NICE National Institute for Health and Care Excellence

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

Diagnostics Assessment Report (DAR) - Comments

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Crohn's & Colitis UK	1.	n/a		As a 3rd sector organisation representing patients, Crohn's & Colitis UK does not have the in-house health economics expertise to comment on the precise methodology used in this document. To have provided a detailed critique, the organisation would have needed to commission external evaluation, with the associated resource and time constraints.	No response required.
Crohn's & Colitis UK	2	V - Vi	Results	Given the assumptions made, there appears to be an elementary question relating to the methodology used in this paper which requires clarification from the patient perspective. If the authors have assumed that the prognostic tests are 100% accurate, then it is difficult to understand (without a precise understanding of the methodology – see comments above) how apparently matching someone with the agreed, most effective treatment for their stage of the condition through the use of such tests, can then adversely affect that patient i.e. result in a worsening of outcomes.	No response required.
Crohn's & Colitis UK	3	161 - 163	7.1 7.2	It is notable that in the conclusions there are multiple references to 'lack of evidence' and 'uncertainty' in the modelling and hence results. Whilst Crohn's & Colitis UK fully supports the move to more individualised treatment for people with Crohn's and colitis, a move facilitated by the development of accurate prognostic tests, we would advocate that consideration of such tests be	No response required.

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				delayed until improved data is available from the studies currently in progress.	
Glycominds LLC	4			**IBDX** Three main limitations are discussed in the DAR, including: i) stage of diagnosis i.e. established CD vs. newly diagnosed, ii) lack of published accuracy performance of the IBDX combined six markers, and iii) lack of study that analyze treatment decision based on test outcome. The following is Glycominds, LLC response to the DAR assessment.	No response required.
Glycominds LLC	5			**Stage of diagnosis** DAR ignored the chronological development of the IBDX test. Studies were presented as all equal while some studies confected and published as discovery of IBDX six marker panel (DAR reference 78), a feasibility (DAR references 75) and validation (DAE reference 76). Although the discovery and feasibility studies were done on established CD cases (retrospectively without clear information on prior complication/surgery events), the prospective validation study was done on CD patients without any prior CD complications or CD-related surgery with a median disease duration of 10.6 months (P25, P75 = 1.7, 52.3) of which 32% of the sera were collected within 3 months and 51% within 1 year of diagnosis (DAR reference 76). The time between the initial manifestation of a disease and its correct diagnosis is termed diagnostic delay. In an online survey promoted by the European Federation of Crohn's and Colitis Associations (EFCCA) involving 4990 patients with inflammatory bowel disease (IBD), 20 % of subjects had to	No changes required. The External Assessment Group (EAG) considers that it was beyond the remit of the project to describe the development of the IBDX kit. The goal of the project is to evaluate the prognostic accuracy and clinical impact of the kit as used by clinicians at this time for use in management of Crohn's disease (CD). The EAG appreciates the company's comments and considers that the points raised are highlighted in the report through discussion of the strengths and limitations of the evidence available on IBDX in terms of study design and patient characteristics. Additionally, full details on studies are provided in the data extractions forms available in the Appendices.

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				wait up to 5 years after symptomatic disease onset in order to receive the correct diagnosis of CD, consequently impairing the quality of their life[1]. In another study that was conducted in three IBD referral centers in France, enrolling 497 patients diagnosed with CD over a 12-year period (2002–2014), the median time to diagnosis was 5 months; early diagnosis was defined as <2 months, whereas late diagnosis was ≥13 months following the onset of symptoms[2]. A third study found that the time from symptom onset (diarrhea and blood feces) until definitive diagnosis was reported to be 62.4–76.3 months[3]. In addition, complications at diagnosis are a frequent event. 36% of newly diagnosed CD patients already exhibit a complication or have to undergo early surgery[4]. **Therefore, since all CD patients in the validation cohort were CD-complications and CD-related surgery naïve, with majority collected within 1st year of diagnosis, the IBDX validation cohort should be considered as newly diagnosed cases for the purpose of this diagnostics assessment.** Moreover, several studies showed that antibodies to anti-glycan antibodies, including ASCA/gASCA, ACCA and AMCA are elevated up to 10 years prior to diagnosis[5-7] which, in addition to marker positive/negative status stability (DAR reference 77) makes the time of diagnosis less relevant while a lack of prior CD complication and surgery is actually the true inclusion criteria for prediction of disease progression.	

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Glycominds LLC	6			**IBDX test accuracy performance** The DAR conclusion that there is no report on the performance of the six IBDX markers combined is not accurate. All reported results analyzed by DAR studied the performance of the six IBDX combined. IBDX anti-glycan antibodies biomarkers are based on fungal microbiota dysbiosis mainly to *Saccharomyces cerevisiae* and *Candida Albicans* [8] and association with innate immune mutations in CARD[8] and β-defensin 1 genes[9-10]. Therefore, due to the nature of the IBDX biomarkers, to avoid a single algorithm score that can be validated in one geographical population but then after be different in another population, a simplistic, but yet robust algorithm was developed which is the number of positive markers in a certain CD population when the entire six biomarkers are analyzed. This algorithm enables the flexibility to have one set of positive anti-glycan antibodies in one population, say gASCA, ACCA and AMCA (like in Chinese population) and another set, anti-L, ALCA and gASCA, for example, in another geographical area. Studies on Chinese population found that ACCA and AMCA are more prevalent than gASCA/ASCA[11-12]. Therefore, the sensitivity and specificity of any set of positive markers (eg, at least 2, at least 3), is out of the measured six anti-glycan antibodies represents the performance of the combined panel on that population. The validation cohort which analyze 76 CD recently diagnosed, complication/surgery naïve German patients reported in Table 1 that 28.3% (15/53) of CD patient which had no complication/surgery event within the follow up	No change required. The EAG appreciates the company's comment. The EAG considers that it is clear in the report that the studies presented in support of the utility of the IBDX kit evaluate all six biomarkers in the panel simultaneously, and that assessment of the accuracy of the tool in predicting risk of developing a complication or need for surgery is based number of biomarkers for which a person tests positive.

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				time were positive for at least 2 IBDX markers while 56.5% (13/23) were positive in patients that had an event (complication, surgery or both) during the same follow-up time. This represents a sensitivity of 56.5% and specificity of 72.7% (1-28.3%). Similarly, the sensitivity for at least 3 positive markers as reported in this table 1 was 26.1% and the specificity 90.6% (5/53 and 6/23 respectively) (DAR reference 76). IBDX biomarker found to be predictors of CD complication and CD surgery **independently of age, sex, BMI, disease activity and duration, age at diagnosis, and disease location** as analyzed by a Coxproportional Hazard regression model taking into consideration above parameters as potential confounders. Data presented in DAR Table 7 and Table 8 discuss complication and surgery separately while the adjusted Time-to-event Analysis, Cox Proportional Hazard Regression Model for combined complication and surgery was not discussed. Although CD complications (fistula and/or stenosis) are different health outcome than a CD-related surgery, from clinical practice perspective related to treatment escalation they are the same. There is no difference in treatment protocols to avoid complication in comparison to the treatment protocol to avoid surgery. Therefore, the Hazard Ratio performance of the IBDX in predicting any escalating event should be presented (DAR reference 76):	

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				<table><tr><th>Outcome</th><th>N</th><th>Population</th><th>Result</th><th>P value</th></tr><tr><td>Complication or Surgery or both No Event</td><td>23 53</td><td>Recently diagnosed CD patients without any prior CD complication or CD related surgery</td><td>Cut off 1: At Least 2 pos. markers out of six measured HR 2.9 (1.3, 6.7) Cut off 2: At Least 3 pos. markers out of six measured HR 3.4 (1.3, 8.7)</td><td> 0.011 0.01</td></tr></table>	
Glycominds LLC	7			**PredictSURE-IBD** Two major limitations of the Biasci *et al.* 2019 study (DAR reference 50) were not discussed in the DAR – verifying the independency of PredictSURE-IBD algorithm with cofounding factors such as Age, Gender, disease duration, disease activity biomarkers and disease location. It is not clear if the PredictSURE-IBD algorithm is an independent predictor and if it will remain as statistically significant factor in a Cox Proportional Hazard Regression Model using these cofounding factors. In addition, although CRP and Albumin were measured as disease activity biomarkers the CRP Albumin ratio (CAR) was not analyzed. CAR was found as a useful biomarker for CD disease activity [13] and should be added as an additional cofounder factor to such Cox Proportional Hazard Regression Model.	No changes required. The project focuses on the prognostic accuracy of the tools as assessed by measures including sensitivity and specificity, and not the functionality of the algorithm developed by PredictImmune.
Glycominds LLC	8			**IBDX - PredictSURE-IBD Head-to-head analysis of the IBDX and PredictSURE-IBD tools** PredictImmune provided a conference abstract that reports the results of a head-to-head comparison of the IBDX and PredictSURE-IBD tools (DAR reference 84). Although the data from this analysis is blanked as confidential in the DAR,	The EAG thanks the company for their comments and will consider the points raised when drafting the addendum to the report.

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				major limitations are available on using the PredictSURE-IBD cohort for such a comparison. In the IBDX validation cohort (DAR reference 76) median follow-up in the complication and surgery naïve group was 53.7 months with a median time for complication or a surgery event of 11.6 months. This follow-up period and time to event are much longer than in the PredictSURE-IBD validation cohort in which the entire follow-up time was only 18 months and end points were mainly related to disease activity and not disease outcome. In addition, although disease activity was defined in the PredictSURE-IBD validation cohort, disease course status i.e. prior CD complications or CD-related surgery was not recorded.	
Glycominds LLC	9			**Other** 'Glycominds International' is not a LEGAL entity and this name was not in any of the documentations provided by Glycominds, LLC.	The EAG thanks the company for pointing out the error and will remove all instances of "Glycominds International".
Glycominds LLC	10			**References** 1. Ghosh S, Mitchell R. Impact of inflammatory bowel disease on quality of life: results of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) patient survey. J Crohns Colitis. 2007;1:10–20. 2. Nahon S, Lahmek P, Lesgourgues B, *et al.* Diagnostic delay in a French cohort of Crohn's disease patients. J Crohns Colitis. 2014;8:964–969.	

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				3. DB Cury, R Oliveira, and MS Cury, Inflammatory bowel diseases: time of diagnosis, environmental factors, clinical course, and management – a follow-up study in a private inflammatory bowel disease center (2003–2017), J inflamm Res. 2019; 12: 127-135. 4. Solberg IC, Vatn MH, Hoie O, *et al.* Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. Clin Gastroenterol Hepatol. 2007;5:1430_1438. 5. Israeli E, Grotto I, Gilburd B, Balicer RD, Goldin E, Wiik A, Shoenfeld Y., Anti-Saccharomyces cerevisiae and antineutrophil cytoplasmic antibodies as predictors of inflammatory bowel disease. Gut. 2005 Sep;54(9):1232-6. 6. Israeli, E., Grotto, I., Blank, M., Anafi, L., Goldin, E., & Shoenfeld, Y. (2006). Anti-Laminaribioside and anti-Chitobioside Antibodies as Predictors of Crohn's Disease (Presented at the Digestive Disease Week 2006, Los Angeles, CA, May 20 - 25, 2006.) http://ibdx.net/assets/img/flyers/israeli_poster.pdf 7. R. S. Choung F. Princen T. P. Stockfisch J. Torres A. C. Maue C. K. Porter F. Leon B. De Vroey S. Singh M. S. Riddle J. A. Murray J. F. Colombel, Serologic microbial associated markers can predict Crohn's disease behaviour years before disease diagnosis, AP&T 2016 43:12 1300-1310.	

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				8. Sokol H, Leducq V, Aschard H, *et al.*, Fungal microbiota dysbiosis in IBD 2016 Gut 2017;66:1039–1048. 9. Lakatos, P., Altorjay, I., Mándi, Y., Lakatos, L., Tumpek, J., Kovacs, A., *et al.* (2008). Interaction between seroreactivity to microbial antigens and genetics in Crohn's disease: is there a role for defensins? Tissue Antigens , 71 (6), 552-559. 10. Vasseur, F., Boualem, S., Broly, F., Gower-Rousseau, C., Sarazin, A., *et al.* (2013). The CARD8 p.C10X mutation associates with low anti-glycans antibody response in patients with Crohn's disease. BMC Medical Genetics 14:35 2013, 14:35. 11. Lani Prideaux, Michael A Kamm, Peter De Cruz, Inflammatory bowel disease serology in Asia and the West, World J Gastroenterol. 2013 Oct 7;19(37):6207-13. 12. Fang Yao, Yihong Fan, Bin Lv, Conghua Ji, Diagnostic utility of serological biomarkers in patients with Crohn's disease, Medicine (2018) 97:32. 13. Li Xu, PhDQin G, Tu J, Liu L, Luo L, Wu J, Tao L, Zhang C, Geng X, Chen X, Ai X, Shen B, Pan W, Serum Albumin and C-Reactive Protein/Albumin Ratio Are Useful Biomarkers of Crohn's Disease Activity, Med Sci Monit. 2016 Nov 16;22:4393-4400.	
PredictImmune Ltd	11	vi 65 70 87	6.1.2	**Lack of clinical credibility** It is well established from multiple RCTs in the field that early aggressive (top down) therapy results in improved clinical	No changes required. As discussed in the report, the EAG considers that the evidence base in support of early top-

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		156		outcomes.[1-11] Despite this, the high costs and potential risks of therapy, combined with demonstrated efficacy of conventional (step-up) therapy in some patients, have resulted in a consensus view that a precision medicine strategy with early aggressive therapy for those likely to have the most aggressive disease course, would be the optimal approach.[12-15] The EAG model, however, estimates that personalised treatment of Crohn's disease using a prognostic test with 100% accuracy (i.e. that correctly assigns Top-down therapy to patients with a severe disease course) is dominated by standard of care treatment (Step-Up). The model concludes that top down therapy, when given to high risk cases only, results in fewer QALYs than, and is thus inferior to, standard care. This result alone, which is in direct contrast to the large body of published and presented evidence demonstrating that early aggressive therapy for all has clear benefit, highlights that there are major and fundamental errors in the proposed EAG model in our and current clinical opinion.	down (TD) therapy improving clinical outcomes in CD is uncertain. As part of the project, and as described in the report, the EAG carried out a systematic review for randomised controlled trials (RCTs) evaluating step up (SU) versus TD strategies. The EAG noted heterogeneity across identified studies in terms of intervention schedules followed, agents given, and follow-up times. Of the 11 references cited by the company in support of early use of TD strategies, the EAG evaluated four, the strengths and limitations of which are discussed in the report. Moreover, of the remaining seven citations, one reports results for ulcerative colitis, one reports on maintenance treatment and not induction of remission, and two are *post hoc* subgroup analyses, which the EAG considers should be interpreted with caution. The EAG considers that the PROFILE RCT, which is in progress, was designed to compare the relative efficacy of TD and accelerated SU therapy within the subgroups of high and low risk of following a severe course of CD, and thus provide robust evidence on whether early treatment with biologics is effective, and whether there is additional benefit for those designated to be at high risk of following a severe course of CD. Furthermore, the EAG did not identify any direct evidence on the cost-effectiveness of

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					TD therapy vs SU therapy for high-risk patients. The EAG found two main sources of evidence that could be used to model time to treatment escalation (TTE) and time to surgery (TTS). While the Biasci *et al.* paper could inform TTE and TTS according to high- and low-risk of CD complications (for the SU strategy); the D'Haens *et al.* (and its 10-year follow-up study Hoekman *et al.*) could inform TTE and TTS according to TD and SU treatments (for a population with mixed risk of disease complications). Combining these data is not ideal and creates a patchwork network of evidence, introducing uncertainty in the economic results. It is anticipated by the EAG that this problem will be (at least partially) overcome when results from the PROFILE trial are available to populate the economic model. The long-term follow-up study Hoekman *et al.* (cited by the company) found no difference between SU and TD in 10-year clinical remission rate; endoscopic remission, hospitalisation, surgery or new fistulas. Furthermore, the study concluded that in the long-term a TD strategy had not proven to alter the natural history of CD. However, time to relapse was found statistically significantly different across TD and SU arms in the 2-year

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					analysis of the same data (D'Haens *et al.*). The EAG has incorporated such treatment effects in its analysis. Hoekman *et al.* concluded that their study was the first to compare the long-term outcomes for newly diagnosed CD patients who received combined immunosuppression vs conventional management. In order to mitigate some of the concerns raised by the specialist committee members (SCMs), the EAG conducted a range of analyses to test extreme scenarios around increasing the relative treatment effectiveness of the TD approach while decreasing the relative costs associated with TD. The conclusions of the analysis can be found in the EAG's report and addendum.
PredictImmune Ltd	12	60	4.2	**The EAG assumption that efficacy of biologic treatment is independent of disease stage is unreasonable, and leads to a flawed outcome** One of the key assumptions made in the EAG model is that the clinical effectiveness of biologic treatment is not influenced by the timing of its use i.e. that it is equally effective if used from diagnosis (Top-Down model) compared to delayed use after other treatments have failed (Step-up model). This assumption is incorrect, and in direct opposition to multiple lines of published evidence, the majority of which appear not to have been considered by the EAG. In fact, we	No changes required. The EAG thanks the company for highlighting the references in support of early treatment with biological therapy compared with delayed treatment. To inform the economic model, the EAG focused its review of the literature on SU versus TD at early diagnosis for those with moderate/severe disease activity as this is the position in the pathway where it is proposed that the prognostic tools would potentially afford the greatest benefit.

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				are aware of no clinical evidence that would support the EAG's assumption that disease stage has no bearing on efficacy. We have summarised below key clinical data that indicates that response rates are lower when treatment is delayed: In the PRECiSE 2 study (Certolizumab pegol, another anti-TNFα) it was shown that treatment response was significantly higher if used earlier in the disease course – response rates were 90%, 75%, 62% and 57% in Crohn's disease who had been diagnosed <1 year, 1–2 years, 2–5 years or >5 years previously.[9] This trend has also been observed with other anti-TNFα therapies. For example, in the CHARM and ADHERE studies (adalimumab), clinical response rates were 54%, 49% and 42% in patients with a disease duration of <2 years, 2–5 years and >5 years, respectively.[4,6] More recently, pooled data from 10 clinical trials of adalimumab in patients with moderately to severely active Crohn's disease showed a stepwise reduction in efficacy with increasing disease duration: <1 year: 45.8% remission, ≥1–<2 years: 31.0%; 2–≤5 years: 23.1%; >5 years: 23.6%.[16] A *post-hoc* analysis of the SONIC trial (azathioprine, infliximab or combination therapy) also showed that patients with early Crohn's disease (defined as <18 months since diagnosis) had better outcomes across a range of measures	The EAG did not identify an RCT evaluating clinical effectiveness of sequential treatment, as would occur in SU strategy used in UK clinical practice, to inform the assessment of cost effectiveness. As PROFILE is the first biomarker-stratified trial in inflammatory bowel disease, the EAG considers it important to note that the cited studies are likely to include a mix of people who are at low versus high risk of following a severe course of CD and are difficult to interpret in the context of stratification by risk of disease course. The PROFILE RCT will provide robust evidence on the early use of anti-TNFs in the population of interest for this DAR. Furthermore, the cited studies do not include evidence on either the TD or SU complete treatment sequences (whether in the form of comparative or non-comparative data).

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				compared to those with longer disease duration. For example, deep remission (clinical remission, mucosal healing and normalised CRP) occurred in 65% of early Crohn's patients and 44% of non-early patients when treated with infliximab and azathioprine.[3] This pattern has also been observed with other non-anti-TNFα biologics in Crohn's disease.[17] A recent review article (published by clinical KOLs who are not stakeholders in the current DAG appraisal) evaluated the available evidence, and concluded that "substantial evidence supports earlier use of biologics such as anti–tumour necrosis factors (anti-TNFs; e.g. infliximab, adalimumab, and certolizumab) in CD" and that Step-Up therapy "…ultimately delays introduction of effective disease-modifying therapy and can result in progressive inflammation and irreversible structural bowel damage." The latter observation, that delayed aggressive treatment for high risk patients results in accumulation of clinical complications related to uncontrolled disease activity (including fistulae, strictures, surgery and hospitalisations) is also a consensus viewpoint and supported by multiple lines of evidence.[10,18-22] This evidence is summarised in a recent systematic review, including a total of 16,796 patients, which states:	

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				"In adults, earlier use of biologics was associated with higher rates of clinical remission at week 26 (CD duration < 2 years 54–68%; 2–5 years 47–48%; >5 years 42–44%), corticosteroid-free clinical remission at week 26 (early 60–82%, conventional 36%), mucosal healing at week 12 (<2 years 44%; 2–5 years 40%; >5 years 21%), hospitalisation-free rate (< 2 years 93%; 2–5 years 90%; >5 years 86%), and lower relapse rate at year 1 (<2 years 34%; ≥2 years 47%), lower risk of bowel strictures or perianal fistulas (hazard ratio [HR] ranged 0.28 to 0.43 in early vs. late group) and fewer surgeries in 2 years (top-down 9%; step-up 12%)." https://academic.oup.com/ecco-jcc/article/12/supplement_1/S461/4807864 However, despite concerns being raised by the EAGs own Specialist Committee members (DAR p86), the EAG chose to assume that delay would not result in risk of additional complications. This appears to have been based on long-term follow up of patients following the "Step up-Top down" trial[2] but this fails to recognise that "Top-down" therapy in this study only involved 6 weeks of treatment with infliximab, rather than continued dosing for at least one year (as is now used routinely). Indeed, at the start of follow-up in this study, similar numbers of patients in each arm were on anti-TNFα (15% in step-up and 20% in top-down). This is therefore not a relevant comparison for the model.	

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				In view of the available evidence, the EAG's failure to allocate any treatment effect reflecting the clear benefit of early versus later use of biologic therapy is a critical flaw and contributes to the finding that TD therapy is associated with fewer QALYs in the EAG model.	
PredictImmune Ltd	13	70-72	4.2.4.1	**The analysis of Individual Patient Data conducted by the EAG is methodologically flawed** The EAG based its time to event assumptions on data available from Biasci *et al.*[25] however they chose to exclude over half of the individual patient data (IPD) on the basis that not all patients had followed strictly the model's specified accelerated SU regimen. This decision was founded on a misunderstanding of the treatment regimen for Crohn's disease and (as is shown in Figures 1 and 2 below) markedly skews the model parameters, underestimating the benefit of early aggressive therapy as a result. Page 70 of the EAG report contains the following statement: "Out of the 105 patients included in the Biasci *et al* IPD provided to the EAG, 88 patients were newly diagnosed with CD. Out of these 88 patients, 75 patients received initial treatment with corticosteroids. The EAG also removed 35 patients from the analysis who never received a subsequent IM after corticosteroids (leaving 40 patients for the TTE analysis, Figure 14)." In doing this, the EAG removed over half of the available IPD. Significantly, more data was removed from patients in	No change required. The final 40 patients included in the EAG's analysis consisted of all patients in the dataset who received corticosteroid treatment followed by treatment with IMs. The EAG censored patients who did not have an escalation event after treatment with IM. As explained throughout this document and in the document replying to the company's comments on the model, this was the population considered relevant by the EAG. This is discussed in further detail in the EAG's addendum. Furthermore, the EAG is not clear how the figures obtained by the company were derived. The EAG's DAR shows the fitted curves against the KM data for high- and low-risk patients (Figure 17 and 18, respectively, in the DAR).

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				one prognostic group than the other (the EAG's final dataset contained 23 high-risk patients (58%), compared to the 41% of the patients in the complete dataset who were defined as high-risk). Figure 1 shows how this imbalanced data removal had a large impact on the resulting Kaplan-Meier curves (Figure 1 showing curves modelled with the data, Figure 2 showing curves modelled with the data removed). As can be seen, removing cases who do not require treatment escalation leads to an overestimation of the event rate, significantly reducing the observed difference between high and low risk prognostic groups. Critically, the rationale for removal of this data was fundamentally flawed. As stated on page 70, the EAG removed 35 patients from the analysis who did not receive a subsequent immunomodulator after corticosteroid treatment (reasoning that they had not followed a 'step-up' regimen as they hadn't been stepped up). However, the patients removed received corticosteroid followed by observation, and simply did not require escalation of treatment. This is a clinically valid 1st line treatment approach that is clearly included in NICE guidelines for CD management (NG129, which are actually summarised the DAR). These patients should have been censored not removed. This error is detailed in point 3 above. Figures 1 and 2. Kaplan Meier survival curves fitted to the entire IPD cohort (as per the PredictImmune model, Figure 1) and as estimated by the EAG using an inappropriately sparse set of IPD (Figure 2). Estimating the disease course of patients using the sparse dataset (Figure 2) results in an	

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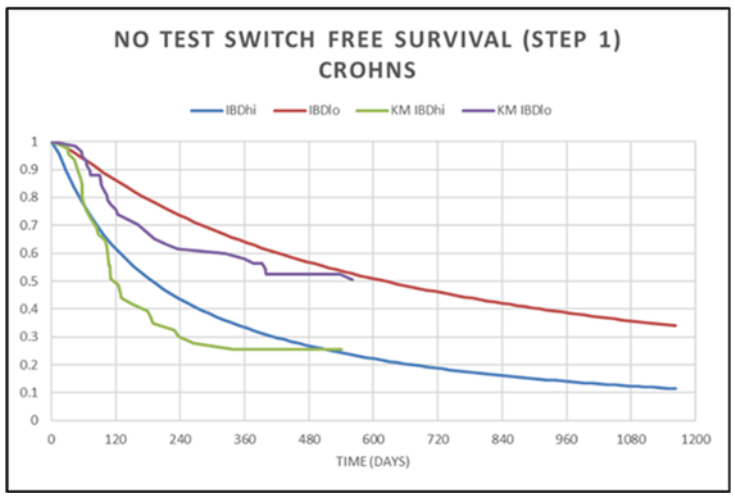
				estimation of more rapid treatment escalation, effectively reducing the difference between prognostic groups. *Figure 1 FIGURE 1 SURVIVAL CURVES FOR HIGH AND LOW RISK BASED ON 88 PATIENT COHORT FROM BIASCI ET AL(25). (PREDICTSURE-IBD ECONOMIC MODEL GENERATED BY COGENTIA)*  	

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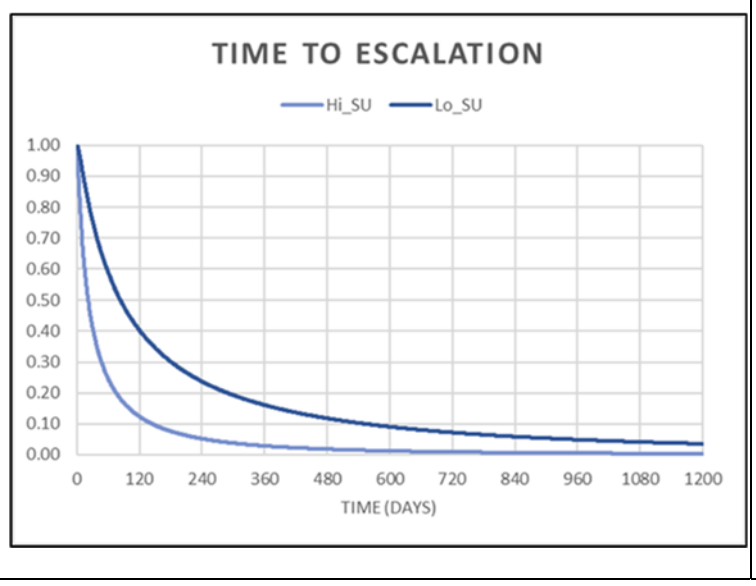
				Figure 2 FIGURE 2 SURVIVAL CURVES FOR HIGH AND LOW RISK BASED ON 40 PATIENT SUBSET (EAG MODEL) 	

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PredictImmune Ltd	14	6, 62, 70	1.1.4.2, 4.2.2 4.2.4	**The treatment sequence proposed by the EAG fails to appropriately reflect UK clinical practice** The EAG outline the NICE guidance for treating Crohn's disease in their report (reproduced in Figure 1 of the DAR, page 6), but then go on to model a treatment sequence for step-up therapy that does not follow NICE guidance, is not in line with existing definitions of step-up or accelerated step up therapy, and is not supported by national or international treatment guidelines for Crohn's disease treatment. On page 70 of the report the EAG states: "The EAG did not model time to escalation from corticosteroid treatment to IM (SU) or to anti-TNF (TD). This decision was based on the fact that the economic analysis is driven by the impact of giving high-risk patients TD vs SU therapy therefore, considering that 100% of patients in the high-risk group would receive initial treatment with corticosteroids, the impact of treatment would cancel out across the TD high-risk and the SU high-risk arms" This implies that in the step-up arm, all patients would immediately commence an immunomodulator. However, this contradicts the guidance, published by NICE in May 2019, which the EAG correctly reproduce:	No changes required. The EAG's model was informed and validated by clinical experts. The same experts explained that NICE guideline NG129 is outdated in terms of describing the clinical pathway for SU. Furthermore, TD has not been included in NICE guidance yet, therefore it was not possible to refer to national guidance to model this treatment strategy. Additionally, the reason why the EAG considered that the impact of including treatment with corticosteroids in the model would cancel out across the TD high-risk and the SU high-risk arms is precisely because it assumed that patients receive induction therapy with corticosteroids in both treatment arms. While for TD, the EAG's clinical experts' opinion is in accordance with the company's view that, "the only need for steroids is to provide some form of initial treatment [in TD] while the logistics of arranging anti-TNFα are arranged. The EAG's clinical experts' view on the use of corticosteroids in SU for the high-risk group of CD's patients with moderate/severe disease was that 100% of

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				"NICE NG12930 advises starting treatment with a glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone [for in patients]) to induce remission in those with a first presentation or a single inflammatory exacerbation of CD in a 12-month period..." "…Should remission not be achieved after induction therapy, the next step in the treatment pathway is addition of an immunomodulator (IM; azathioprine, mercaptopurine or methotrexate) to conventional glucocorticosteroid or budesonide, specifically in cases where: • a person experiences two or more inflammatory exacerbations in a 12-month period; Or • the glucocorticosteroid dose cannot be tapered." This is the correct treatment sequence in step up therapy, and is what was used in the REACT trial[5,11] of accelerated step up therapy and is currently being tested in the PROFILE trial.[23] It is also the recommended treatment sequence in national (BSG) and international guidelines (ECCO, AGA). The EAG's failure to include this initial step (corticosteroid followed by observation and disease reassessment) leads to their erroneous statement on page 62:	patients would receive an IM. Thus, for high-risk patients, the initial treatments modelled are IM vs anti-TNF. The SCMs raised a concern for the potential risk of additional complications associated with the SU strategy given the delay for initiating treatment with biologics. The EAG notes 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 TD and SU arms. Furthermore, even though not based on comparative evidence, the Biasci *et al.* IPD reported, only very few events that required surgery, and no patients had more than one surgery within their follow up period while receiving a SU strategy. Therefore, the EAG considers that the SCMs view that early biologics are better than later biologics may apply only to those who do not respond to treatment with IMs. However, removing this step entirely from the model, would mean taking away the benefit for those who do respond to IMs. As well as losing this benefit, there would also be the addition of highly expensive biologics that are potentially unnecessary for those who would have responded well to IM.

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				"The difference in treatment strategies thereafter are based solely on the fact that the SU strategy includes an additional treatment step with IMs at the beginning of the sequence". This error has 2 direct consequences. First, it leads to the generation of additional QALYs for patients in the SU arm compared to those in the TD arm, and second, it also leads to a large proportion of the patients in the Biasci *et al.* data[25] being inappropriately removed since they received a corticosteroid but did not require additional therapy to the end of follow up. The EAG also incorrectly model top-down therapy as anti-TNFα therapy that begins only after the induction of remission with corticosteroids. In fact, the goal of top-down therapy is to use anti-TNF therapy at presentation. Indeed, the only need for steroids is to provide some form of initial treatment while the logistics of arranging anti-TNFα are arranged. Anti-TNFα begins as soon as possible – almost always before completion of the steroid course. While this may seem to be a trivial detail, it results in the EAG ignoring the response rates in the one trial that used anti-TNFα from diagnosis[1] since they recognise that there may be some additional benefit of giving anti-TNF first line, not after corticosteroid, which does not fit with the sequence they model. This will lead to an underestimate of the benefit of top-down. Collectively, these errors mean that the EAG model fundamentally misrepresents the standard treatment pathway	Nonetheless, the EAG has varied these assumptions in a range of scenarios analyses described in Section 5.2 of the DAR. Additionally, these issues are further discussed in the EAG's addendum.

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				for Crohn's disease, and is therefore not fit for purpose without substantial revision.	
PredictImmune Ltd	15	xxiv, 37, 38, 44 161	3.3.3.2, 3.3.4.2 7.1	**EAG conclusion that "no robust evidence was identified on the prognostic accuracy PredictSURE-IBD"** The EAG chose to use the validated QUIPS tool to assess quality of prognostic studies that were identified. Applying this tool to the Biasci et al Gut publication results in 2 of 6 domains being designated of 'unclear' risk of bias, while the other 4 domains were at 'low risk' of bias. Despite this, the EAG concluded overall that "no robust evidence was identified on the prognostic accuracy of PredictSURE-IBD" and that only "low quality" evidence was available. This conclusion is at odds with the classification of the evidence using the QUIPS tool as presented and is not consistent with the proposed QUIPS interpretation ("Tools for assessing risk of reporting biases in studies and syntheses of studies: a systematic review. BMJ Open 2018;8:e019703): "Rate the overall methodological quality of the study, using the following as a guide: High quality (+++): Majority of criteria met, little or no risk of bias. Results unlikely to be changed by further research. Acceptable (++): Most criteria met. Some flaws in the study with an associated risk of bias, Conclusions may change in the light of further studies. Low quality (+): Either most criteria not met, or significant flaws relating to key aspects of study design." The EAG further assert that only 'limited evidence' was available (DAR xxiv). This is despite all individual patient data	No change required. The EAG is grateful to the company for making available the IPD data. The EAG assessed the data in the context of the decision problem that was the focus of the project. For the reasons highlighted in the report, including small numbers of people included in the analysis, uncertainty around extent of disease activity at baseline, and treatment at physician discretion, the EAG considers that the data informing the analysis are not fully generalisable to the goals and objectives of the review question. The lack of robust evidence on prognostic accuracy refers to limited data being available on prognostic accuracy of the tools in stratifying risk of severe course of CD in terms of standard measures of test accuracy, for example, sensitivity and specificity, which the EAG considers to be clear from the report. The EAG maintains that various criteria could be applied to determine a true positive or true negative in categorisation of high versus low risk of severe course for CD, for example, number of treatment escalations or need for

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				being made available from the PredictSURE-IBD validation cohort and with the full IPD of the discovery cohort also available on request. This can easily be provided to the EAG and would have been had it been requested. Note that such IPD data is not routinely included in supplementary information of publications due to data protection constraints. At least part of this assessment (reflecting 1 of the 6 QUIPS domains) appears to have reflected the EAGs reservations around the lack of 'standardised algorithm of treatment" (p.44) followed in the prospective validation study. However, while treatment was not protocolised, patients were treated with a step up regimen as defined by the current NICE treatment guidelines (that includes the option of non-corticosteroid first line therapy). While the exact choice of therapy was at the physicians' discretion, this does not invalidate the comparison of risk profiling in patients following the step-up regimen (the very approach advocated by the EAG, see below). Furthermore, use of non-corticosteroid first line therapy was balanced between the risk groups (to which treating clinicians were blinded). The EAG assessment of the PredictSURE-IBD validation study is in part based on a misrepresentation of the treatment pathway for CD. As outlined in comments relating to the economic model, the assumption that corticosteroid followed by observation is not a valid treatment strategy for CD is erroneous and at odds with NICE treatment guidance (NG129).	surgery or development of a complication. As highlighted in the report, the EAG considers it would be challenging to ascertain an accurate estimate of prognostic accuracy of IBDX and PredictSURE-IBD in stratifying the course of CD. Establishing prognostic accuracy of the tools would require carrying out a prospective study that included a group that received only SU treatment after determination of their risk of course of CD with clear prespecified criteria for following a severe course of CD. As noted above, the ongoing PROFILE RCT randomises people to accelerated SU or TD treatment after determination of high or low risk of following a severe course of CD and so data from the two SU groups will provide robust data to inform estimates of prognostic accuracy.

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				Certain parameters were not available which were of uncertain relevance resulting in an 'unclear' risk of bias in two QUIP domains. The other 4 were assigned low risk of bias (Table 5, p.38 DAR) yet despite this the overall assessment of quality was "low". The rationale for this summary dismissal of the evidence provided is incongruous with the actual assessment detailed. The EAG go on to outline the type of study they feel is required to accurately assess prognostic accuracy (p161, DAR) and, in doing so, describe the very validation study that was undertaken for PredictSURE-IBD. p161: "…to do so would require carrying out a prospective study that included a group that received only step-up (SU) treatment after determination of risk of course of CD". This describes the validation study undertaken in which patients were treated with a step-up regimen as described by NICE guidelines. The EAG have misinterpreted these guidelines.	
PredictImmune Ltd	16	38	3.3.3.2.1	**Assay sensitivity and specificity** Regarding sensitivity and specificity, the EAG state (DAR p.38) that "the publication does not provide a cut-off as to how the sensitivity and specificity for multiple escalations were derived". This demonstrates a fundamental misunderstanding of the biomarker discovery process employed. The decision boundary for risk subgroup allocation was defined during training of the penalised logistic regression model on the discovery cohort as described in the publication. This establishes a 'fixed' model with a decision boundary (defining high and low risk). This 'fixed' model was	No changes required. The EAG appreciates that the algorithm developed by PredictImmune categorises people as high or low risk. However, the EAG's point around prognostic accuracy is that the accuracy of the algorithm in assigning people to risk of severe course of CD has to be measured using an objective measure of course of disease followed from which sensitivity and specificity can be determined. Ideally, prognostic accuracy would be based

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				then applied to the validation cohort and high/low risk allocated accordingly.	on the number of people classed as high risk of following a severe CD who subsequently follow a severe course of CD. Nevertheless, as commented by the EAG's clinical experts, given the complexity of the course of CD, there are various potential measures of severe course of CD, including need for surgery or hospitalisation, frequent escalation of treatment, development of a fistula or stenosis. The EAG's suggestion that surgery should be considered separately was based on the finding that 10.6% (7/66) of people underwent surgery as their first escalation, which, if they underwent no further treatment during follow-up, would mean that, for the sensitivity and specificity calculations, they would be classed as low-risk of CD but having surgery as a first treatment could indicate that the person would be designated clinically as a severe course of CD. The EAG wanted to flag that it might be helpful to assess specificity and sensitivity in terms of other measures of severe course of CD. The EAG appreciates the company's clarification that the cut off applied of two or more treatment escalations to categorise a person as following severe course of CD was pre-specified - this is unclear from the full publication.

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PredictImmune Ltd	17	xxv 46	3.3.5.1	**Lack of a validated definition of a severe course of Crohn's disease** Page 46 the EAG states, "The EAG is unaware of a validated definition for determination of whether a person has followed a severe course of CD". It is unclear what the EAG mean by a 'validated' definition. Prognosis can be defined using different clinical endpoints. In the case of PredictSURE IBD the number of treatment escalations was chosen following extensive clinical consultation (evidence of which was provided to the DAP) as a clear, unambiguous endpoint reflecting discrete, clinically relevant episodes of active disease. While other endpoints could have been chosen (such as disease-related complications) we do not see why the selected definition is unclear or invalid, as it was selected prior to commencing the discovery study and its definition has remained constant throughout conception, discovery and validation stages and it facilitates clear assessment/modelling of clinical impact. Furthermore, the EAG state (p.46) that "the EAG… considers the choice of two escalations to be an arbitrary value". This was not an arbitrary value but a pre-defined endpoint selected at the discovery stage.	No changes required Please see response to comment 16.
PredictImmune Ltd	18	32 37	3.3.2, 3.3.3.2	**Inclusion criteria were misrepresented** The statement on page 32 that "any level of disease activity" was included is incorrect and is contradicted by the EAG description of the study on page 37. As made clear on page 37, inclusion criteria for both discovery and validation cohorts required active, untreated disease with an intention to treat (i.e. moderate/severe disease).	No change required. The EAG considers, when taken in the context of the full report, the EAG's meaning that the Biasci study included people with any level of disease activity, that is, included mild, moderate and severe disease activity, is clear.

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					The EAG does not imply that those with absence of active disease were included in the study.
PredictImmune Ltd	19	163	7.2, 7.3	**Inclusion of surgery as a form of treatment escalation** The EAG suggest that surgery should not be considered as a form of 'treatment escalation' triggering the prognostic endpoint used. They suggest that time to surgery should be treated as an independent outcome (indeed surgery was not included as an endpoint in the 'stacked density' plots included in the Gut paper, Biasci *et al.*, Figure. 2 C,D, Figure 3 D). However, while surgery could also be considered as a discrete outcome, this would address a different question to the PredictSURE-IBD assay and would diverge from the apriori defined clinical endpoint used. Surgery is unequivocally a form of treatment escalation and remains a valid inclusion in the a priori defined clinical endpoint of treatment escalation. It could not credibly be excluded from such a definition.	No change required. Please see response to comment 16.
PredictImmune Ltd	20	13 37	1.2.1, 3.3.3.2	**Assay development misrepresented** Page 37 "mRNA extracted from unseparated PBMC from the training cohort informing biomarker discovery". Instead, mRNA from purified CD8 T cells and peripheral venous blood was used for the discovery cohort. Page 13 and elsewhere: "PredictSURE-IBD facilitates stratification….. through detection of a gene sequence". The assay measures expression level of mRNA transcripts and does not involve gene sequencing.	The EAG thanks the company for highlighting this error and will amend the text in line with the company's comment.
PredictImmune Ltd	21	65	4.2.3	**Assumption that the IPD does not capture primary non-response**	No change required.

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				The DAR states that escalation to next treatment step occurs due to two reasons in the model: lack of response to induction therapy; or relapse while on maintenance therapy. It is assumed that time to treatment escalation (taken from Biasci *et al.*) reflects a relapse while on maintenance treatment. This is incorrect, as the Biasci data will inherently capture both primary non-response and secondary response-loss. It appears that the EAGLE has made some adjustments in the model to additionally capture loss of response to induction therapy when this is not necessary. It is unclear what effect this has had on the model results.	The EAG had to make modelling assumptions in order to be able to model response to induction and response to maintenance therapy separately. This was necessary to know what was the proportion of patients entering the maintenance model and therefore transitioning between the different CDAI states. Given that the Biasci data did not differentiate between induction and maintenance, the EAG used trial data to model response to induction treatment. Furthermore, the first escalation event in Biasci (EAG's analysis set) occurred after approximately 8.3 weeks, which is longer than any induction periods assumed in the economic model.
PredictImmune Ltd	22	vi 53	4.1.1.2	**Summary** In summary, the company's opinion is that that the DAR, and particularly the health economic model, are currently not fit for purpose due to fundamental errors in how the treatment sequences are modelled and inappropriate removal of large amounts of data leading to a misrepresentation of the clinical course experienced by patients. This leads to a conclusion – that personalised therapy using a test with 100% accuracy would result in a loss in QALYs compared to step up therapy – which is at odds with the majority of equivalent analyses in the literature (Table 10, DAR[24]), and the consensus view in the field.	

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				Indeed, following repeated observations that early aggressive therapy (top down) results in better outcomes than step up therapy, the question in IBD is not whether early targeted therapy will be clinically effective, but whether it can also be cost effective.[26] This is therefore not a suitable basis for the development of guidance on the utility of prognostic assays to guide precision medicine for adult Crohn's disease, nor is it appropriate for use as a "structural framework for analysing future available data on prognostic accuracy", as stated.	
PredictImmune Ltd	23			**References** 1 D'Haens, G. *et al.* Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet 371, 660-667, doi:10.1016/S0140-6736(08)60304-9 (2008). 2 Hoekman, D. R. *et al.* Long-term Outcome of Early Combined Immunosuppression Versus Conventional Management in Newly Diagnosed Crohn's Disease. J Crohns Colitis 12, 517-524, doi:10.1093/ecco-jcc/jjy014 (2018). 3 Colombel, J. F. *et al.* Randomised clinical trial: deep remission in biologic and immunomodulator naive patients with Crohn's disease - a SONIC post hoc analysis. Aliment Pharmacol Ther 41, 734-746, doi:10.1111/apt.13139 (2015).	

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				4 Colombel, J. F. *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 132, 52-65, doi:S0016-5085(06)02522-4 [pii] 10.1053/j.gastro.2006.11.041 (2007). 5 Khanna, R. *et al.* Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. Lancet 386, 1825-1834, doi:10.1016/S0140-6736(15)00068-9 (2015). 6 Panaccione, R. *et al.* Clinical Benefit of Long-Term Adalimumab Treatment in Patients With Crohn's Disease Following Loss of Response or Intolerance to Infliximab: 96-Week Efficacy Data From GAIN/ADHERE Trials. J Crohns Colitis 12, 930-938, doi:10.1093/ecco-jcc/jjy050 (2018). 7 Sandborn, W. J. Step-up versus top-down therapy in the treatment of ulcerative colitis. Gastroenterol Hepatol (N Y) 3, 16-17 (2007). 8 Sandborn, W. J. *et al.* Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med 357, 228-238, doi:357/3/228 [pii] 10.1056/NEJMoa067594 (2007). 9 Schreiber, S. *et al.* Maintenance therapy with certolizumab pegol for Crohn's disease. The New	

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				15 Vermeire, S., Ferrante, M. & Rutgeerts, P. Recent advances: Personalised use of current Crohn's disease therapeutic options. Gut 62, 1511-1515, doi:10.1136/gutjnl-2012-303958 (2013). 16 Panaccione, R. *et al.* Efficacy and Safety of Adalimumab by Disease Duration: Analysis of Pooled Data From Crohn's Disease Studies. J Crohns Colitis 13, 725-734, doi:10.1093/ecco-jcc/jjy223 (2019). 17 Faleck, D. M. *et al.* Shorter Disease Duration Is Associated With Higher Rates of Response to Vedolizumab in Patients With Crohn's Disease But Not Ulcerative Colitis. Clin Gastroenterol Hepatol 17, 2497-2505 e2491, doi:10.1016/j.cgh.2018.12.040 (2019). 18 Ma, C. *et al.* Anti-TNF Therapy Within 2 Years of Crohn's Disease Diagnosis Improves Patient Outcomes: A Retrospective Cohort Study. Inflammatory bowel diseases 22, 870-879, doi:10.1097/MIB.0000000000000679 (2016). 19 Oh, E. H. *et al.* Early anti-TNF/immunomodulator therapy is associated with better long-term clinical outcomes in Asian patients with Crohn's disease with poor prognostic factors. PloS one 12, e0177479, doi:10.1371/journal.pone.0177479 (2017).	

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				20 Rubin, D. T., Uluscu, O. & Sederman, R. Response to biologic therapy in Crohn's disease is improved with early treatment: an analysis of health claims data. Inflammatory bowel diseases 18, 2225-2231, doi:10.1002/ibd.22925 (2012). 21 Mandel, M. D. *et al.* Decreasing trends in hospitalizations during anti-TNF therapy are associated with time to anti-TNF therapy: Results from two referral centres. Dig Liver Dis 46, 985-990, doi:10.1016/j.dld.2014.07.168 (2014). 22 Safroneeva, E. *et al.* Impact of the early use of immunomodulators or TNF antagonists on bowel damage and surgery in Crohn's disease. Aliment Pharmacol Ther 42, 977-989, doi:10.1111/apt.13363 (2015). 23 Parkes, M. *et al.* PRedicting Outcomes For Crohn's dIsease using a moLecular biomarkEr (PROFILE): protocol for a multicentre, randomised, biomarker-stratified trial. BMJ Open 8, e026767, doi:10.1136/bmjopen-2018-026767 (2018). 24 Marchetti, M., Liberato, N. L., Di Sabatino, A. & Corazza, G. R. 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, doi:10.1007/s10198-012-0430-7 (2013).	

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				25 Biasci D, Lee JC, Noor NM, Pombal DR, Hou M, Lewis N, Ahmad T, Hart A, Parkes M, McKinney EF, Lyons PA, Smith KGC. A blood-based prognostic biomarker in IBD.Gut. 2019 Aug;68(8):1386-1395. doi: 10.1136/gutjnl-2019-318343 26 Hart AL, Lomer M, Verjee A, Kemp K, Faiz O, Daly A, Solomon J, McLaughlin J. What Are the Top 10 Research Questions in the Treatment of Inflammatory Bowel Disease? A Priority Setting Partnership with the James Lind Alliance. J Crohns Colitis. 2017 Feb;11(2):204-211. doi: 10.1093/ecco-jcc/jjw144.	