in remission drives higher QALY gain under top-down treatment, and in the PredictImmune model greater remission additionally drives lower disease management costs. The gain in quality of life from improved remission rates on early biologic was in fact the largest driver of the ICER in the PredictImmune model, an outcome which was completely absent from the EAG model structure despite the considerable body of clinical evidence supporting it. Sensitivity analysis of the EAG model similarly identified the benefit of early top-down treatment as the key factor influencing outcome. We also note concerns raised by Specialist Committee Members that no benefit of early top-down therapy was considered.
</td><td>EAG's base case model for which a treatment effect is applied.

The committee heard that patients in the top down arm benefited from an initial treatment (anti-TNF), which is more effective than the first treatment in the step up arm (immunomodulators) in keeping patients from escalating to the next treatment step.

Furthermore, anti-TNFs are associated with the highest probability of achieving remission in the EAG model (37% for anti-TNF compared with 16% for immunomodulators and 13% for second line biologics after induction treatment) and maintaining remission (33% for anti-TNF compared with 25% for immunomodulators and 28% for second line biologics for maintenance treatment). The rates of remission do not change with time in the model, only the probability of relapse (and escalating to next treatment) changes with time. Furthermore, the remission state in the model is associated with higher QALYs and lower costs than the response or no-response states.

The committee also heard from the EAG that the remission rates in the EAG's model were those previously accepted in TA352 and were derived through a network meta-analysis. The EAG complemented the network meta-analysis data with its own meta-analysis (for details see section 4.2.4.3</td></tr>
</table>

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 7 October 2020

THEME: Model structure

Comment number	Name and organisation	Section number	Comment	NICE response
				in the EAG's report). Additionally, in D'Haens et al.; the rates of clinical remission, albeit statistically significant at year 1 (42.2% for step up and 61.5% for top down), become non-statistically significant at 78 and 104 weeks, with clinical remission rates being similar across treatment arms. The committee heard that the follow-up study (Hoekman et al.) concluded that in the long-term (10 year follow up) there was no difference found in mucosal healing for top down versus versus step up. For Colombel et al., the EAG could not find the values that the company reported, but instead found the probability of patients being in a corticosteroid-free clinical remission state of 28.2% for immunomodulators; 39.6% for anti-TNFs; and 72.2% for anti-TNFs+ immunomodulators). The EAG notes that there was no follow-up data after the 50-week data results. Additional text has been included in section 4.12 to clarify that the relative treatment effect in the company's model was capped at 10 years. The committee consideration is described in sections 4.7 and 4.8 of the diagnostics guidance.

NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 7 October 2020

THEME: Children and young people

Comment number	Name and organisation	Section number	Comment	NICE response
13	Crohn's & Colitis UK	4.13	We would support a distinct focus on children and young people given that Crohn's Disease when diagnosed in children and young people tends to be more severe in nature and there is a higher rate of usage of biologics in the treatment of paediatric Crohn's Disease and greater use of enteral nutrition to reduce/avoid steroid usage. This reinforces the need for early intervention with appropriate treatment regimes, as these young people may be living with this condition for more than 50 years. Without a personalised approach, with the potential to alter the disease course, these young people are potentially faced with many decades of medication with known side effects; medical and/or surgical procedures; adverse effects on mental wellbeing and significantly poorer quality of life.	Thank you for your comment, which the committee has considered. The committee considered that future research should take into account the different pathways that children may follow. The committee noted that this was described in sections 4.13 and 5.1 of the diagnostics guidance document, and that no changes were needed.

Diagnostics Assessment Programme

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

Outcome of the resolution panel meeting held on 19 July 2021

Resolution request 1 (transcribed from PredictImmune Ltd. submission)

The standard of care comparator in the economic model has deviated significantly from the comparator in the Scope.
The DAP Scope, sections 5, 3.2.2 and 3.2.2, explains the comparator, as well as Figure 1, all of which cite NICE's own guidelines NG129 published in 2019:

• Section 5: "The comparator is current standard care in the NHS in which most people are offered 'stepup' therapy or 'accelerated step-up therapy'.

• Section 3.2.2:"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.
• Section 3.2.3: "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)."

h In Top Down, patients are given corticosteroid (CS) only if they need it to induce remission while awaiting aTNF Conversely, in Step Up, patients only require IM if CS cannot be tapered or if they relapse. CS does not therefore cancel out.

PredictImmune repeatedly raised this issue, both in their responses to the Diagnostics Assessment Report (DAR) and during consultation. PredictImmune's evidence included:
• Pointing out that the Step Up sequence was not in line with NG129 and the Scope wording itself
• Referring to the UK NIHR IBD BioResource (https://www.ibdbioresource.nihr.ac.uk/); 43.7% Crohn's Disease (CD) patients recently recruited to the IBD Bioresource had not received an immunomodulator or biologic at time of recruitment (474/1083)
• Pointing out that in the PROFILE study (in moderate-severe Crohn's disease), which recruited 45 UK centres, the Step Up sequence commences with CS and patients ONLY escalate to IM if they do not respond sufficiently to CS or relapse
The EAG's rationale for their approach was that moderate-severe Crohn's Disease (CD) patients would systematically receive IM, underpinned by the opinion of two clinical advisors and British Society of Gastroenterology (BSG) guidelines (section 4.7 of the DGD). This demonstrates a total misunderstanding of the utility of the test. As explained in the PredictSURE Gut paper. there was no correlation between measures of inflammation at baseline (including endoscopic severity or steroid need) and risk group membership. If, as the EAG believes, all moderate to severe patients are being systematically treated with IM, then a sizeable proportion of patients in the UK is also currently being overtreated with IM. Under the current EAG model structure, it is not possible to test this hypothesis.

The EAG approach had severe consequences for the economic model. Not only did it result in a model that cannot test a key hypothesis of the PredictSURE test, but it led the ERG to censor all patients who had not escalated to an IM (the consequences of which we focus on later).

Much of this misinterpretation could have potentially been avoided early on had PredictImmune had the opportunity to provide explanation at the first committee meeting, as we discuss later.

Panel response to resolution request 1
Ground 1: not met
Ground 2: met
The panel felt that due process was followed but believed there is validity that modelling around standard of care as outlined in the NICE guideline would have benefited the appraisal process. The external assessment group will be asked to conduct a scenario analysis reflecting the pathway in the clinical guideline which is presented to Committee. The Committee can then consider this new analysis and any potential impact on the evaluation and recommendations

Resolution request 2 (transcribed from PredictImmune Ltd. submission)
The cost effectiveness results are underpinned by patient data that are not representative of the definition of standard of care in the Scope

The EAG censored all patients in the PredictSURE study who had not escalated to IM when extracting outcomes for the model in order to represent their interpretation of the treatment algorithm. In doing so, they censored the very outcome measure, time to IM, that the test is designed to predict. The net result was to skew the model cohort towards patients who escalated faster (patients testing as high-risk) despite there being no correlation between baseline severity and risk group membership as determined by PredictSURE

This faster escalation affects the time on each treatment, affecting costs and quality of life. Patients also reach the end of treatment state, where patients have poor quality of life, much faster. This faster escalation may have ultimately aggravated any errors or other reasons for QALY differences in the model. If the EAG's intention was to restrict the cohort to patients with moderate to severe disease, they should have done this based on severity at baseline.

Panel response to resolution request 2
Ground 1: not met
Ground 2: met

The panel felt that due process was followed but believed there is validity that modelling around standard of care as outlined in the NICE guideline would have benefited the assessment process. The external assessment group will be asked to conduct a scenario analysis reflecting the pathway in the clinical guideline which is presented to Committee. The Committee can then consider this new analysis and any potential impact on the evaluation and recommendations

Resolution request 3 (transcribed from PredictImmune Ltd. submission)
Despite signalling that there were critical issues that needed clarification, PredictImmune was not given the opportunity by the Chair to correct factual inaccuracies during the first committee meeting.

PredictImmune tried several times to signal that they had issues with the discussion at first Committee by 'raising their hand' and privately messaging the NICE project manager but at no stage were asked for their input. This was acknowledged in a letter from Rebecca Albrow on the 20th August. We note that section 7.1.2 of the Diagnostics Program manual states: "The Chair may ask these representatives to respond to questions from the Committee. The Chair may also ask the representatives to comment on any matters of factual accuracy before concluding part 1 of the meeting."

The spirit of an appraisal is that Committee members should be able to consider all relevant evidence. Not allowing the PredictImmune to correct key misunderstandings about the evidence base was a major failure in the process which ultimately led to a conclusion that is clinically and economically invalid.

Furthermore, the meeting process was perverse in that it was not possible for PredictImmune to correct factual inaccuracies stated during the meeting, with the EAG having the final say, even if factually incorrect, including:
• Committee 2, response to PredictImmune comment regarding EAG model remission rates. "It was not possible to directly compare the EAG model remission rates at one year with those reported in key 'biologic first' RCTs". This was untrue, as PredictImmune was able to do this. We do not understand why the EAG

was unwilling to report this key face validity check (more of later) which PredictImmune was unable to challenge in the meeting

• Committee 2, response to PredictImmune's comment that patients in the d'Haens study would not have had access to 2nd line biologics "Patients in the d'Haens 'top-down vs step-up' study would have received other biologics during the longer-term Hoekman follow-up" This was also untrue. The final year of follow-up was 2014, the year that vedolizumab gained its EU marketing authorisation in Crohn's disease, ustekinumab only following several years later. We do not understand why the EAG made this untrue statement which PredictImmune was unable to challenge in the meeting

• Committee 2, regarding responses from (absent) NICE clinical experts "Responses from NICE's clinical experts support the EAG model structure." These statements included those made on committee 2 slides 16 to 17, which are clearly supportive of PredictImmune's comments that NICE NG129 guidance is still followed. We do not understand why the EAG stated that these were supportive of their model, which PredictImmune was unable to further challenge in the meeting

Many of these points are crucial to explaining the invalid results of the EAG model.

Panel response to resolution request 3
Ground 1: not met
Ground 2: not met

The panel felt that due process was followed in that the company were able to raise their issues outside of the first Committee Meeting.

Resolution request 4 (transcribed from PredictImmune Ltd. submission)
PredictImmune's comments on the model and EAG responses were not published in the updated assessment report

As part of their comments on the DAR, PredictImmune submitted a model feedback form with their comments on the model, including the results of key validation checks that suggested that there were systematic errors in the model (that do not appear to have been fixed – see later). These comments have not been published anywhere in the DAR. Though the EAG appears to have addressed some of these in the DAR addendum, it is unclear whether the Committee had access to these comments at any point during the appraisal.

Panel response to resolution request 4
Ground 1: not met
Ground 2: not met

Due process was followed as the Programme Manual does not state the model comments document should be published. The EAG were made aware of the errors highlighted by the company and the addendum was published. It was agreed that NICE should clarify in the programme manual whether the model comments document is published.

Resolution request 5 (transcribed from PredictImmune Ltd. submission)
The EAG failed to present the results of key validity checks to the Committee which had been requested by PredictImmune at consultation

Section 15.1.3 of the Diagnostics Handbook (Measuring and Valuing health effects) states: "The analysis should include all relevant patient outcomes that change in the care pathway as a result of the diagnostic test or sequence of tests."

Section 15.2 of the Diagnostics handbook (Modelling Methods) handbook states: "Estimates of treatment effect should be based on the results of the systematic review and modelling where appropriate." "Assumptions used to extrapolate treatment effects should have clinical validity, be reported transparently and be clearly justified" "Alternative scenarios should be considered to compare the implications of different assumptions around extrapolation for the results. For example, for the duration of treatment effects

scenarios might include the treatment benefit in the extrapolated phase: being nil; being the same as during the treatment phase and continuing at the same level; or diminishing in the long term."

Remission rates are a fundamental driver of QALY gain in this model, and PredictImmune repeatedly tried to point out, both in their DAR and DCD comments, that key evidence on differences between remission rates on Biologic vs CS first had been excluded from the EAG model.

As can be seen from the table below, the EAG model's remission rates are not only wildly inaccurate in the Step Up arm at 1 year, they failed to capture differences between remission rates during a period where key evidence from the Systematic Review was available for Top Down vs Step Up treatment. Following 1 year, remission rates in the EAG model SoC arm overtake those in the PredictImmune arm and exceed them for a further 40 years. No scenario analyses were carried out whereby the difference was reduced gradually over time, or set equal, (as concluded by the Hoekman long-term follow-up study). It is therefore not surprising that the EAG model yielded more QALYs in the Step Up arm, though this is not explained anywhere in the DGD.

Remission rates EAG model vs. RCTs at 52 weeks

Study	Conventional/accelerated step-up arm	Anti-TNF + immunomodulator (top down) arm	Difference in remission rates
D'Haens et al., 2008	42.2%	61.5%	19.3%
Colombel et al., 2010	54.7%	74.1%	19.4%
EAG model – all patients set to 'high risk' group	70%	69%	1%
EAG model – all patients set to 'low risk' group	72%	72%	0%
EAG model – base case	70%	69%	-1%

Note: in the d'Haens study the difference between arms was observed by 14 weeks and was as high as 30%. Patients only received induction infliximab followed by episodic treatment, and no follow-on biologic was available.

Panel response to resolution request 5
Ground 1: not met
Ground 2: met

The panel felt that this was covered under comment 1 and due process was followed but believed there is a validity that modelling around standard of care as outlined in the NICE guideline would have benefited the assessment process. It was agreed that NICE should clarify the process for key validity checks.

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

Second addendum to the Diagnostic Assessment Report

October 2021

This report was commissioned by the NIHR Systematic Reviews Programme as project number 128968/T

BMJ Technology Assessment Group

SUMMARY

This addendum provides the results for the additional analyses undertaken by the External Assessment Group (EAG), as a result of resolution requests submitted by the stakeholders for this diagnostic assessment. Concerns were raised by the stakeholders that patients on the step-up (SU) strategy receive a watchful waiting strategy with corticosteroids. PredictImmune noted that the EAG did not originally model those patients in the Biasci *et al.* dataset who never escalated from treatment with corticosteroids as they achieved a response with this treatment under the SU strategy. In the addendum produced by the EAG in March 2021, the EAG noted that the decision to exclude this step from the economic model was based on clinical experts advising the implausibility of moderate to severe CD patients responding to corticosteroids alone. The EAG also noted that if such modelling approach had been taken, and if the EAG assumed that a proportion of patients in the SU strategy responded to initial treatment with corticosteroids (thus not needing to escalate to immunomodulators), the benefit associated with the SU arm in the economic analysis would be greater (compared to the EAG's base case modelling approach), as a proportion of patients could be successfully managed with a very inexpensive treatment in the SU arm compared with the top-down (TD) arm.

The additional scenario analysis requested by NICE to the EAG was to model an initial treatments step with corticosteroids at the beginning of the SU treatment arm, using the individual patient level data from Biasci *et al.* on time to escalation from corticosteroid to immunomodulators (IMs).

The EAG conducted the following range of analyses incorporating the corticosteroid treatment step in the SU arms, as requested by NICE:

- The EAG's base case results.
- The scenario adding an additional step of treatment with IMs at the end of the TD arm (Section 2.2.1 in the EAG's March addendum).
- The scenario varying the assumptions around the measure of relative treatment effectiveness for time to treatment escalation (Section 2.1.2 in the EAG's March addendum).
- The scenario varying the assumptions around treatment discontinuation in the model (Section 2.1.3 in the EAG's March addendum).

1 ADDITIONAL ANALYSIS UNDERTAKEN

1.1 Use of Biasci et al. *individual patient-level data to estimate time to treatment escalation with corticosteroids*

The EAG re-analysed the individual patient level data in order to estimate time to treatment escalation with corticosteroids from the Biasci *et al.* dataset. The EAG censored patients who did not have an escalation event after treatment with corticosteroids, or patients who received surgery instead of IMs as a subsequent treatment. The EAG's analysis included 64 patients (30 high-risk and 34 low-risk patients) who received either prednisolone or budesonide as first treatment. Time to treatment escalation with corticosteroids is provided in Figure 1, with numbers of patients at risk at the bottom of the figure.

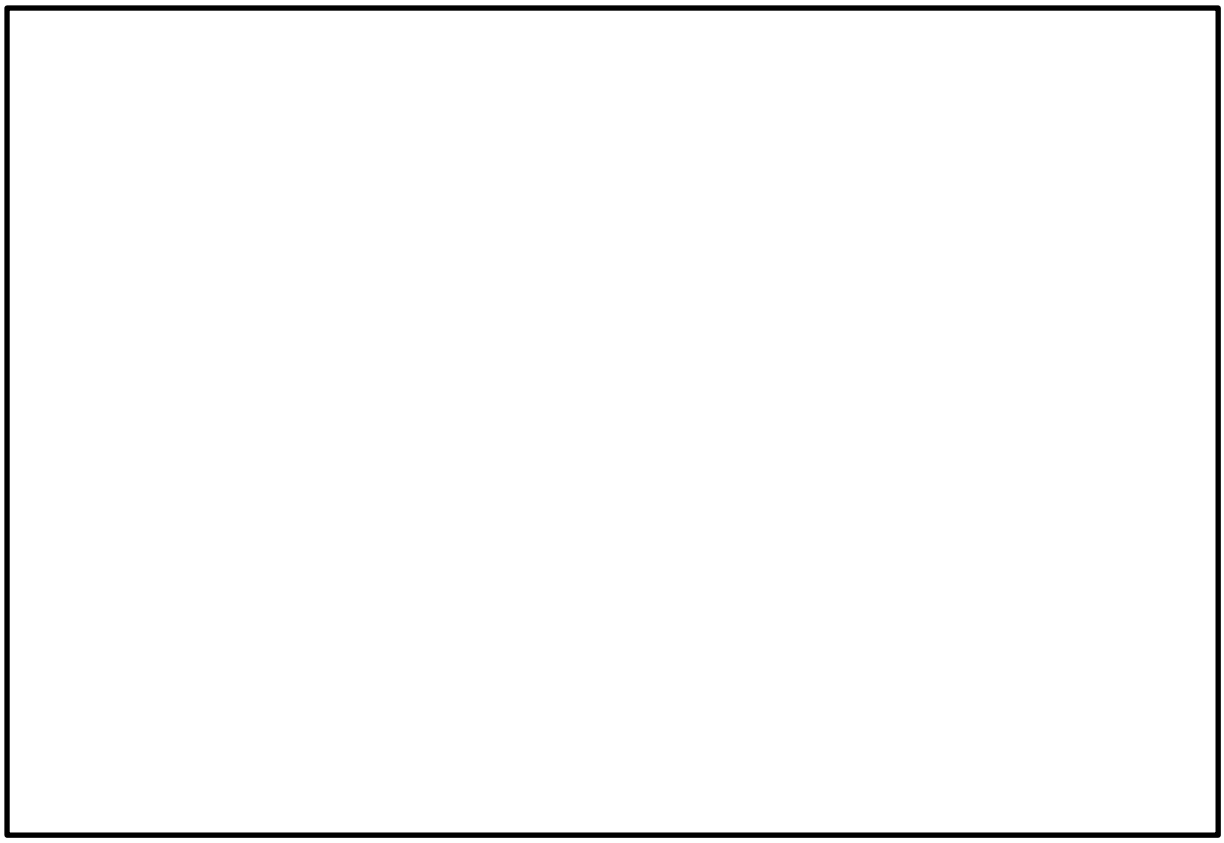
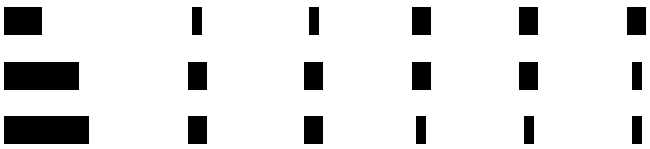


Figure 1. Time to escalation from corticosteroid treatment in Biasci *et al.*



The EAG fitted parametric survival curves to the KM data in Figure 1, in order to extrapolate time to treatment escalation (TTE) with corticosteroids into the model time horizon. The TTE KM data were fitted with an exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma models in accordance with guidance from NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[113] The fit of each parametric model was compared with the observed KM data and statistical fit was assessed using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC).

According to the AIC and BIC statistics reported in Table 1 and Table 2, for high- and low-risk patients, respectively, the best-fitting model to the high-risk KM data from Biasci *et al*. is the gamma, while the lognormal is the best-fitting model for the low-risk group. Figure 2 shows the fitted curves for high-risk patients along with the TTE KM data, while Figure 3 shows the equivalent curves for low-risk patients.

The EAG acknowledges that the DSU advises against fitting different models to same-study arms unless a strong clinical argument exists. The EAG considers that such a clinical argument is present in this case as clinical expert opinion provided to the EAG explained that high-risk patients are unlikely to respond to treatment with corticosteroids, while low-risk patients could potentially be managed with corticosteroid treatment for a longer period of time. Furthermore, the EAG notes that the same approach (i.e. using different parametric models for high- and low-risk patients) was used to model time to treatment escalation from IMs to biologics.

Table 1. Measure of fit statistics for time to treatment escalation - high-risk patients

	AIC	**BIC**
Exponential	152.4	153.8
Weibull	151.8	154.6
Gompertz	140.5	143.3
Lognormal	141.7	144.5
Loglogistic	141.2	144.0
Gamma	**132.3**	**136.5**
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion		

Table 2. Measure of fit statistics for time to treatment escalation - low-risk patients

	AIC	**BIC**
Exponential	187.3	188.8

Weibull	182.5	185.6
Gompertz	178.2	181.3
Lognormal	**177.1**	**180.1**
Loglogistic	179.0	182.0
Gamma	No convergence	No convergence
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion		

Figure 2. High-risk time to treatment escalation Kaplan-Meier and fitted curves

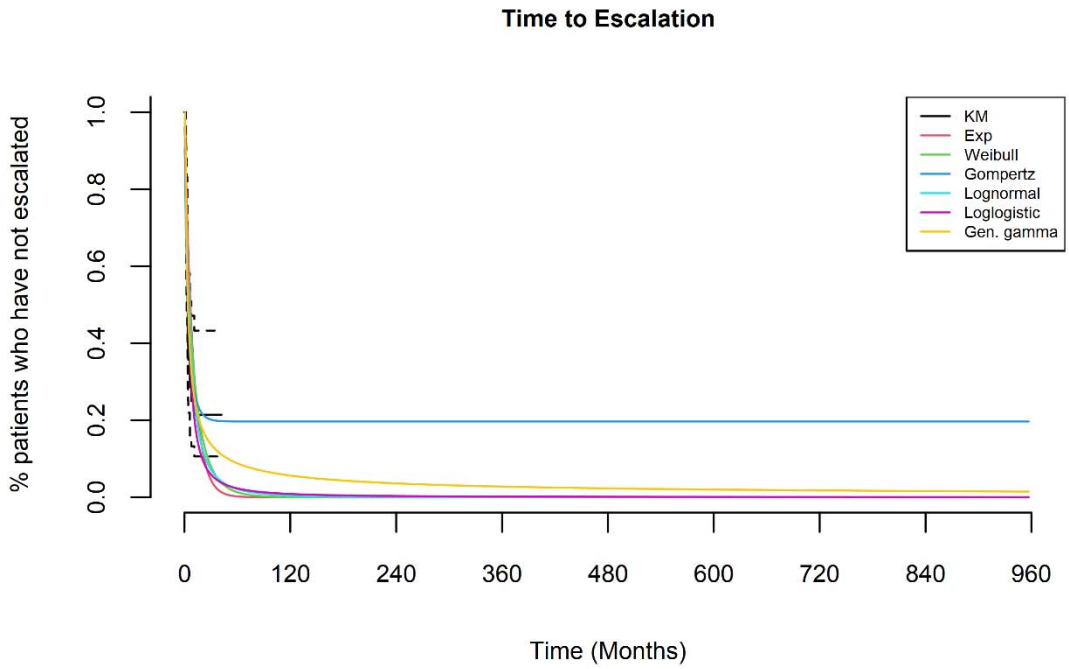
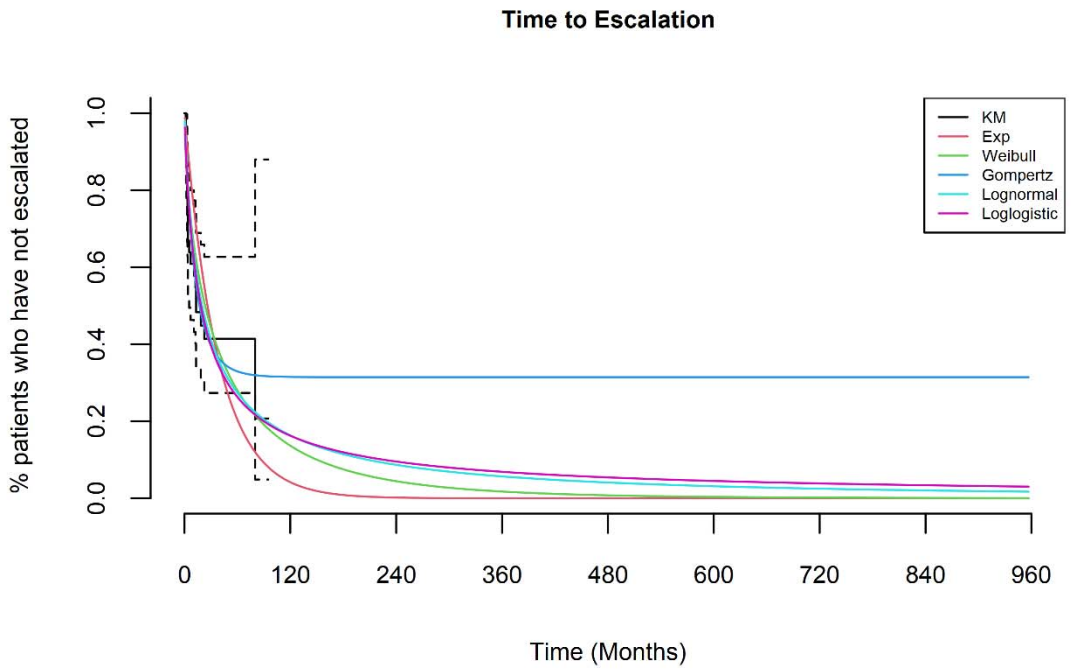


Figure 3.Low-risk time to treatment escalation Kaplan-Meier and fitted curves



The EAG costed treatment with corticosteroids according to the list price for prednisolone reported in the BNF of £0.04 per unit (28-unit pack). The EAG assumed a mean dose of 36mg in every treatment cycle (duration of 2 weeks), resulting in a cost of £0.58 per treatment cycle.

The EAG assumed that while patients received corticosteroids, there was a response to treatment. In other words, treatment escalation was used as a proxy for loss of response to corticosteroid treatment.

Given the EAG's clinical experts' view that patients with moderate to severe CD are highly unlikely to enter remission with treatment with corticosteroids, the EAG assumed that patients on corticosteroids could either have a mild or moderate response to treatment (but not enter complete remission). Therefore, while patients received corticosteroids in the model, the EAG estimated the utility accrued by these patients from the utility values originally used in the DAR model for patients in the mild (0.73) and moderate/severe (0.57) states. As per the original analysis, the EAG assumed that 79% of responders were mild patients while 21% of responders had moderate/severe disease. Therefore, patients on corticosteroids accrued a weighted utility value of 0.70 before escalating. Once patients discontinued treatment, they were assumed to move to treatment with IMs.

2 RESULTS

Table 3 presents the EAG's deterministic base case ICER for PredictSURE IBD™ compared with SC, and the equivalent ICER with the scenario described in Section 1.1. The results show that PredictSURE IBD™ remains dominated against SC, with an additional cost of £17,184 and a QALY loss of 0.10. As discussed in the EAG's addendum (March 2021), including corticosteroids as the first treatment step in the SU arm increased the benefit associated with SC, as a proportion of patients are successfully managed with a very inexpensive treatment in the SU arm compared with the TD arm.

Table 3. Base case deterministic cost effectiveness results (discounted)

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
EAG's base case ICER (as reported in the March addendum)					
Standard of Care	£201,925	15.86	–	–	–
PredictSURE IBD™	£211,009	15.79	£9,084	-0.08	Dominated
EAG's base case ICER with scenario described in Section 1.1.					
Standard of Care	£181,803	15.90	–	–	–
PredictSURE IBD™	£198,987	15.80	£17,184	-0.10	Dominated
Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.					

2.1.1 Varying the assumptions around the measure of relative treatment effectiveness for time to treatment escalation

To aid the interpretation of this scenario analysis, the EAG reproduced the modelled treatment sequences and respective relative treatment effects in the EAG's model in Figure 4 and in Figure 5 for the TD and the SU strategies, respectively.

The relative treatment effect of TD vs SU was applied only in the IM vs anti-TNF step in the EAG's model and taken from D'Haens *et al.* (in the form of a hazard function applied to TTD and TTS SU data). As some high-risk patients who receive SU treatment respond to IM treatment, having the additional IM step in the SU strategy is advantageous to patients in the EAG's base case analysis as patients in the SU still subsequently receive treatment with biologics, which are assumed to have the same benefit as biologics is the TD arm (see Figure 4 and in Figure 5).

The EAG varied these assumptions in two scenario analyses:

a) High-risk patients on anti-TNF after IM (second step on SU arm) do not do as well as high-risk patients on first-line anti-TNF (first step on TD arm) and thus, the former escalate treatment quicker than the latter. This assumes that anti-TNF treatment is less effective in the SU strategy than in the TD strategy. Given that the EAG did not find any data to support this reduction in relative treatment effect across strategies, a theoretical assumption was made and varied:

    i. Half of the risk of relapse from D'Haens *et al.* for TD (anti-TNF) vs SU (IMs) was assumed for anti-TNFs in the TD approach vs the risk of relapse with anti-TNFs in the SU approach (thus making anti-TNFs more effective in TD than in SU);

    ii. The difference in risk of relapse identified in D'Haens for TD (anti-TNF) vs SU (IMs) was applied to anti-TNFs in TD vs anti-TNFs in SU (thus making anti-TNFs more effective in TD than in SU).

Scenario a also assumes that the benefit in the anti-TNF step of the TD strategy compared to the anti-TNF step in the SU strategy carries through to the next treatment steps. Therefore, patients on second line biologic treatment in the TD strategy receive an increase in benefit comparatively to second line biologic treatment in the SU arm (as do patients on third line biologics). It is also assumed that second and third line biologic treatment is as effective as anti-TNF treatment within the respective TD and SU arms, and thus there is a benefit associated with biologic treatment in the TD arm compared to biologic treatment in the SU arm (see Figure 4 and in Figure 5 and Table 4).

b) Same assumptions as in scenario a with regards to the benefit of anti-TNF in TD and SU, with the exception that once patients have moved on to second and third-line biologics, there is no further benefit for TD vs SU. In the base case treatment with anti-TNF and second and third-line biologics are assumed to be equally effective. However, as an alternative to scenario a, where the increased benefit of TD vs SU carries through all of these treatment steps, scenario b assumes that the increased benefit only applies to treatment with ant-TNF (i.e. second and third-line biologics are considered equally effective to the same treatments in the SU strategy) (see Figure 4 and in Figure 5 and Table 4).

Results for these scenarios are presented in Table 5.

Figure 4. Top-down treatment strategy

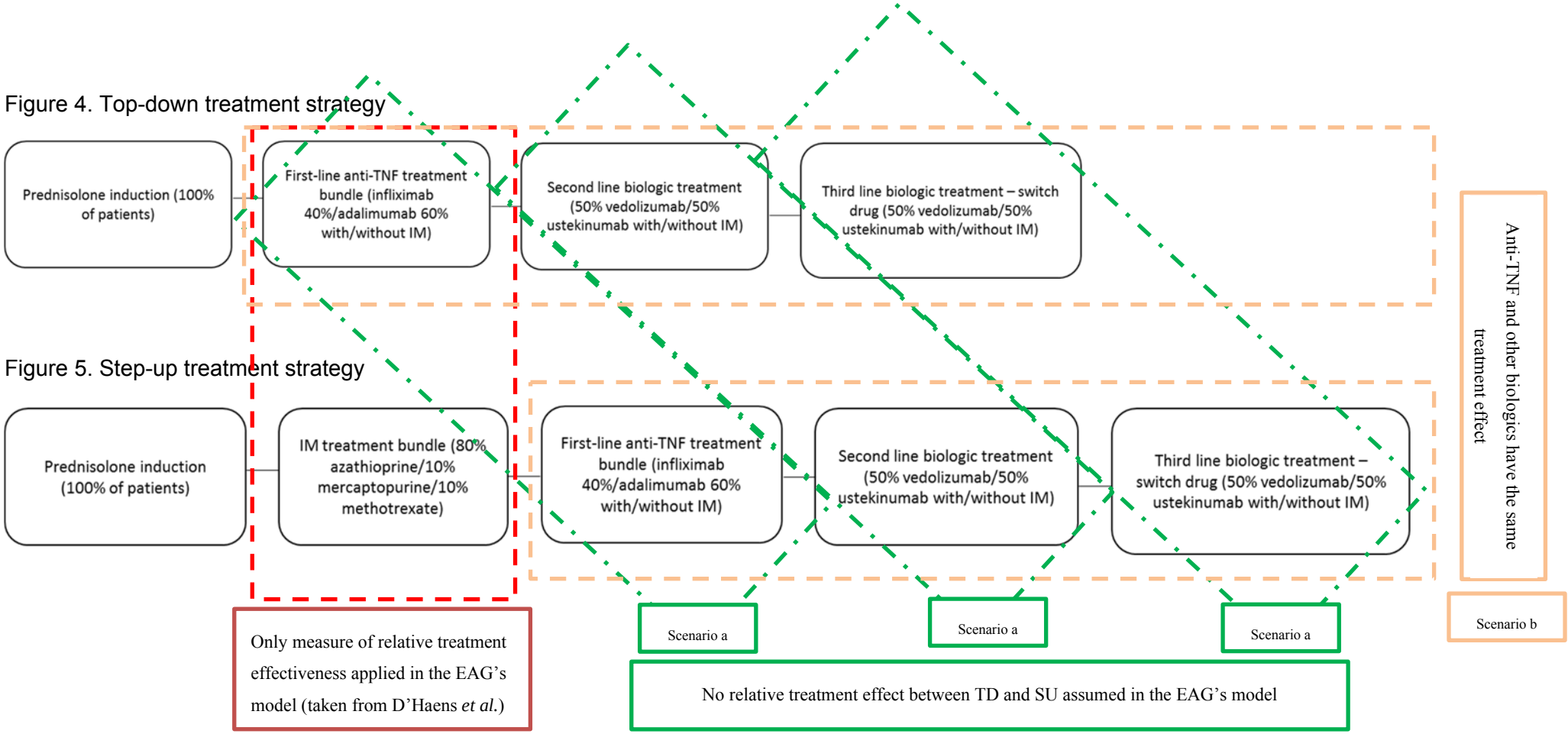


Figure 5. Step-up treatment strategy

Table 4. Summary of exploratory analyses

Steps in the model	Base case	Scenario a	Scenario b
Anti-TNF (TD) vs IM (SU)	Risk of relapse identified in D'Haens *et al*. for TD (anti-TNF) vs SU (IMs)	Same as base case	Same as base case
Anti-TNF (TD) vs anti-TNF (SU)	No relative benefit	i)Half of the risk of relapse from D'Haens *et al.* for TD (anti-TNF) vs SU (IMs) was assumed for anti-TNFs in the TD approach vs the risk of relapse with anti-TNFs in the SU approach; ii) The difference in risk of relapse identified in D'Haens for TD (anti-TNF) vs SU (IMs) was applied to anti-TNFs in TD vs anti-TNFs in SU	Same as scenario a
Second and third line biologic (TD) vs second and third line biologic (SU)	No relative benefit	i)Half of the risk of relapse from D'Haens *et al.* for TD (anti-TNF) vs SU (IMs) was assumed for biologics in the TD approach vs the risk of relapse with biologics in the SU approach; ii) The difference in risk of relapse identified in D'Haens for TD (anti-TNF) vs SU (IMs) was applied to biologics in TD vs biologics in SU	No relative benefit
Second and third line biologic (TD) vs anti-TNF (TD)	No relative benefit	No relative benefit	i)Half of the risk of relapse from D'Haens *et al.* for TD (anti-TNF) vs SU (IMs) was assumed for biologics in the TD approach vs the risk of relapse with anti-TNFs in the TD approach; ii) The difference in risk of relapse identified in D'Haens for TD (anti-TNF) vs SU (IMs) was applied to biologics in TD vs anti-TNFs in TD
Second and third line biologic (SU) vs anti-TNF (SU)	No relative benefit	No relative benefit	No relative benefit

2.1.2 Assumptions around treatment discontinuation in the model

a) The EAG assumed that after 2 years in remission with any biologic treatment, a proportion of patients experience mucosal healing and therefore, stop treatment permanently. The EAG used the Marchetti *et al.* paper to inform this scenario. The study reports that after 2 years in remission, 76% of patients in the TD strategy experience mucosal healing, while 40% of patients in the SU arm experience the same outcome (which the EAG has ran in the model in scenario 2.1.3 a i).

   The EAG also varied the Marchetti *et al.* assumptions and explored the possibility of TD and SU therapies having the same impact on the 2-year probability of mucosal healing. Therefore, the EAG assumed that both TD and SU arms would experience the same probability (either 76% in scenario 2.1.3 a ii or 40% in scenario 2.1.3 a iii) of mucosal healing.

   The EAG notes that Hoekman *et al.* concluded that in their 10-year follow-up study, "*mucosal healing 2 years after the start of treatment was associated with a reduced use of anti-TNF treatment during long-term follow-up. Other outcomes, however, did not differ significantly between patients with and without mucosal healing 2 years after the start of treatment, which is in contrast to a recent meta-analysis of 12 studies with 673 patients that showed that mucosal healing is associated with an increased likelihood of long-term clinical remission*." Furthermore, Hoekman *et al.* also reported that another study has shown that 2–4 years after randomisation, mucosal healing at week 104 after randomisation, but not treatment allocation, was associated with stable, corticosteroid-free remission (Baert *et al*.).

   Therefore, while there is some evidence supporting that 2-year endoscopic mucosal healing is associated with long-term, corticosteroid-free clinical remission, there does not seem to be any evidence supporting that mucosal healing at 2 years differs according to TD or SU treatment. To note is that estimates used in Marchetti *et al.* were taken from another study, which the EAG did not have access to (Baert *et al*.).

b) The company in TA352 assumed that patients discontinued treatment with biologic agents approximately 1 year after maintenance treatment. The EAG in TA352 was concerned that a discontinuation rule may not have been appropriate for patients who are not in remission as the NICE recommendation for infliximab and adalimumab suggests that, "*specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least*

every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again". The EAG notes that duration of treatment with biologics in clinical practice remains uncertain. The clinical experts advising the EAG reported that treatment with anti-TNF and second-line biologics would be given as long as patients continue to show a response.

For completeness, the EAG ran an additional scenario analysis assuming that 100% of patients in continuous remission for 12 months with maintenance treatment of any biologic (i.e. anti-TNF, second- or third-line biologics), discontinue treatment.

Results for these scenarios are presented in Table 5.

2.2 Results of individual scenario analysis

Results of the individual scenario analysis are reported in Table 5. The EAG notes that all the originally dominated (against PredictSURE IBD™) ICERs remained dominated.

The only exception was scenario 2.1.3 a i, where the ICER changed from £46,263 for SC vs PredictSURE IBD™ (where the prognostic tool was less expensive than SC by £3,506 but also less effective by 0.08 QALYs), to dominated against PredictSURE IBD™.

Table 5. Results of scenario analyses

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Scenario 2.1.2 a i - Assuming half of the base case risk of relapse (in the first treatment steps) for TD vs SU for second and subsequent treatment steps					
Standard of Care	£177,588	15.82	–	–	–
PredictSURE IBD™	£196,602	15.76	£19,014	-0.07	Dominated
Scenario 2.1.2 a ii - Assuming the same as base case risk of relapse (in the first treatment steps) for TD vs SU for second and subsequent treatment steps					
Standard of Care	£173,988	15.75	–	–	–
PredictSURE IBD™	£194,844	15.72	£20,856	-0.03	Dominated
Scenario 2.1.2 b i - Assuming half of the base case risk of relapse (in the first treatment steps) for TD vs SU for anti-TNF vs biologics in TD					

Standard of Care	£177,588	15.82	–	–	–
PredictSURE IBD™	£195,423	15.74	£17,835	-0.09	Dominated
Scenario 2.1.2 b ii - Assuming the same as base case risk of relapse (in the first treatment steps) for TD vs SU for anti-TNF vs biologics in TD					
Standard of Care	£173,988	15.75	–	–	–
PredictSURE IBD™	£192,482	15.68	£18,494	-0.07	Dominated
Scenario 2.1.3 a i – Assuming discontinuation of biologic treatment for 76% TD; 40% SU.					
Standard of Care	£165,654	15.90	–	–	–
PredictSURE IBD™	£168,919	15.80	£3,264	-0.10	Dominated
Scenario 2.1.3 a ii - Assuming discontinuation of biologic treatment for 76% TD; 76% SU.					
Standard of Care	£151,121	15.90	–	–	–
PredictSURE IBD™	£162,773	15.80	£11,652	-0.10	Dominated
Scenario 2.1.3 a iii - Assuming discontinuation of biologic treatment for 40% TD; 40% SU.					
Standard of Care	£165,654	15.90	–	–	–
PredictSURE IBD™	£179,927	15.80	£14,273	-0.10	Dominated
Scenario 2.1.3 b - Assuming discontinuation of biologic treatment for 100% TD; 100% SU.					
Standard of Care	£141,432	15.90	–	–	–
PredictSURE IBD™	£151,337	15.80	£9,905	-0.10	Dominated

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; TTS, time-to-surgery.

*This ICER is for SC vs PredictSURE IBD™, meaning that the prognostic tool is cheaper than SC but also less effective.

2.2.1 Adding an additional step of treatment with immunomodulators at the end of the top-down arm

As per the request from NICE, the EAG has conducted a scenario analysis where patients in the TD arm of the model had the option to receive IMs at the end of the treatment pathway (after relapsing on second line biologics). However, the EAG reiterates that according to its clinical experts' opinion, this is not a clinically realistic treatment pathway.

Given the lack of alternative data, the EAG assumed that patients on IMs as the last treatment step of the TD arm have the same probability of remission and relapse as patients receiving IMs on the first treatment step in the SU approach. When patients relapse on IMs there are no more treatment options and so these are assumed to remain in the moderate to severe health state of the model.

When this option is implemented in the model, the EAG's deterministic base case ICER (dominated against TD) changes to £363,595 per QALY gained, with TD (via the use of PredictSURE IBD™) generating 0.04 additional QALYs compared to SU, at an additional cost of £15,603. This compares to an ICER of £105,148 per QALY gained when corticosteroids are not included in the SU arms (0.07 additional QALYs and an additional cost of £7,502 for PredictSURE IBD™ vs SoC).

2.3 Combined scenario analysis

The EAG combined a range of the scenarios described above in order to assess the impact of increasing the effectiveness of the TD strategy while decreasing costs with biologic treatments. These combinations are described, in turn, below and results are reported in the text and summarised in Table 6.

2.3.1 Varying the assumptions around the measure of relative treatment effectiveness on time to treatment escalation and assumptions around treatment discontinuation in the model

The EAG explored the impact of combining scenario 2.1.3 (where costs associated with biologics were decreased) with changing the effectiveness of TD through the assumptions made for TTE in the model. The EAG used scenario 2.1.2. a ii for all the analyses as this is the scenario that assumes the highest benefit for TD vs SU in terms of TTE.

a) The EAG combined scenario 2.1.2 a ii with scenario 2.1.3 a i, where it was assumed that after 2 years in remission, 76% of patients in the TD strategy experience mucosal healing, while 40% of patients in the SU arm experience the same outcome.

b) The EAG also combined scenario 2.1.2 a ii with scenario 2.1.3 a ii, where it was assumed that after 2 years in remission, 76% of patients in the TD and the SU strategies experience mucosal healing.

c) The EAG also combined scenario 2.1.2 a ii with scenario 2.1.3 a iii, where it was assumed that after 2 years in remission, 40% of patients in the TD and the SU strategies experience mucosal healing.

2.4 Results of combined scenario analysis

Results of the EAG's scenario analyses are reported in Table 6. Scenario 2.3.2 a, b and c, explored increasing the effectiveness of TD vs SU with respect to TTE, combined with decreasing the treatment costs with biologics. All scenarios resulted in dominated ICERs against the prognostic tool.

The EAG's scenario analyses (both individual and combined) show that there is a small difference in QALYs in favour of the SU approach, suggesting that this strategy might be more beneficial than TD. However, the EAG notes that the difference in incremental QALYs is small throughout all scenarios, meaning that the final ICER is mainly driven by the difference in costs for TD (via PredictSURE IBD™) compared with SU (via the SC arm).

Table 6. Results of scenario analyses

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Scenario 2.3.2 a (Assuming the same as base case risk of relapse for second and subsequent treatment steps + assuming discontinuation of biologic treatment for 76% TD; 40% SU)					
Standard of Care	£158,874	15.75	–	–	–
PredictSURE IBD™	£165,104	15.72	£6,230	-0.03	Dominated
Scenario 2.3.2 b Assuming the same as base case risk of relapse for second and subsequent treatment steps + assuming discontinuation of biologic treatment for 76% TD; 76% SU)					
Standard of Care	£145,271	15.75	–	–	–
PredictSURE IBD™	£159,253	15.72	£13,982	-0.03	Dominated
Scenario 2.3.2 c (Assuming the same as base case risk of relapse for second and subsequent treatment steps + assuming discontinuation of biologic treatment for 40% TD; 40% SU)					

Standard of Care	£158,874	15.75	–	–	–
PredictSURE IBD™	£176,112	15.72	£17,238	-0.03	Dominated

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; TTS, time-to-surgery.

*This ICER is for SC vs PredictSURE IBD™, meaning that the prognostic tool is cheaper than SC but also less effective.

2.4.1 Conclusions

Including an initial treatment step with corticosteroids at the beginning of the SU treatment strategy increases the cost-effectiveness of SU (and therefore SC), given the lower costs of treatment and the possibility that patients respond to corticosteroids (even if just temporarily), before escalating to more effective (albeit more expensive) treatments such as IMs and biologics.

3 REFERENCES

D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008; 371: 660-7.

International Standard Randomised Controlled Trials Number Registry. PROFILE - personalised medicine in Crohn's disease. 2019. Available from: http://www.isrctn.com/ISRCTN11808228. Date accessed: 9 Oct 2019.

Hoekman D, Stibbe J, Baert F, Caenepeel P, Vergauwe P, De VM, et al. Long-term Outcome of Early Combined Immunosuppression Versus Conventional Management in Newly Diagnosed Crohn's Disease. 2018. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01656067/full. Date accessed.

National Institute for Health and Care Excellence (NICE). Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy. Technology appraisal guidance [TA352]. 2015. Available from: https://www.nice.org.uk/guidance/ta352. Date accessed: July 2019

Marchetti M, Liberato NL, Di Sabatino A, Corazza GR. Cost-effectiveness analysis of top-down versus step-up strategies in patients with newly diagnosed active luminal Crohn's disease. *European Journal of Health Economics* 2013; 14: 853-61.

Baert, F.J., Moortgat, L., Van Assche, G.A., Caenepeel, P., Vergauwe, P.L., De Vos, M., Stokkers, P.C., Hommes, D.W., Vermeire, S., Ritgeerts, P.J., Feagan, B.G., D'Haens, G.: Mucosal healing predicts sustained clinical remission in early Crohn's disease. Gastroenterology 134(suppl. 1), A640 (2008)

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British Society of Gastroenterology (BSG)	1.			Having reviewed the changes made to the model on behalf of the BSG we are satisfied that the models have been made realistic if not a little skewed in favour of the new technology. Clearly under all circumstances the new technology is dominated and hence not advisable at present. We are mindful that when the pivotal trail reports in the next 12-18 months hopefully this might all change. For the time being we are satisfied that the model is reasonable.	The Evidence Assessment Group (EAG) thanks the BSG for their comments and agree that results from the PROFILE trial should hopefully provide definitive evidence on the effectiveness of the tools under assessment, as well as the clinical effectiveness of "step up" (SU) compared with "top down" (TD) strategies.
PredictImmune Ltd	2	General	General	**While the updated model now appropriately captures time to treatment escalation (TTE), it still fails to appropriately capture differences in Crohn's disease activity observed in key top-down (TD) vs. step-up (SU) RCTs, which is the largest driver of QALY gain (Resolution request 5, upheld by the panel).** • PredictImmune is pleased to see that the EAG has attempted to update the SU TTE analysis in line with the current NICE treatment algorithm (Resolution requests 1 and 2). The model does not however, appear to include clinical input values (health state occupancy) for the additional step in the algorithm, which we would expect to see had it been incorporated appropriately (see model comments form issue 1). • Furthermore, the updated model does not provide updated analyses in line with Resolution request 5, which was upheld on factual inaccuracy grounds. • In Resolution request 5, PredictImmune pointed out that the remission rates in the EAG model did not reflect differences between SU and TD observed in key RCTs. That is, while the EAG model utilised effect on TTE from the d'Haens 2008 TD vs SU RCT, it failed to incorporate the impact on disease activity scores, which are the largest single driver of QALY gain in the model. PredictImmune demonstrated that the EAG model was generating higher QALY in the standard of care (SU) arm from week 36 to the end of the model time	Inclusion of corticosteroids in the EAG's model: The EAG undertook a simplified modelling approach to include corticosteroids in the model: as explained in the second addendum, the EAG assumed that while patients received corticosteroids, there was a response to treatment. In other words, time to treatment escalation (estimated from the KM time to treatment escalation with corticosteroids from the Biasci et al. dataset.) was used as a proxy for loss of response to corticosteroid treatment. Given the EAG's clinical experts' view that patients with moderate to severe CD are highly unlikely to enter remission with treatment with corticosteroids, the EAG assumed that while patients were on treatment with corticosteroids, they could either have a mild or moderate response to treatment (but not enter complete remission). Therefore, while patients received corticosteroids in the model, the EAG estimated the utility accrued by these patients from the utility values originally used in the DAR model for patients in the mild (0.73) and moderate/severe (0.57) states. As per the original analysis, the EAG assumed that 79% of responders were mild patients while 21% of responders had moderate/severe disease. Once patients discontinued treatment (i.e. escalated), they were assumed to move to treatment with IMs.

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				horizon, contrary to results from RCTs which demonstrate superior efficacy from TD. • The updated EAG model continues to use the previous network meta-analysis (NMA) to capture impact of early biologic on the Crohn's disease activity index (CDAI). This NMA only compares CDAI scores between treatments in patients who had previously failed initial therapy and not newly diagnosed Crohn's disease patients. As NICE is aware, the number of prior lines of therapy impacts efficacy in almost every disease area. Current evidence indicates this to be equally true of biologics in Crohn's disease (Ungaro et al., 2020). • Failure of the EAG model to capture impact of TD on the CDAI explains why the EAG model still leads to a QALY loss for TD vs. SU and by inference a loss in the PredictSURE arm. In contrast, both the published Marchetti cost-effectiveness analysis and the unpublished PredictImmune model capture the impact of early biologic on remission rates. Both of these models generate higher QALYs in the TD arm. • Table 1 presents a comparison between EAG model remission rates and those observed in key TD vs. SU RCTs. The results remain similar to those presented as part of Resolution request 5, which was upheld by the panel on grounds of factual inaccuracy. Specifically, the remission rates in the standard of care (SU) arm of the model are far higher than observed in the clinical studies and the differences between TD vs. SU are therefore substantially smaller. • As a further step we have also added together the % of patients in either Remission or with Mild disease in the EAG model. As seen in Table 1, patients in the standard of care (SU) arm of the model occupy the better CDAI health states within 6 months and higher QALYs are generated in the SU arm as early as week 36. The EAG has therefore not fulfilled	Comparisons undertaken by the company between the proportion of patients in remission in D'Haens et al. and it the EAG's model: The comparisons undertaken by the company in Table 1 are not appropriate. Firstly, the EAG could not replicate the model estimates provided by the company, however, based on the company's description of "adding together the % of patients in either remission or with mild disease in the EAG model" the EAG assumes that the company added the proportion of patients in these states in the traces of the model. To do so, provides incorrect estimates as these need to be weighted by the model cohort. For example, for the TD strategy, the proportion of patients in remission (or the mild state) at week 26 in the model is 54%, which compares to 26% estimated in the SU arm when only high-risk patients are considered in the SU arm (28% difference) or with 39% in the SU arm when high- and low-risk patients are considered in the SU arm (15% difference). Secondly, it is not possible to identify the appropriate treatments steps underlying the remission rates at week 26 for the conventional arm vs the immunosuppression arm in the D'Haens et al. study (35.9% vs 60%, respectively) and at week 52 (42.2% vs 61.5%, respectively) cited by the company – the treatments included in D'Haens et al. were either combined immunosuppression (three infusions of infliximab at weeks 0, 2, and 6, with azathioprine with additional treatment with infliximab and corticosteroids, if necessary, to control disease activity); or corticosteroids, followed, in sequence, by azathioprine and infliximab if needed. If patients responded to treatment with corticosteroids, treatment tapering was initiated. If patients' symptoms worsened during the course of

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				the panel's request to model standard of care in line with the NICE guideline and address key model validity issues.	corticosteroid tapering and did not respond to an increase in treatment dose, treatment with azathioprine was initiated. Patients who relapsed after withdrawal of corticosteroids were given a second course of corticosteroids in combination with azathioprine. Any patient who remained symptomatic after 16 weeks of azathioprine treatment received an induction course of infliximab (5 mg/kg bodyweight at weeks 0, 2, and 6) and continued antimetabolite treatment. Therefore, the EAG cannot ascertain if (for example) the 35.9% of patients in the conventional treatment arm of the D'Haens et al. study who had a remission had received only corticosteroids or had already escalated to infliximab. This greatly impacts the relevant comparison with the model estimates – for example, for the SU strategy, the proportion of patients in remission at week 26 in the model receiving only corticosteroids is 26%, however, the proportion of patients in remission (or the mild state) at week 26 in the model receiving corticosteroids and also receiving IMs is 34%. EAG's approach to incorporating the effect of TD vs SU on TTE and on clinical disease activity index (CDAI) scores: As discussed in the DAR and in the first addendum, there is no available evidence to suggest that TD is more effective than SU as an entire treatment sequence, with the only treatment effect available in the published literature being the D'Haens et al. estimate for a proxy of the anti-TNF vs IM step, which is the only step in the EAG's base case model for which a treatment effect is applied.

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					In the EAG's model, the rates associated with entering the remission (CDAI<=150); mild (CDAI 150-220); or moderate to severe (CDAI 220-600) health states reflected the differences in treatment effectiveness as separate treatments steps (for example, a patient on anti-TNF has a probability of entering remission of 37% regardless of when anti-TNF is received, while a patient receiving IMs has a probability of remission of 16%). The EAG has not found any evidence to substantiate that treatment effectiveness changes depending on where in the treatment pathway patients receive treatment. The company cites a review by Ungaro et al. in support of the proposal that the number of prior lines of therapy impacts clinical effectiveness of biologics in Crohn's disease. The EAG considers that the authors of the systematic review highlighted by PredictImmune (Ungaro et al.) do not comment on the clinical effectiveness of biologics based on number of lines of prior therapy or on status of diagnosis of Crohn's disease (new versus established). Ungaro et al. assess the effectiveness of early versus late/conventional treatment in Crohn's disease in terms of timing of treatment (≤2 years versus >2 years of diagnosis), irrespective of treatment sequence (there is no formal comparison or consideration of the treatment pathway described as SU and TD in the DAR) and of prior treatment (more detail given below). Thus, the EAG considers the conclusions reached by the authors cannot be applied to the treatment pathway assessed in the EAG's economic model. The review reports no new RCTs to those identified by the EAG from its systematic literature review. Ungaro et al. define early treatment as treatment within 2 years of diagnosis OR TD therapy, whereas

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					late/conventional treatment is defined as treatment initiated at a time longer than 2 years after diagnosis OR SU therapy. Consequently, the studies informing the meta-analysis of early versus late/conventional treatment for the outcome of clinical remission are a mix of response to induction treatment and maintenance of response, and of newly diagnosed versus established Crohn's disease, specifically: • Schreiber 2010: reports maintenance of response to certolizumab – people responding to induction with certolizumab were randomised to continued treatment with certolizumab or to placebo; • d'Haens 2008: evaluates induction treatment of SU versus TD in those with newly diagnosed Crohn's disease; • Colombel 2015: post hoc analyses of clinical remission based on early versus late treatment as defined by time since diagnosis (≤18 months versus >18 months) in those who were immunomodulator and biologic naïve and had an inadequate response to one or more conventional therapies; • Panaccione 2019: pooled analysis of data derived from 10 studies evaluating adalimumab in the treatment of Crohn's disease, includes a mix of induction treatment and maintenance of response; • Faleck 2019: observational study (retrospective analysis) analysing response to treatment with vedolizumab based on early stage versus later stage Crohn's disease, includes people who were anti-tumour necrosis factor (TNF) naïve, as well as those with prior exposure to TNF antagonists. Given the heterogeneous nature of the populations informing the meta-analysis reported in Ungaro et al., the

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					EAG considers that the results for clinical remission do not relate directly to number of prior lines of therapy, as suggested by PredictImmune. The EAG maintains that the NMA reported in TA352 provides the most robust data set to inform the economic evaluation, with the caveats noted in the original EAG report. Moreover, the EAG considers that the most relevant study identified within the systematic review (d'Haens 2008) is used to inform the TTE in the model. The EAG appreciates that there are limitations with using d'Haens 2008, which are discussed in detail in the DAR. The EAG reiterates that, to account for the lack of evidence on the clinical effectiveness of SU versus TD, treatment effect of TD vs SU was thoroughly varied in exploratory analysis reported in the DAR, in the first; and in the second addendum, where extreme scenarios around increasing the treatment effectiveness of the TD approach while decreasing the costs associated with TD were tested. The scenario analyses conducted by the EAG assumed that anti-TNF treatment is less effective in the SU strategy than in the TD strategy; that patients on second line biologic treatment in the TD strategy receive an increase in benefit comparatively to second line biologic treatment in the SU arm (as do patients on third line biologics). Differences in modelling approaches and model results: The TD strategy in the company's model has the IM step as the last treatment option after treatment with biologics, hence TD patients have the opportunity to respond to IMs, which is not the case in the TD arm in EAG's model. Therefore, the IM step at the beginning of SU in the

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					company's model "cancels out" (not entirely because of deaths but these are few) with the IM step at the end of TD, while in the EAG's model the IM step contributes to a proportion of patients entering remission. The EAG has discussed this thoroughly with its three clinical experts, who have all said that IMs would not be given after biologics. Therefore, the EAG's model does not include this as the last step at the end of TD. Nonetheless, as a response to a request made by NICE, the EAG has undertaken an additional scenario analysis where the IM step was included as the last treatment option in the TD treatment sequence (results are provided in section 2.2.1 of the first EAG addendum). The company's model assumes a constant relative risk of treatment escalation of 0.4 (at least for the first 10 years) for TD vs SU, whereas the EAG's modelling approach (i.e., fitting survival curves to the KM TTE data) implies that the relative effect diminishes over time (i.e. the relative risk gets closer to 1 and TD and SU become equally effective as time goes by in the model). The relative risk in the EAG's model starts below 0.4 but rises above that after less than 3 months. After a year the relative risk in the EAG's model is at 0.7 and continues increasing after that. Therefore, the company's effectiveness estimates, based on a very simplified approach are potentially overestimating the effect of TD vs SU. Furthermore, the company applies the relative risk of treatment escalation of 0.4 for every step in the sequence. As discussed in the DAR and in the first addendum, there is no published evidence available to suggest that TD is more effective than SU as an entire treatment sequence, with the only treatment effect available in literature being the D'Haens et al. estimate for a proxy of the anti-TNF vs IM step, which is the only

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					step in the EAG's base case model for which a treatment effect is applied. Even though the D'Haens et al. evidence is in support of the relative advantage of anti-TNFs vs IMs, there is still a proportion of patients with moderate to severe CD who will derive a temporary benefit from receiving treatment with corticosteroids or IMs. These patients eventually escalate to treatment with anti-TNFs and further biologics, However, they can respond to corticosteroids or IMs (a less expensive treatment than biologics) for a period of time. This is in accordance with the evidence the EAG found and with clinical expert opinion provided to the EAG. The EAG reiterates that the QALY gain in the EAG's model associated with SU comes from the fact that the SU model arm has an additional initial treatment step with IMs (and with corticosteroids as per the second addendum), whereas the TD strategy does not include these steps as it begins with anti-TNF treatment. Therefore, the period of response to corticosteroids and IMs in the model yields a benefit (that of a response to treatment) at a much lower cost than patients who have a response to anti-TNFs in the TD arm. In the first addendum, the EAG conducted scenario analyses to test the impact of decreasing patients' response to IMs in the model and provides results in Section 2 of the first addendum. The Marchetti et al. 2013 study included treatment strategies which are not representative of UK NHS practice. The study compared the cost effectiveness of TD (step 1: infliximab plus azathioprine, step 2: additional

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					infliximab plus azathioprine, step 3: methylprednisolone plus azathioprine) and SU (step 1: methylprednisolone, step 2: methylprednisolone plus azathioprine, step 3: infliximab plus azathioprine) approaches in Italy. The study reported that a TD strategy is associated with more QALYs than SU (0.14 QALY gain over a 5-year time horizon). The EAG reduced the time horizon in its model to 5 years and also obtained a QALY gain associated with TD, albeit smaller (0.004) and at a greater cost (£13,728), obtaining an ICER of £3,814,576. The EAG notes that its' 5-year estimate is still based on fundamental structural differences when compared to the Marchetti study (mainly around the assumption of a constant probability of escalation in the Marchetti study and the fact that the study did not explicitly model the different levels of response to maintenance therapy throughout time). As discussed in TA352, the DSU has reported the importance of capturing partial response to maintenance treatment (as well as remission, relapse, surgery and post-surgical remission) in CD's modelling approaches. Therefore, the EAG based its model on the Bodger et al. structure in order to capture different levels of response. Finally, the EAG notes that the 5-year analysis included the TTE curves fitted by the EAG to a time horizon of 65 years (instead of 5 years). In conclusion, the EAG maintains its view that the PROFILE RCT, which is in progress and was designed to compare the efficacy of TD and SU therapy for high- and low-risk CD, will provide robust evidence on whether early treatment with biologics yields a benefit compared with SU treatment.
PredictImmune Ltd	3	General	General	**The EAG systematically generates higher remission rates and QALYs in the standard of care (SU) arm of the model over the remaining lifetime time horizon, though this is not**	The authors of Hoekman *et al.* (a 10-year follow up of the D'Haens *et al.* study) concluded that, "*Combined immunosuppression early in the disease course may be*

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				supported by any available data. This was also pointed out to the Resolution panel in request 5, upheld on factual inaccuracy grounds. • The updated EAG model generates higher QALYs as early as week 36 in the SU arm, as was the case prior to the Resolution panel. This advantage is sustained in the SU arm to the end of the model time horizon, although no data are available that support this result: o While no RCT data are available to inform clinical outcomes between TD and SU beyond 2 years, Hoekman et al. followed patients recruited to the d'Haens TD vs. SU RCT for a period of 8 years. Although outcomes did not differ statistically, almost all clinically relevant outcomes were numerically superior in the TD arm in this study (Table 2). As NICE is aware, an outcome does not have to demonstrate statistical significance to be incorporated into an economic model. • Furthermore, the EAG model results contradict themselves in that the model predicts a faster TTE, more surgeries and lower life years in the SU arm, while simultaneously predicting higher QALYs. That is, the EAG model predicts better disease control in the SU arm but a shorter time to disease flare and greater need for surgical intervention (Table 3). • As explained to (and upheld by) the Resolution panel, the lower QALYs generated in this extrapolated period would remain unchanged by any results from the ongoing PROFILE trial, or any other future trial, no matter how positive. Use of the current EAG model structure for future decision-making could therefore systematically deprive Crohn's disease patients in England and Wales of the opportunity of accessing more effective treatment which could profoundly alter the course of their disease.	*more effective in the short term than conventional management in patients with recently diagnosed CD. In this study, […] no difference was found in clinical remission rate. Likewise, no differences were found in rates of endoscopic remission, hospitalization, surgery or new fistulas. However, top-down treatment was associated with a significantly lower relapse rate as well as a longer time to relapse compared to step-up treatment. Furthermore, step-up patients were treated more frequently with corticosteroids and anti-TNF agents. Top-down treatment was associated with a more favourable endoscopic outcome, although this was not statistically significant. These results indicate that the early introduction of combined immunosuppression may yield a better long-term outcome*." The EAG notes that the only outcome found statistically significantly different across the TD and SU arms was the 2-year analysis of time to relapse (D'Haens *et al.*), which the EAG has incorporated into the model. The EAG also notes that extensive scenario analyses were performed to test extreme scenarios around treatment effectiveness. The EAG lists (some of) the analyses conducted: 1. Assuming that 100% of high-risk patients who receive SU do not respond to treatment and therefore escalate to anti-TNF after induction with IMs (Section 5.2 of the DAR). 2. Applying the induction vectors and transition probabilities based on TA352 studies (Section 5.2 of the DAR). 3. Increasing the treatment effectiveness of the TD approach while decreasing the costs associated

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					with TD. The scenario analyses conducted by the EAG assumed that anti-TNF treatment was less effective in the SU strategy than in the TD strategy; that patients on second- and third-line biologic treatment in the TD strategy received an increase in benefit comparatively to SU (Section 5.2 of the DAR, Section 2.1. in the first addendum; and Section 2.1.1 in the second addendum). 4. Assuming that after 2 years in remission with any biologic treatment, a proportion of patients experience mucosal healing and therefore, stop treatment permanently. The EAG used the Marchetti *et al.* paper to inform this scenario (Section 2.1.3. in the first addendum; and Section 2.1.2 in the second addendum). For completeness, the EAG also ran an additional scenario analysis assuming that 100% of patients in continuous remission for 12 months with maintenance treatment of any biologic (i.e. anti-TNF, second or third line biologics), discontinue treatment (Section 2.1.3. in the first addendum). The EAG reiterates that the QALY gain in the EAG's model associated with SU comes from the fact that the SU model arm has an additional initial treatment step with IMs (and with corticosteroids as per the second addendum), whereas the TD strategy does not include these steps. Even though the D'Haens *et al.* evidence is in support of the relative advantage of anti-TNFs vs IMs, there is still a proportion of patients with moderate to

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					severe CD who will derive a temporary benefit from receiving treatment with corticosteroids or IMs (which could be observed from patients who did not escalate treatment in the Biasci IPD). These patients eventually escalate to treatment with anti-TNFs in the model and further biologics, however, the period of response to corticosteroids and IMs in the model yields a benefit (that of a response to treatment) at a much lower cost than patients who have a response to anti-TNFs in the TD arm. Furthermore, the EAG reduced the time horizon in its model to 5 years and also obtained a QALY gain associated with TD of 0.004, which decreases over time. A time horizon of 3 and 4 years produced a QALY gain of 0.02 and 0.01, respectively. The extremely small gain in undiscounted life years gained in the PredictSURE arm of the model is related to the difference in time to surgery outcomes for the two groups given that patients on TD had a lower probability of surgery and surgery was related with a small increase in mortality in the model. The EAG disagrees with the company's assessment that model outcomes (i.e., the higher QALY gain for SU vs TD) would remain unchanged by any results from the ongoing PROFILE trial, or any other future trial. Firstly, if the results from PROFILE are able to demonstrate that SU is, overall, less effective than TD (as entire treatment sequences) then this would be reflected in the model. Secondly, upon investigation of the trial results it is entirely plausible that the EAG's model structure would have to change to reflect the appropriate trial and disease

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					outcomes. The EAG reiterates its view (discussed in Section 7.2 of the DAR) that given the lack of robust evidence on the prognostic accuracy of the biomarker-stratification tools, the development of the economic model to assess the cost-effectiveness of PredictSURE-IBD™ consisted mainly of a theoretical exercise. The EAG anticipated that the economic model developed provides only a possible structural framework for analysing future available data.
PredictImmune Ltd	4	General	General	**In summary, the additional EAG scenario fails to address Resolution comment 5, which pointed out key model validity issues and was upheld by the panel on grounds of factual inaccuracy.** • The EAG model ignores TD vs. SU effect on Crohn's disease quality of life (via CDAI health state utility) during the 1-2 year period when data from RCTs in newly diagnosed patients are available • In the following period, to the end of the model time horizon, the model assumes poorer quality of life in patients who receive TD treatment, despite the availability of 8-year observational data indicating numerically superior clinical outcomes in patients receiving TD. • The model predicts a faster TTE and more surgeries in the SU arm, while simultaneously predicting better disease control and QALYs. • These major modelling issues are further compounded by the lifetime time horizon, which captures an excessively long period of uncertainty, in contrast with previous NICE assessments in this disease area (Table 4). The lack of exploration of alternative time horizons was an issue raised by Prof Neil Hawkins during the first consultation.	As discussed in comment 2, the EAG's model takes into account of the different rates of remission associated with the individual treatment steps within TD and SU (for example, a patient on anti-TNF has a probability of entering remission of 37% regardless of when anti-TNF is received, while a patient receiving IMs has a probability of remission of 16%). Given that the different CDAI states in the EAG's model [remission (CDAI<=150); mild (CDAI 150-220); or moderate to severe (CDAI 220-600)] are associated with different utility values (0.82;0.73; and 0.57, respectively), the EAG's model takes into account the impact of the different treatments included in the TD and SU strategies on CDAI-related utility. The EAG also applied a relative hazard function to TTE curves in the first step in the TD strategy (anti-TNF). The underlying assumption in the EAG's base case approach is that high-risk patients who initiate treatment with IMs (SU arm) escalate treatment quicker than high-risk patients who initiate treatment with anti-TNF (supported by the data presented in D'Haens *et al*.) however, once SU patients initiate treatment with anti-TNF (their second

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				PredictImmune has included some suggestions on how these deficiencies could be addressed in the model in the model comments form.	treatment step), they "catch-up" with patients on the TD treatment strategy. The EAG's model does not assume "*poorer quality of life in patients who receive TD treatment*" in later years of the model as stated by the company. The rates of remission associated with maintenance anti-TNFs and biologic treatments are consistently higher than the maintenance remission rates associated with IMs or corticosteroids throughout the model (Section 4.2.4 in the DAR for more details). Finally, the EAG explored reducing the time horizon in its model to 5 years and obtained a QALY gain associated with TD, albeit small (0.004) and at a greater cost than SU (£13,728), obtaining an ICER of £3,814,576 per QALY gained.

PredictImmune Ltd: Table 1: Comparison of model remission rates with key TD vs. SU RCTs

Source	Endpoint	Step-up	IM only	IM + anti-TNF	Difference (TD vs. SU)*	Notes
D'Haens at al., 2008 Colombel et al., 2010	Remission, 26 weeks	35.9%		60%	24.1%	Protocol only included 3 induction infusions of infliximab, no maintenance therapy as per current clinical practice. No 2nd line biologics were available
	Remission, 52 weeks	42.2%		61.5%	19.4%	
	Remission, 26 weeks		30%	56.8%	26.8%	
	Remission, 50 weeks		54.7%	74.1%	19.4%	Web table 3. Patients who entered the trial extension
	Remission, 50 weeks		24.1%	47.3%	23.2%	Web table 4. All patients assuming that patients who did not enter the trial extension did not achieve the endpoint through Week 50.

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Source	Endpoint	Step-up	IM only	IM + anti-TNF	Difference (TD vs. SU)*	Notes
EAG model, all patients in PredictSURE arm set to receive TD**	Remission, 26 weeks	56%		63%	7%	Remission rates in the Step-Up arm exceed those in the Top-Down arm from week 92 to the end of the model time horizon.
	Remission, 52 weeks	68%		71%	3%	
As above	Remission + Mild, 26 weeks	84%		81%	-3%	Mild rates in the Step-Up arm exceed those in the Top-Down arm from week 10 to the end of the model time horizon.
	Remission + Mild, 52 weeks	85%		81%	-4%	

IM, immunomodulator
**The IM + anti-TNF arm vs. the Step-up or IM only arm, depending on the trial.*
*** achieved by assuming 0% test accuracy for patients testing low-risk..*

PredictImmune Ltd: Table 2: Summary of key clinical outcomes from the Hoekman et al., 2018 follow-up study of d'Haens

Outcome	TD arm	SU arm
Clinical remission	73%	70%
Time to flare (median)	9 semesters	5 semesters
Use of corticosteroids	41%	62%
Anti-TNF use	54%	73%

Note: Patients in the TD arm of the d'Haens RCT were not offered maintenance anti-TNF, which is now accepted practice, and no later line biologics were as yet licensed in Crohn's disease during the Hoekman follow-up period. The results can therefore potentially be considered conservative with respect to the outcomes in the TD arm.

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Comments on additional analysis

PredictImmune Ltd: Table 3: Comparison of clinical effects in EAG model

Model arm	Total QALYs	Total discounted LYs	Total undiscounted LYs	Total surgeries
PredictSURE	15.785	23.425	50.440	0.996
Standard of care	15.861	23.422	50.433	0.998
Difference	-0.076	0.003	0.007	-0.002

PredictImmune Ltd: Table 4: Model time horizons employed in NICE appraisals of Crohn's disease

NICE assessment	Model time horizon	Comments
TA352 Vedolizumab: .	10 years	
TA456 Ustekinumab: lifetime, but	Lifetime	The Evidence Review Group (ERG) also explored 5 and 10 year horizons because of *"considerable uncertainty over the long-term benefits and costs of ustekinumab given the short duration of the clinical effectiveness data available"…" the ERG considers it worth considering the impact of a shorter time horizon which effectively imposes the assumption that costs and benefits are the same for the treatment and comparator arms after the time horizon"*
TA185 Infliximab and adalimumab:	1 year	
CG152 (CD management):	30 weeks	

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Comments on additional analysis

Comments on the economic model

Stakeholder	Comment	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG response
PredictImmune Ltd	1	Although the new analyses are meant to reflect current UK standard of care, with a first step of induction corticosteroid followed by observation, there do not appear to be any input values for this step in the model sheets '*Induction vectors*' or '*Transition matrices*'.	CDAI health state occupancy parameters and costs for the step of 'Corticosteroid induction followed by observation' should be incorporates	The model should correctly reflect the better CDAI response and remission rates from TD therapy and should therefore produce higher QALYs in the PredictSURE arm.	The EAG undertook a simplified modelling approach to include corticosteroids in the model: as explained in the second addendum, the EAG assumed that while patients received corticosteroids, there was a response to treatment. In other words, time to treatment escalation (estimated from the KM time to treatment escalation with corticosteroids from the *Biasci et al.* dataset.) was used as a proxy for loss of response to corticosteroid treatment. Given the EAG's clinical experts' view that patients with moderate to severe CD are highly unlikely to enter remission with treatment with corticosteroids, the EAG assumed that while patients were on treatment with corticosteroids, they could either have a mild or moderate response to treatment (but not enter complete remission). Therefore, while patients received corticosteroids in the model, the EAG estimated the utility accrued by these patients from the utility values originally used in the DAR model for patients in the mild (0.73) and moderate/severe (0.57) states. As per the original analysis, the EAG assumed that 79% of responders were mild patients while 21% of responders had moderate/severe disease. Once patients

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Comments on additional analysis

Stakeholder	Comment	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG response
					discontinued treatment (i.e. escalated), they were assumed to move to treatment with IMs.
PredictImmune Ltd	2	The model does not appropriately reflect differences in disease control on the CDAI observed in key TD vs. SU RCTs. The model uses the TTE data from the d'Haens et al. RCT but fails to use the data on remission rates. As a result, the model generates higher QALYs in the standard of care (SU) arm as early as week 36.	A correction factor (e.g. an odds ratio) could be applied to the CDAI health state occupancy in the model to reflect the differences in remission observed in the d'Haens RCT. This approach was utilised in the published Marchetti model.	The model should generate higher QALYs in the PredictSURE arm during the first two years of the model.	See EAG's response to comment 4.
PredictImmune Ltd	3	The model does not appropriately reflect the numerically superior outcomes observed in the TD arm in the Hoekman et al. 8-year observational follow-up study. Instead, the model generates lower QALYs in the PredictSURE (TD) arm from week 36 to the end of the model time horizon.	Following on from Issue 2, the correction factor (e.g. odds ratio) could be tapered down over the 8-year Hoekman observational period. A check and correction should be incorporated in the model that ensures that in the extrapolated period, when no data are available, both arms generate equal QALYs. Such corrections are commonplace in e.g. partitioned survival models to ensure that survival curves do not cross, or that cancer mortality is never lower than general population mortality. Alternatively the model time horizon should be capped at 10 years, as no data to inform	The model would cease to generate lower QALYs in the PredictSURE arm and instead should generate greater QALYs in the PredictSURE arm. The QALY gain will reflect the better outcomes observed for patients receiving TD treatment in both the d'Haens RCT and the Hoekman observational period.	See EAG's response to comment 3.

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Comments on additional analysis

Stakeholder	Comment	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG response
			effectiveness are available following that timepoint.		
PredictImmune Ltd	4	It is unclear whether the treatment effect on TTE has been applied to the updated TTE analysis of high-risk patients. In sheet 'Time to escalation' column T the treatment effect appears to be applied to the original EAG analysis (cell name TTE_HI_SU) and not the updated EAG analysis (cell name TTE_Hi_CS)	EAG to check that the range beginning TTE_Hi_CS should not be used instead.	The impact is unknown.	Please see answer to comment 1 in this table on the application of TTE with corticosteroids in the model. The ERG is unclear why column T in the "time to escalation" sheet would have any formulae references to corticosteroids given column T includes TTE data for first line biologics. The relevant TTE data for corticosteroids (including the cell reference TTE_Hi_CS mentioned by the company) are located in column X of the same tab.

References

Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. (2010). Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. N Engl J Med;362:1383–95. doi:10.1056/NEJMoa0904492.

D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, et al. (2008) Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet 2008;371:660–7. doi:10.1016/S0140-6736(08)60304-9.

Hoekman DR, Stibbe JA, Baert FJ, Caenepeel P, Vergauwe P, De Vos M, et al. (2018) Long-term outcome of early combined immunosuppression versus conventional management in newly diagnosed Crohn's disease. J Crohn's Colitis;12:517–24. doi:10.1093/ecco-jcc/jjy014.

Marchetti M, Liberato NL, Di Sabatino A, Corazza GR. Cost-effectiveness analysis of top-down versus step-up strategies in patients with newly diagnosed active luminal Crohn's disease. European Journal of Health Economics 2013; 14: 853-61.

Ungaro RC, Aggarwal S, Topaloglu O, Lee WJ, Clark R, Colombel JF. (2020) Systematic review and meta-analysis: efficacy and safety of early biologic treatment in adult and paediatric patients with Crohn's disease. Aliment Pharmacol Ther;51:831–42. doi:10.1111/apt.15685.

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

Appendix to the EAG's response to comments on the EAG's second addendum

November 2021

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BMJ Technology Assessment Group

1 ADDITIONAL ANALYSIS UNDERTAKEN

Table 1 presents the EAG's deterministic base case ICER for PredictSURE IBD™ compared with SC as per the EAG's second addendum (65-year time horizon), while Table 2 presents the results for the 5-year time horizon. Given that it takes approximately 1 day to run PSA in the EAG's model, the EAG has only presented deterministic results, however notes that deterministic and probabilistic results presented in the first addendum are similar.

Table 1. Base case deterministic cost effectiveness results (discounted)

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
EAG's base case ICER					
Standard of Care	£181,803	15.90	–	–	–
PredictSURE IBD™	£198,987	15.80	£17,184	-0.10	Dominated
Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.					

Table 2. Base case deterministic cost effectiveness results (discounted, 5-year time horizon)

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
EAG's base case ICER					
Standard of Care	£40,522	3.365			
PredictSURE IBD™	£54,250	3.369	£13,728	0.004	£3,814,576
Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.					

2 SCENARIO ANALYSES PREVIOUSLY UNDERTAKEN

2.1 Varying the assumptions around the measure of relative treatment effectiveness for time to treatment escalation

To aid the interpretation of this scenario analysis, the EAG reproduced the modelled treatment sequences and respective relative treatment effects in the EAG's model in Figure 1 and in Figure 2 for the TD and the SU strategies, respectively.

The relative treatment effect of TD vs SU was applied only in the IM vs anti-TNF step in the EAG's model and taken from D'Haens *et al.* (in the form of a hazard function applied to TTD and TTS SU data). As some high-risk patients who receive SU treatment respond to IM treatment, having the additional IM step in the SU strategy is advantageous to patients in the EAG's base case analysis as patients in the SU still subsequently receive treatment with biologics, which are assumed to have the same benefit as biologics is the TD arm (see Figure 1 and in Figure 2).

The EAG varied these assumptions in two scenario analyses:

a) High-risk patients on anti-TNF after IM (second step on SU arm) do not do as well as high-risk patients on first-line anti-TNF (first step on TD arm) and thus, the former escalate treatment quicker than the latter. This assumes that anti-TNF treatment is less effective in the SU strategy than in the TD strategy. Given that the EAG did not find any data to support this reduction in relative treatment effect across strategies, a theoretical assumption was made and varied:

    i. Half of the risk of relapse from D'Haens *et al.* for TD (anti-TNF) vs SU (IMs) was assumed for anti-TNFs in the TD approach vs the risk of relapse with anti-TNFs in the SU approach (thus making anti-TNFs more effective in TD than in SU);

    ii. The difference in risk of relapse identified in D'Haens for TD (anti-TNF) vs SU (IMs) was applied to anti-TNFs in TD vs anti-TNFs in SU (thus making anti-TNFs more effective in TD than in SU).

Scenario a also assumes that the benefit in the anti-TNF step of the TD strategy compared to the anti-TNF step in the SU strategy carries through to the next treatment steps. Therefore, patients on second line biologic treatment in the TD strategy receive an increase in benefit comparatively to second line biologic treatment in the SU arm (as do patients on third line biologics). It is also assumed that second and third line biologic treatment is as effective as anti-TNF treatment within the respective TD and SU

arms, and thus there is a benefit associated with biologic treatment in the TD arm compared to biologic treatment in the SU arm (see Figure 1 and in Figure 2 and Table 3).

b) Same assumptions as in scenario a with regards to the benefit of anti-TNF in TD and SU, with the exception that once patients have moved on to second and third-line biologics, there is no further benefit for TD vs SU. In the base case treatment with anti-TNF and second and third-line biologics are assumed to be equally effective. However, as an alternative to scenario a, where the increased benefit of TD vs SU carries through all of these treatment steps, scenario b assumes that the increased benefit only applies to treatment with ant-TNF (i.e. second and third-line biologics are considered equally effective to the same treatments in the SU strategy) (see Figure 1 and in Figure 2 and Table 3).

Results for these scenarios are presented in Table 4.

Figure 1. Top-down treatment strategy

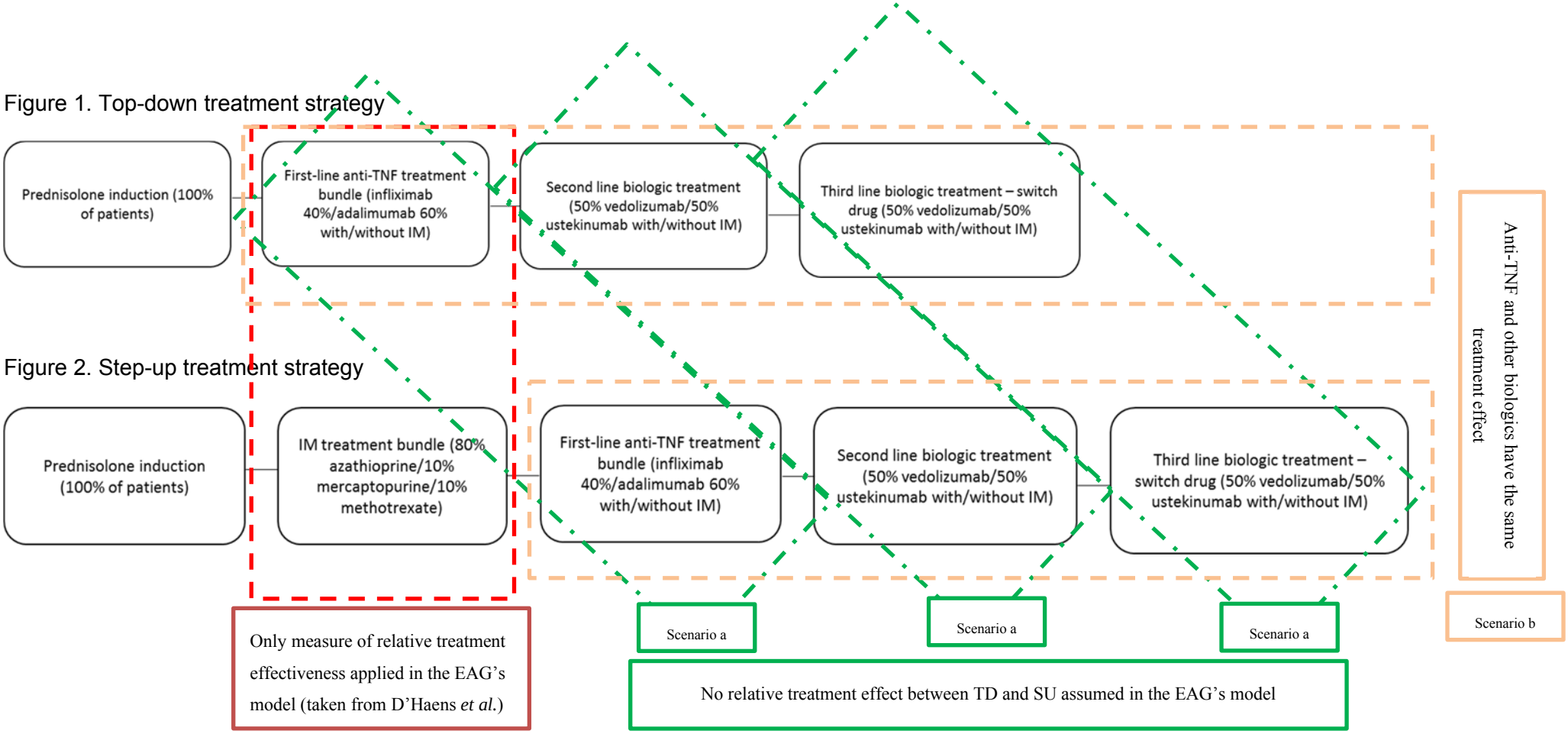


Figure 2. Step-up treatment strategy

Table 3. Summary of exploratory analyses

Steps in the model	**Base case**	**Scenario a**	**Scenario b**
Anti-TNF (TD) vs IM (SU)	Risk of relapse identified in D'Haens *et al*. for TD (anti-TNF) vs SU (IMs)	Same as base case	Same as base case
Anti-TNF (TD) vs anti-TNF (SU)	No relative benefit	i)Half of the risk of relapse from D'Haens *et al.* for TD (anti-TNF) vs SU (IMs) was assumed for anti-TNFs in the TD approach vs the risk of relapse with anti-TNFs in the SU approach; ii) The difference in risk of relapse identified in D'Haens for TD (anti-TNF) vs SU (IMs) was applied to anti-TNFs in TD vs anti-TNFs in SU	Same as scenario a
Second and third line biologic (TD) vs second and third line biologic (SU)	No relative benefit	i)Half of the risk of relapse from D'Haens *et al.* for TD (anti-TNF) vs SU (IMs) was assumed for biologics in the TD approach vs the risk of relapse with biologics in the SU approach; ii) The difference in risk of relapse identified in D'Haens for TD (anti-TNF) vs SU (IMs) was applied to biologics in TD vs biologics in SU	No relative benefit
Second and third line biologic (TD) vs anti-TNF (TD)	No relative benefit	No relative benefit	i)Half of the risk of relapse from D'Haens *et al.* for TD (anti-TNF) vs SU (IMs) was assumed for biologics in the TD approach vs the risk of relapse with anti-TNFs in the TD approach; ii) The difference in risk of relapse identified in D'Haens for TD (anti-TNF) vs SU (IMs) was applied to biologics in TD vs anti-TNFs in TD
Second and third line biologic (SU) vs anti-TNF (SU)	No relative benefit	No relative benefit	No relative benefit

2.2 Assumptions around treatment discontinuation/mucosal healing in the model

a) The EAG assumed that after 2 years in remission with any biologic treatment, a proportion of patients experience mucosal healing and therefore, stop treatment permanently. The EAG used the Marchetti *et al.* paper to inform this scenario. The study reports that after 2 years in remission, 76% of patients in the TD strategy experience mucosal healing, while 40% of patients in the SU arm experience the same outcome (which the EAG has ran in the model in scenario 2.1.3 a i).

   The EAG also varied the Marchetti *et al.* assumptions and explored the possibility of TD and SU therapies having the same impact on the 2-year probability of mucosal healing. Therefore, the EAG assumed that both TD and SU arms would experience the same probability (either 76% in scenario 2.1.3 a ii or 40% in scenario 2.1.3 a iii) of mucosal healing.

   The EAG notes that Hoekman *et al.* concluded that in their 10-year follow-up study, "*mucosal healing 2 years after the start of treatment was associated with a reduced use of anti-TNF treatment during long-term follow-up. Other outcomes, however, did not differ significantly between patients with and without mucosal healing 2 years after the start of treatment, which is in contrast to a recent meta-analysis of 12 studies with 673 patients that showed that mucosal healing is associated with an increased likelihood of long-term clinical remission*." Furthermore, Hoekman *et al.* also reported that another study has shown that 2–4 years after randomisation, mucosal healing at week 104 after randomisation, but not treatment allocation, was associated with stable, corticosteroid-free remission (Baert *et al*.).

   Therefore, while there is some evidence supporting that 2-year endoscopic mucosal healing is associated with long-term, corticosteroid-free clinical remission, there does not seem to be any evidence supporting that mucosal healing at 2 years differs according to TD or SU treatment. To note is that estimates used in Marchetti *et al.* were taken from another study, which the EAG did not have access to (Baert *et al*.).

b) The company in TA352 assumed that patients discontinued treatment with biologic agents approximately 1 year after maintenance treatment. The ERG in TA352 was concerned that a discontinuation rule may not have been appropriate for patients who are not in remission as the NICE recommendation for infliximab and adalimumab suggests that, "*specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who*

continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again". The EAG notes that duration of treatment with biologics in clinical practice remains uncertain. The clinical experts advising the EAG reported that treatment with anti-TNF and second-line biologics would be given as long as patients continue to show a response.

For completeness, the EAG ran an additional scenario analysis assuming that 100% of patients in continuous remission for 12 months with maintenance treatment of any biologic (i.e. anti-TNF, second- or third-line biologics), discontinue treatment.

Results for these scenarios are presented in Table 4.

2.2.1 Results of individual scenario analysis

Results of the individual scenario analysis are reported in Table 4. The EAG notes that all the originally dominated (against PredictSURE IBD™) ICERs remained dominated.

The only exception was scenario 2.1.3 a i, where the ICER changed from £46,263 for SC vs PredictSURE IBD™ (where the prognostic tool was less expensive than SC by £3,506 but also less effective by 0.08 QALYs), to dominated against PredictSURE IBD™.

Table 4. Results of scenario analyses

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Scenario 2.1.2 a i - Assuming half of the base case risk of relapse (in the first treatment steps) for TD vs SU for second and subsequent treatment steps					
Standard of Care	£177,588	15.82	–	–	–
PredictSURE IBD™	£196,602	15.76	£19,014	-0.07	Dominated
Scenario 2.1.2 a ii - Assuming the same as base case risk of relapse (in the first treatment steps) for TD vs SU for second and subsequent treatment steps					
Standard of Care	£173,988	15.75	–	–	–
PredictSURE IBD™	£194,844	15.72	£20,856	-0.03	Dominated

Scenario 2.1.2 b i - Assuming half of the base case risk of relapse (in the first treatment steps) for TD vs SU for anti-TNF vs biologics in TD					
Standard of Care	£177,588	15.82	–	–	–
PredictSURE IBD™	£195,423	15.74	£17,835	-0.09	Dominated
Scenario 2.1.2 b ii - Assuming the same as base case risk of relapse (in the first treatment steps) for TD vs SU for anti-TNF vs biologics in TD					
Standard of Care	£173,988	15.75	–	–	–
PredictSURE IBD™	£192,482	15.68	£18,494	-0.07	Dominated
Scenario 2.1.3 a i – Assuming discontinuation of biologic treatment for 76% TD; 40% SU.					
Standard of Care	£165,654	15.90	–	–	–
PredictSURE IBD™	£168,919	15.80	£3,264	-0.10	Dominated
Scenario 2.1.3 a ii - Assuming discontinuation of biologic treatment for 76% TD; 76% SU.					
Standard of Care	£151,121	15.90	–	–	–
PredictSURE IBD™	£162,773	15.80	£11,652	-0.10	Dominated
Scenario 2.1.3 a iii - Assuming discontinuation of biologic treatment for 40% TD; 40% SU.					
Standard of Care	£165,654	15.90	–	–	–
PredictSURE IBD™	£179,927	15.80	£14,273	-0.10	Dominated
Scenario 2.1.3 b - Assuming discontinuation of biologic treatment for 100% TD; 100% SU.					
Standard of Care	£141,432	15.90	–	–	–
PredictSURE IBD™	£151,337	15.80	£9,905	-0.10	Dominated

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; TTS, time-to-surgery.

*This ICER is for SC vs PredictSURE IBD™, meaning that the prognostic tool is cheaper than SC but also less effective.

2.2.2 Adding an additional step of treatment with immunomodulators at the end of the top-down arm

As per the request from NICE, the EAG has conducted a scenario analysis where patients in the TD arm of the model had the option to receive IMs at the end of the treatment pathway (after relapsing on second line biologics). However, the EAG reiterates that according to its clinical experts' opinion, this is not a clinically realistic treatment pathway.

Given the lack of alternative data, the EAG assumed that patients on IMs as the last treatment step of the TD arm have the same probability of remission and relapse as patients receiving IMs on the first treatment step in the SU approach. When patients relapse on IMs there are no more treatment options and so these are assumed to remain in the moderate to severe health state of the model.

When this option is implemented in the model, the EAG's deterministic base case ICER (dominated against TD) changes to £363,595 per QALY gained, with TD (via the use of PredictSURE IBD™) generating 0.04 additional QALYs compared to SU, at an additional cost of £15,603. This compares to an ICER of £105,148 per QALY gained when corticosteroids are not included in the SU arms (0.07 additional QALYs and an additional cost of £7,502 for PredictSURE IBD™ vs SoC).

2.2.3 Combined scenario analysis

The EAG combined a range of the scenarios described above in order to assess the impact of increasing the effectiveness of the TD strategy while decreasing costs with biologic treatments. These combinations are described, in turn, below and results are reported in the text and summarised in Table 5.

2.2.3.1 Varying the assumptions around the measure of relative treatment effectiveness on time to treatment escalation and assumptions around treatment discontinuation in the model

The EAG explored the impact of combining scenario 2.1.3 (where costs associated with biologics were decreased) with changing the effectiveness of TD through the assumptions made for TTE in the model. The EAG used scenario 2.1.2. a ii for all the analyses as this is the scenario that assumes the highest benefit for TD vs SU in terms of TTE.

a) The EAG combined scenario 2.1.2 a ii with scenario 2.1.3 a i, where it was assumed that after 2 years in remission, 76% of patients in the TD strategy experience mucosal healing, while 40% of patients in the SU arm experience the same outcome.

b) The EAG also combined scenario 2.1.2 a ii with scenario 2.1.3 a ii, where it was assumed that after 2 years in remission, 76% of patients in the TD and the SU strategies experience mucosal healing.

c) The EAG also combined scenario 2.1.2 a ii with scenario 2.1.3 a iii, where it was assumed that after 2 years in remission, 40% of patients in the TD and the SU strategies experience mucosal healing.

2.2.3.2 Results of combined scenario analysis

Results of the EAG's scenario analyses are reported in Table 5. Scenario 2.3.2 a, b and c, explored increasing the effectiveness of TD vs SU with respect to TTE, combined with decreasing the treatment costs with biologics. All scenarios resulted in dominated ICERs against the prognostic tool.

The EAG's scenario analyses (both individual and combined) show that there is a small difference in QALYs in favour of the SU approach, suggesting that this strategy might be more beneficial than TD. However, the EAG notes that the difference in incremental QALYs is small throughout all scenarios, meaning that the final ICER is mainly driven by the difference in costs for TD (via PredictSURE IBD™) compared with SU (via the SC arm).

Table 5. Results of scenario analyses

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Scenario 2.3.2 a (Assuming the same as base case risk of relapse for second and subsequent treatment steps + assuming discontinuation of biologic treatment for 76% TD; 40% SU)					
Standard of Care	£158,874	15.75	–	–	–
PredictSURE IBD™	£165,104	15.72	£6,230	-0.03	Dominated
Scenario 2.3.2 b Assuming the same as base case risk of relapse for second and subsequent treatment steps + assuming discontinuation of biologic treatment for 76% TD; 76% SU)					
Standard of Care	£145,271	15.75	–	–	–
PredictSURE IBD™	£159,253	15.72	£13,982	-0.03	Dominated
Scenario 2.3.2 c (Assuming the same as base case risk of relapse for second and subsequent treatment steps + assuming discontinuation of biologic treatment for 40% TD; 40% SU)					

Standard of Care	£158,874	15.75	–	–	–
PredictSURE IBD™	£176,112	15.72	£17,238	-0.03	Dominated
Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; TTS, time-to-surgery. *This ICER is for SC vs PredictSURE IBD™, meaning that the prognostic tool is cheaper than SC but also less effective.					

2.3 Using the induction vectors and transition probabilities based on TA352 studies

The EAG also performed a scenario analysis that used only data from TA352 to inform the induction and maintenance vectors. The transition probabilities were re-estimated using these data. The induction and maintenance vectors for the scenario are given in Table 6 and Table 7, respectively, and the updated transitions for TD and SU are given in Table 8 and Table 9, respectively. The results of this scenario are given in Table 10.

Table 6. Estimated induction vectors for step up and top down with levels of response (TA352 data)

Clinical outcomes	**Induction**			
	Remission	**Mild**	**Moderate/Severe**	**No response**
Top Down				
Biologics	13%	25%	7%	55%
Anti-TNF	32%	23%	6%	38%
Step Up				
Biologics	13%	25%	7%	55%
Anti-TNF	32%	23%	6%	38%
Immunomodulator	16%	18%	5%	62%

Table 7. Estimated maintenance vectors for step up and top down with levels of response (TA352 data)

Clinical outcomes	**Maintenance**			
	Remission	**Mild**	**Moderate/Severe**	**No response**
Top Down				
Biologics	28%	1%	0%	70%

Anti-TNF	48%	9%	3%	41%
Step Up				
Biologics	28%	1%	0%	70%
Anti-TNF	48%	9%	3%	41%
Immunomodulator	25%	12%	3%	60%

Table 8. Estimated 2-week transition probabilities for top down (TA352 data)

Annual transitions	**Remission**	**Mild**	**Moderate/Severe**
Anti-TNF			
Remission	0.9691	0.0309	0.0000
Mild	0.1665	0.8335	0.0000
Moderate/Severe	0.0000	0.0548	0.9452
1st and 2nd line biologics			
Remission	0.9982	0.0018	0.0000
Mild	0.1136	0.8864	0.0001
Moderate/Severe	0.0000	0.0795	0.9205

Table 9. Estimated 2-week transition probabilities for step up (TA352 data)

Annual transitions	**Remission**	**Mild**	**Moderate/Severe**
Immunomodulator			
Remission	0.9736	0.0264	0.0000
Mild	0.0616	0.9302	0.0082
Moderate/Severe	0.0000	0.0482	0.9518
Anti-TNF			
Remission	0.9691	0.0309	0.0000
Mild	0.1665	0.8335	0.0000
Moderate/Severe	0.0000	0.0548	0.9452
1st and 2nd line biologics			
Remission	0.9982	0.0018	0.0000
Mild	0.1136	0.8864	0.0001
Moderate/Severe	0.0000	0.0795	0.9205

Table 10. Results of scenario analysis

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Scenario 3: Applying induction vectors and transition probabilities based on TA352 studies					
Standard of Care	£181,592	15.90	–	–	–
PredictSURE IBD™	£198,866	15.79	£17,274	-0.10	Dominated

2.4 Assuming that 100% of high-risk patients who receive SU do not respond to treatment and therefore escalate to anti-TNF after induction with IMs.

Under the new base case analysis (incorporating corticosteroids as a first treatment step for SU), when the EAG assumed that 100% of high-risk patients who receive SU therapy do not respond to IMs (therefore not deriving any benefit from response to this treatment). The ICER for PredictSURE-IBD™ compared to SU changed from dominated (against the diagnostic tool) to £13,206. The EAG tested the impact of varying the proportion of patients who do not respond to IM treatment in the analysis. When the EAG assumed that 50% of high-risk patients who receive SU therapy do not respond to IMs (therefore not deriving any benefit from response to this treatment), the ICER reached the £30,000 threshold. When the EAG assumed that 41% (or less) of high-risk patients who receive SU therapy do not respond to IMs, the ICER remained dominated against PredictSURE-IBD™.

Table 11. Results of scenario analysis

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Scenario 7: 100% of high-risk patients who receive SU do not respond to IM treatment					
Standard of Care	£82,657	6.99	–	–	–
PredictSURE IBD™	£198,987	15.80	£116,330	8.81	£13,206
Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; TTS, time-to-surgery.					

2.5 One-way sensitivity analysis

In the first addendum, the EAG conducted a number of deterministic one-way sensitivity analyses around the model inputs as described in Table 12. Figure 3 ranks the model key drivers by their impact on the incremental net monetary benefit (INMB) of PredictSURE-IBD™ compared to standard care, based on a willingness-to-pay (WTP) threshold of £30,000 per QALY. The lower and upper bounds of

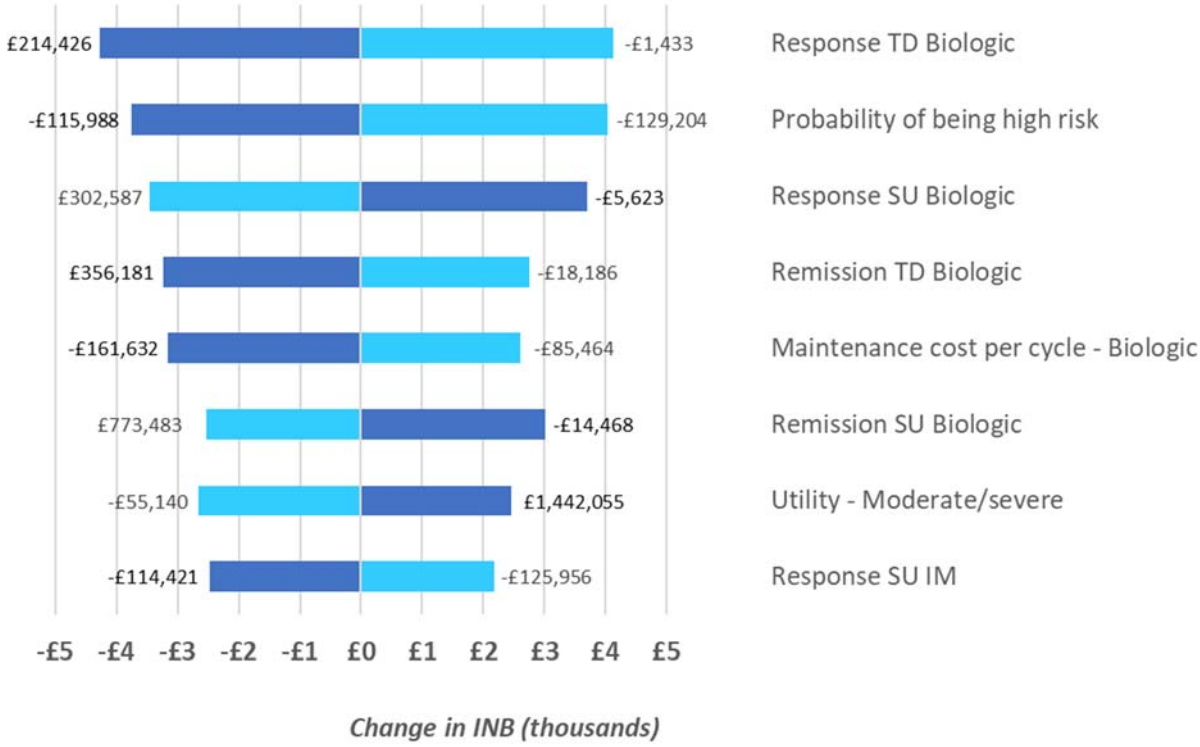
each parameter input were derived from the lower and upper bounds of the 95% confidence intervals of the distributions specified for the probabilistic sensitivity analysis (PSA). The inputs with the highest impact on the model results were the response to biologic treatments in both the TD and the SU arms. To note is that these results do not include the corticosteroid initial step in the SU arm, however, given that the latter change in the model only increased the dominance of SU, the conclusions derived from the OWSA results in the first addendum are applicable to the results of the second addendum (where corticosteroids were included).

Table 12. Inputs and results of OWSAs

Model Parameter	Lower bound	Upper bound	ICER (Lower Bound)	ICER (Upper Bound)
Age	22.7	50.0	-£113,635	-£136,727
Crohn's disease expected body weight	46.2	102.0	-£120,774	-£118,762
Proportion of males	0.23	0.53	-£119,367	-£120,394
Probability of being high risk	0.34	0.79	-£129,204	-£115,988
Proportion on infliximab in anti-TNF biologics class	0.25	0.56	-£119,684	-£120,059
Proportion on vedolizumab in non-anti-TNF biologics class	0.31	0.69	-£116,088	-£123,642
Proportion on azathioprine for immunomodulators	0.41	0.99	-£120,489	-£119,559
Proportion of 6-mercaptopurine for immunomodulators	0.06	0.14	-£119,906	-£119,841
Proportion of anti-TNF with IM bundle	0.19	0.42	-£119,874	-£119,856
Proportion of Biologics with IM bundle	0.13	0.28	-£119,735	-£120,016
Response TD Biologic	0.20	0.44	-£1,433	£214,426
Remission TD Biologic	0.08	0.19	-£18,186	£356,181
Response TD anti-TNF	0.16	0.36	-£97,736	-£185,310
Remission TD anti-TNF	0.23	0.52	-£89,429	-£266,559
Response SU Biologic	0.20	0.44	£302,587	-£5,623
Remission SU Biologic	0.08	0.19	£773,483	-£14,468
Response SU anti-TNF	0.16	0.36	-£203,848	-£71,062
Remission SU anti-TNF	0.23	0.52	-£280,003	-£58,931

Response SU IM	0.14	0.32	-£125,956	-£114,421
Remission SU IM	0.10	0.22	-£129,351	-£111,917
Probability of death following surgery	0.0010	0.0021	-£118,576	-£121,465
Health state cost - Remission	£11	£24	-£120,223	-£119,432
Health state cost - Mild	£17	£38	-£120,554	-£119,029
Health state cost - Moderate/severe	£79	£174	-£113,183	-£127,978
Health state cost - No response	£79	£174	-£120,757	-£118,783
Induction cost per cycle - Anti TNF	£982	£2,169	-£119,157	-£120,725
Induction cost per cycle - Biologic	£1,000	£2,207	-£117,755	-£122,428
Induction cost per cycle - Immunomodulator	£3	£6	-£119,924	-£119,794
Maintenance cost per cycle - Anti TNF	£346	£765	-£121,205	-£118,239
Maintenance cost per cycle - Biologic	£425	£938	-£85,464	-£161,632
Maintenance cost per cycle - Immunomodulator	£8	£17	-£121,021	-£118,462
IV administration first attendance	£129	£284	-£119,607	-£120,179
IV administration follow-up	£137	£303	-£109,074	-£132,967
Cost of surgery	£5,704	£12,589	-£122,801	-£116,301
Utility - Remission	0.40	1.00	-£2,438,927	-£109,748
Utility - Mild	0.40	0.95	-£1,283,717	-£83,963
Utility - Moderate/severe	0.34	0.78	-£55,140	£1,442,055
Disutility for surgery	0.03	0.06	-£120,664	-£118,917

Figure 3. Tornado plot showing OWSAs that have the greatest impact on incremental net monetary benefit (ICERs given at the top and lower end of bars)



Abbreviations in figure: ICER, incremental cost effectiveness ratio; INMB, incremental net monetary benefit; OWSA, one-way sensitivity analysis; SU, step up; TD, top down.

Note: The bars in the graph represent the change in INMB and the respective ICERs are presented at both ends of the bars. Light blue bars represent the lower bound of the parameter changed while dark blue bars represent the upper bound of the parameter changed.

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

Erratum related to the Appendix accompanying the EAG's response to comments on the EAG's second addendum

November 2021

This report was commissioned by the NIHR Systematic Reviews Programme as project number 128968/T

BMJ Technology Assessment Group

This document contains an erratum on the Appendix accompanying the EAG's response to comments on the EAG's second addendum to address a factual inaccuracy raised by stakeholders. The table below lists the page to be replaced in the original document and the nature of the change. The change relates to a correction made to the economic model. References to the EAG's updated results in the table below correspond to the corrections made in the economic model.

Page No of the relevant Appendix	**Change**
Section 2.4	Text updated to reflect revisions to the base case

1 SCENARIO ANALYSES PREVIOUSLY UNDERTAKEN

1.1 Assuming that 100% of high-risk patients who receive SU do not respond to treatment and therefore escalate to anti-TNF after induction with IMs.

Under the new base case analysis (incorporating corticosteroids as a first treatment step for SU), assuming that 100% of high-risk patients who receive SU therapy do not respond to corticosteroids or IMs (therefore not deriving any benefit from response to this treatment) does not change the ICER compared to this scenario analysis in the model excluding corticosteroids. The ICER for PredictSURE-IBD™ compared to SU amounts to £170,180. To note, is that the EAG tested the impact of varying the proportion of patients who do not respond to IM treatment in the analysis. When the EAG assumed that 97% of high-risk patients who receive SU therapy do not respond to IMs (therefore not deriving any benefit from response to this treatment), the two strategies (TD and SU) became clinically equivalent.

Table 11. Results of scenario analysis

Intervention	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Scenario 7: 100% of high-risk patients who receive SU do not respond to IM treatment					
Standard of Care	£209,797	15.78	–	–	–
PredictSURE IBD™	£211,009	15.79	£1,212	0.01	£170,180
Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; TTS, time-to-surgery.					