



Original Article

# A Matrix-based Model Predicts Primary Response to Infliximab in Crohn's Disease

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## Abstract

**Background:** Prediction of primary non-response [PNR] to anti-tumour necrosis factors [TNFs] in inflammatory bowel disease [IBD] is direly needed to select the optimal therapeutic class for a given patient. We developed a matrix-based prediction tool to predict response to infliximab [IFX] in Crohn's disease [CD] patients.

**Methods:** This retrospective single-centre study included 201 anti-TNF naïve CD patients who started with IFX induction therapy. PNR occurred in 16 [8%] patients. Clinical, biological [including serum TNF and the IBD serology 6 panel and genetic [the 163 validated IBD risk loci] markers were collected before start. Based on the best fitted regression model, probabilities of primary response to IFX were calculated and arranged in a prediction matrix tool.

**Results:** Multiple logistic regression withheld three final independent predictors [ $p < 0.05$ ] for PNR: age at first IFX, {odds ratio (OR) (95% confidence interval [CI] of 1.1 (1.0–1.1)}, body mass index [BMI] (0.86 [0.7–1.0]), and previous surgery (4.4 [1.2–16.5]). The accuracy of this prediction model did not improve when the genetic markers were added (area under the curve [AUC] from 0.80 [0.67–0.93] to 0.78 [0.65–0.91]). The predicted probabilities for PNR to IFX increased from 1% to 53% depending on the combination of final predictors.

**Conclusions:** Readily available clinical factors [age at first IFX, BMI, and previous surgery] outperform serological and IBD risk loci in prediction of primary response to infliximab in this real-life cohort of CD patients. This matrix tool could be useful for guiding physicians and may avoid unnecessary or inappropriate exposure to IFX in IBD patients unlikely to benefit.

**Keywords:** Anti-TNF; Crohn's disease; primary non-response

## 1. Introduction

Targeting tumour necrosis factor alpha, or TNF- $\alpha$ , in the treatment of patients with inflammatory bowel disease [IBD] has resulted in a shift of therapeutic algorithms. The use of these TNF inhibitors has

led to superior outcomes, healing of mucosal lesions, and a reduction in hospitalisation and surgery rates in both Crohn's disease [CD] and ulcerative colitis [UC].<sup>1</sup> However, 10–30% of patients will not show any clinical benefit ['primary non-response']<sup>2</sup> and the mechanisms

underlying this primary non-response are still unclear.<sup>3</sup> With the prospect of several new therapeutic drug classes (anti-leucocyte adhesion molecules, anti-IL-12/23 monoclonal antibodies, janus kinase [JAK] inhibition), treatment options for IBD patients will expand and prediction of response will become essential to guide physicians in selecting the optimal therapeutic class for an individual patient. By doing so, these biologicals can be used more selectively and alternative therapies can be initiated earlier in those who are unlikely to respond. Previous studies have hinted at clinical [eg disease duration, age, disease location], serological (eg C-reactive protein [CRP], perinuclear anti-neutrophil cytoplasmic antibodies [pANCA], and anti-*Saccharomyces cerevisiae* antibodies [ASCA]), and individual genetic markers to be associated with primary response to TNF inhibitors in IBD [recently reviewed elsewhere].<sup>3</sup> The majority of the results, especially the pharmacogenetic analyses, were inconsistent or could not be confirmed in larger cohorts.<sup>4</sup> Unbiased genome-wide association [GWA] has been very successful in identifying susceptibility loci for IBD, with the most recent multi-centre endeavour resulting in 163 confirmed susceptibility loci.<sup>5</sup> Of these 163 loci, 30 [18%] were CD specific, 23 [14%] UC specific and 110 [68%] were common to CD and UC. The combined effect of these 163 risk loci has not been investigated in a pharmacogenetic study before.

In other chronic conditions such as coronary heart disease, matrix-based prediction models have been used frequently in clinical practice.<sup>6</sup> In ankylosing spondylitis, the response to treatment with anti-TNFs has been evaluated in a matrix-based prediction model. Based on a post hoc analysis of 479 patients treated with anti-TNF therapy in randomized controlled trials [RCTs], the authors could identify C-reactive protein [CRP], HLA-B27 genotype, BASFI [Bath ankylosing spondylitis functional index], age, enthesitis, and choice of therapy to be independent predictors of a variety of outcome instruments.<sup>7</sup> More recently, the IBSEN study group developed a similar matrix model for prediction of the need for surgery in CD patients. The final risk model, comprising ASCA status, disease behaviour, age at diagnosis, and the need for systemic steroids, demonstrated probabilities of surgery ranging from 12.4% to 96.7%, depending on the combinations of these risk factors.<sup>8</sup>

The primary aim of this study was to construct a similar matrix model to predict primary non-response to infliximab [IFX] in CD patients, based on clinical, serological, and genetic factors. To identify the latter, a comprehensive approach was applied to calculate a unique genetic risk score for each individual patient based on the overall genetic risk burden for IBD, determined by information from the 163 susceptibility loci.

## 2. Methods

### 2.1 Patients and samples

A total of 201 CD patients [with either luminal and/or perianal fistulising disease] who initiated IFX between April 1999 and August 2013 were included in this retrospective single-centre cohort. All patients were treated by experienced clinicians at the University Hospital of Leuven. Only patients naïve to anti-TNF and treated with IFX induction therapy 5 mg/kg infliximab [Weeks 0-2-6] were included. Patients who had to undergo resective surgery, as a result of intestinal obstruction before induction schedule could be completed, were excluded. Baseline characteristics were collected before the first infusion of IFX [see Table 1]. Primary response to IFX was determined at Week 14. Serum samples taken just before the first infusion of IFX [at baseline] were measured for CRP and albumin. Also, serum TNF load was measured with the Singulex Erenna

TNF $\alpha$  Immunoassay [according to the manufacturer's instructions]. Moreover, serum IFX concentrations taken just before the infusion of Week 14 were available and measured with an in-house developed and clinically validated enzyme-linked immunosorbent assay [ELISA].<sup>9</sup> The IBD serology 6 panel, a panel of antimicrobial antibodies [anti-*Saccharomyces cerevisiae* antibodies IgA and IgG [ASCAA and ASCAG], anti-outer membrane protein C of *Escherichia coli* antibodies [anti-OmpC] and anti-flagellin antibodies [CBir1, Fla2, and Fla-X]], measured by Prometheus Laboratories, was available at baseline. Quartile scores for each of these six antibodies were calculated by assigning a quartile score of 1, 2, 3, and 4 for patients whose antibody concentrations were in the first, second, third, and fourth quartile of the distribution, respectively. For each patient, a quartile sum score reflecting the cumulative immune response toward all six antigens was obtained by adding individual quartile scores for each antimicrobial antibody.

### 2.2. Ethical considerations

This study was approved by the Ethical Committee UZ Leuven in the framework of the Flemish inheritance study for Crohn's and colitis [B322201213950/S53684]. Informed consent was provided by all patients.

### 2.3. Definitions

Primary non-response [PNR] was defined at Week 14 for CD patients with luminal disease as complete absence of clinical improvement after induction therapy, and as no reduction of at least 50% of the number of draining fistulas for CD patients with perianal fistulising disease, based on physician global assessment. Previous surgery was defined as the occurrence of any resection of a part of the gut, or stricturoplasty for stenosing complications, or a fistulectomy or fistulotomy in the presence of complicated perianal disease. Percutaneous drainage of an abscess or endoscopic dilatations were not counted as previous surgery.

### 2.4. Genotyping and genetic risk score calculation

Information from the 163 susceptibility loci was available in 81% [163/201] of our CD cohort through the Illumina ImmunoChip platform. This custom-designed chip contains around 200 000 loci involved in different autoimmune diseases and is the result of an international collaboration.<sup>10</sup> The 19% who were not genotyped initiated treatment after completion of this project.

For each of these 163 patients, we calculated the total genetic risk [genetic risk score, GRS] for CD with the 140 known CD and IBD risk loci, leaving out the 23 UC-specific loci. To generate this score, we used for each risk allele odds ratios for IBD versus healthy controls derived from Jostins *et al.*<sup>5</sup> Standard logistic risk scores were then computed for all samples by combining these odds ratios and allele frequencies taken from healthy controls using the R package 'Mangrove' [<http://cran.r-project.org/web/packages/Mangrove/index.html>].<sup>11</sup>

### 2.5. Statistical analysis and matrix construction

Continuous variables were reported as medians with interquartile ranges [IQR] and categorical variables as proportions and percentages. Univariate analyses were performed to investigate the individual association of different markers with primary response to IFX. Mann-Whitney U and chi-square tests [or Fisher's exact test where needed] were used for comparison of continuous and categorical variables, respectively. We performed Spearman correlation analyses to detect multi-collinearity. Correlation factors above 0.7 were considered significant.

**Table 1.** Baseline characteristics.

	Baseline variables	Crohn's disease
		N = 201
Demographic	Male patients, [%]	91 [45]
	Age at 1° IFX, median [IQR], years	35 [25–47]
	BMI at 1° IFX, median [IQR]	22.7 [20–25.9]
	Smoking at 1° IFX, [%]	61 [30]
	Ex-smoker, [%]	41 [20]
Disease characteristics	Duration of disease, median [IQR], years	5.5 [1–15.2]
	Disease location:	
	L1 [ileal disease]	40 [20]
	L2 [colonic disease]	40 [20]
	L3 [ileocolonic disease]	121 [60]
	Presence of upper GI disease, [%]	17 [8]
	Behaviour:	
	B1 [non stricturing, non penetrating], [%]	100 [50]
	B2 [stricturing], [%]	68 [34]
	B3 [penetrating], [%]	33 [16]
	Perianal disease, [%]	124 [62]
	Presence of extraintestinal manifestations, [%]	84 [42]
	Indication: luminal disease only, [%]	105 [52]
	Perianal fistulising disease only, [%]	39 [19]
	Combined luminal and perianal disease, [%]	57 [29]
Previous surgery, [%]	91 [45]	
Therapy	Concomitant immunomodulator therapy:	
	AZA, 6MP, or MTX during induction R, [%]	127 [63]
	Corticosteroids, [%]	40 [20]

6MP, 6-mercaptopurine; AZA, azathioprine; BMI, body mass index; CD, Crohn's disease; GI, gastrointestinal; IFX, infliximab; IQR, interquartile range; MTX, methotrexate; R/, therapy.

Non-correlated variables were then entered in a multiple logistic regression analysis to construct the optimal predictive model. Final model selection was based on the optimal AICc value. This is based on the Akaike information criterion [AIC] but also corrects for finite sample sizes and typically results in a greater penalty for extra parameters. Receiver operating characteristics [ROC] and area under the curve [AUC] analysis were performed to measure the performance of the final model. Odds ratios [OR] with 95% confidence intervals [CI] were calculated for these final predictors. Final predictors were used to construct the matrix. In a first step, the continuous variables were categorised according to a clinically relevant threshold. In a next step, predicted probabilities were calculated for every possible combination of categories and these were organised into a matrix. These probabilities were then colour-coded to visually demonstrate the predicted probabilities of primary response to infliximab in this cohort. All statistical analyses were performed in SPSS [version 22, IBM] and R [version 3.1.2].  $p < 0.05$  was considered significant.

### 3. Results

#### 3.1. Baseline characteristics and univariate association

The baseline characteristics are presented in [Table 1](#); 60% [121] of patients suffered from ileocolonic disease at IFX initiation. Half of the patients had non-stricturing and non-penetrating disease behaviour and the majority of patients [63%] were receiving concomitant immunomodulators at baseline. The incidence of PNR in this cohort of 201 CD patients was 8% [ $n = 16$ ] [see [Table 2](#)]. We did not observe any time trends for primary response. Patients with PNR to infliximab were significantly older (median 46 years [IQR

34–58]) and had a longer disease duration (14 years [4–26]) at first IFX, than patients who responded (34 years [25–46],  $p = 0.02$  and 5 years [1–14],  $p = 0.008$ ). The presence of previous surgery was also associated with PNR [81% vs 42%,  $p = 0.003$ ]. Concentrations of the different serological measurements are presented in [Figure 1](#) [for absolute numbers see [Supplementary material, available as Supplementary data at JCC online](#)]. TNF load at baseline was similar in those who responded (1.6 pg/ml [1.0–2.7]) as in the PNR (2.1 pg/ml [1.1–3.2],  $p = 0.44$ ). IFX concentrations at Week 14 did not differ significantly between responders (5.4 µg/ml [1.8–10.1]) and PNR (2.6 µg/ml [1.3–10.4],  $p = 0.48$ ). There was no difference for the concentrations of the individual antimicrobial antibodies [see [Supplementary Table 1, available as Supplementary data at JCC online](#)] nor for the quartile sum scores of the antimicrobial antibodies [ $p = 0.72$ ] between both groups. Likewise, the median GRS did not differ significantly [1.6 and 1.2, respectively,  $p = 0.11$ ] between both groups [[Figure 2](#)].

#### 3.2. Matrix model construction

In a first step, we constructed a prediction model without taking into account the GRS. As none of the clinical or serological markers showed signs of collinearity [correlation coefficient > 0.7], all markers could be entered in a multiple logistic regression model. Based on the lowest AICc value, this model withheld the following factors as predictive for PNR: age at first IFX (OR [95% CI] 1.05 [1.01–1.08],  $p = 0.01$ ), presence of previous surgery (OR 4.4 [1.2–16.5],  $p = 0.03$ ) and BMI (OR 0.86 [0.74–1],  $p < 0.05$ ). Age at first IFX was then categorised into four groups:  $\leq 25$  years [27% of patients], 26–40 years [38%], 41–64 years [30%], and  $\geq 65$  years [5% of patients]. BMI was categorised according to the World Health Organization [WHO]

**Table 2.** Univariate association analyses of clinical markers for primary response to infliximab.

	Baseline variables	Responders	PNR	<i>p</i> -value*
		<i>n</i> = 185 [92%]	<i>n</i> = 16 [8%]	Univariate
<b>Demographic</b>	Male patients, [%]	86 [47]	5 [31]	0.3
	Age at 1° IFX, median [IQR], years	34 [25–46]	46 [34–58]	0.02
	BMI at 1° IFX, median [IQR]	22.9 [19.9–26]	22 [18.6–24.2]	0.3
	Smoking at 1° IFX, [%]	55 [30]	6 [37]	
	Ex-smoker, [%]	36 [20]	5 [31]	0.3
<b>Disease characteristics</b>	Duration of disease, median [IQR], years	5 [1–14]	14 [4–26]	0.008
	Disease location:			
	L1 [ileal disease], [%]	39 [21]	1 [6]	
	L2 [colonic disease], [%]	38 [21]	2 [13]	
	L3 [ileocolonic disease], [%]	108 [58]	13 [81]	0.2
	Presence of upper GI disease, [%]	16 [9]	1 [6]	1
	Behaviour:			
	B1 [non stricturing, non penetrating], [%]	94 [51]	6 [37.5]	
	B2 [stricturing], [%]	62 [33]	6 [37.5]	
	B3 [penetrating], [%]	29 [16]	4 [25]	0.5
	Perianal disease, [%]	113 [61]	9 [56]	0.8
	Presence of extraintestinal manifestations, [%]	77 [42]	7 [44]	0.9
	Indication: Fistulising disease only, [%]	36 [20]	3 [19]	
	Luminal and fistulising disease, [%]	149 [80]	13 [81]	1
	Previous surgery, [%]	78 [42]	13 [81]	0.003
<b>Therapy</b>	Concomitant immunomodulator therapy:			
	AZA, 6MP, or MTX during induction R/, [%]	116 [63]	11 [69]	0.8
	Corticosteroids, [%]	38 [21]	2 [13]	0.7

PNR, primary non-response; 6MP, 6-mercaptopurine; AZA, azathioprine; BMI, body mass index; CD, Crohn's disease; GI, gastrointestinal; IFX, infliximab; IQR, interquartile range; MTX, methotrexate; R/, therapy.

\*Mann-Whitney U test for continuous variables and chi-square for proportions.

classification: < 18.5 or underweight [12% of patients], 18.5–24.9 or normal range [57%], and ≥ 25 or overweight [31% of patients]. We then applied the same multiple logistic regression model using age and BMI as categorical instead of continuous variables. This resulted in the same selection of independent predictors [ $p < 0.05$ ] for PNR: age at first IFX [groups 1 to 4], previous surgery, and BMI [groups 1 to 3] with very similar OR [data not shown]. We calculated predicted probabilities for every possible combination of these categories and these were arranged in a colour-coded matrix-based model [Table 3], demonstrating the probabilities of PNR to IFX.

### 3.3. Performance of the final matrix model

According to the subcategories of age at first IFX, previous surgery, and BMI, this model could predict PNR to IFX with rates ranging from 0.2% for those in the lowest risk categories [age ≤ 25 years, no previous surgery, and BMI ≥ 25] to 53.0% in the highest risk categories [age ≥ 65, previous surgery, and BMI < 18.5]. The ROC-AUC [95% CI] for this final model was 0.8 [0.67–0.93]. When the GRS was also added as a predictor in this final model, the ROC-AUC decreased to 0.78 [0.65–0.91].

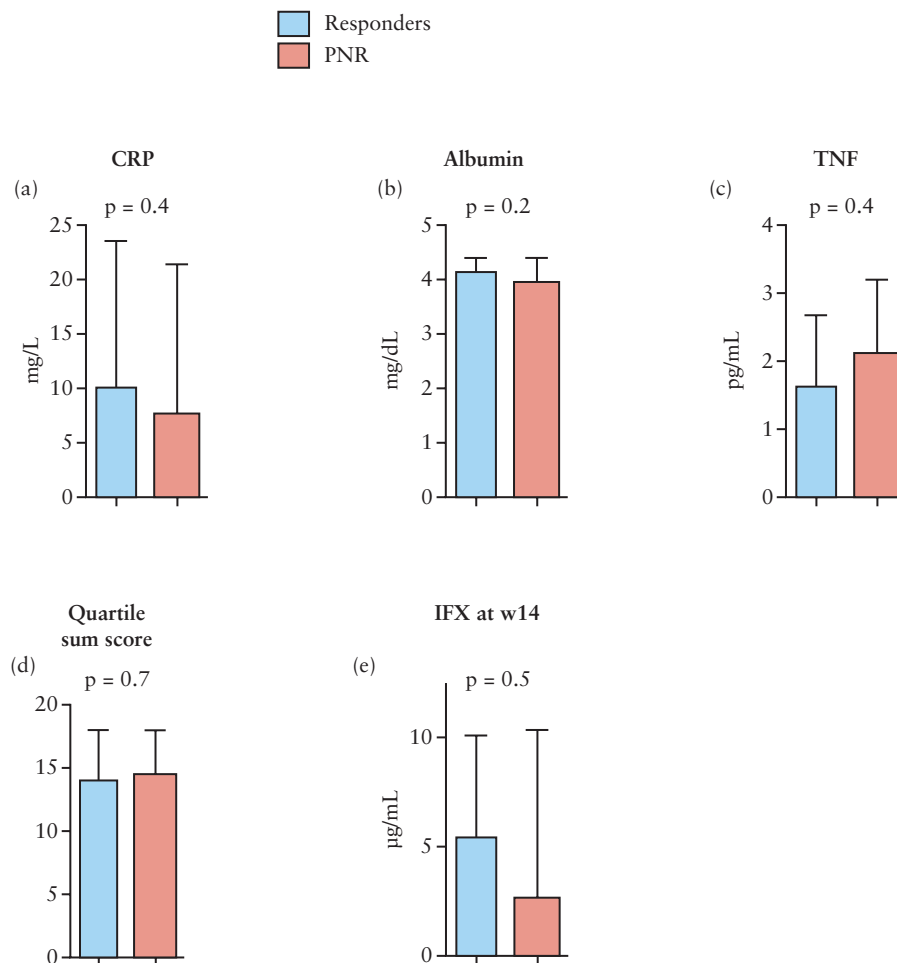
## 4. Discussion

TNF inhibitors are currently the most effective therapeutic agents for patients with refractory IBD.<sup>1</sup> The arrival of several new biological therapies targeting different pathways in the inflammatory cycle will certainly challenge their position. Treating the right patient at the right time with the optimal therapeutic drug class, and thereby avoiding unnecessary exposure in patients who are unlikely to benefit, will become the ultimate goal. Although the subject of prediction

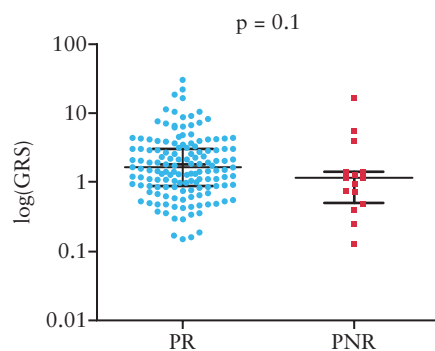
of response to TNF inhibitors in IBD has been studied, this has not yet resulted in clinically useful recommendations.<sup>12</sup>

In this real-life cohort of 201 well characterised CD patients who received IFX induction therapy, we showed that clinical factors such as age at first IFX, BMI and previous surgery outperformed serological and IBD-related genetic risk markers and that these could independently predict primary non-response to infliximab.

Most of the clinical factors that we identified have been linked with PNR to IFX in previous studies. A first variable was age at start of IFX. The response rates to IFX in paediatric populations have been reported as higher than in adults,<sup>13</sup> and our group has recently shown that the opposite is true for the elderly [defined as > 65 years] where response rates are lower than those observed in the general population.<sup>14</sup> The presence of previous surgery at IFX start has also previously been associated with PNR in CD patients<sup>15</sup> and might reflect a more refractory disease. A lower BMI has previously not been associated with PNR to IFX in IBD, but this might reflect the weight-based dosing of IFX. To confirm that PNR was not due to under-dosing of IFX, we also determined drug concentrations at Week 14 but could not detect a significant difference between the groups. Intriguingly, several independent studies have recently shown that a high BMI might result in an earlier loss of response to IFX after initial good response.<sup>16,17</sup> The pro-inflammatory effect of mesenteric fat and its contribution to TNF production might play an important role in this association.<sup>18</sup> Although this observation favours lower BMI for long-term response, it does not contradict our finding of primary response at Week 14. Moreover, a recent study in the USA demonstrated that obese IBD patients might experience a less severe disease course than non-obese IBD patients.<sup>19</sup> In our CD cohort, BMI showed only a weak correlation with serum albumin



**Figure 1.** Concentrations of: A] C-reactive protein at baseline; B] albumin at baseline; C] tumour necrosis factor at baseline; D] quartile sum score at baseline; E] infliximab [IFX] concentrations at Week 14 in primary responders [PR] [ $n = 185$ ] and primary non-responders [PNR] [ $n = 16$ ] in the CD cohort. Measurements are presented as column bars with medians and interquartile range as error bars, Mann-Whitney U test.



**Figure 2.** Genetic risk score [GRS] for both primary responders [PR] and primary non-responders [PNR] to infliximab in Crohn's disease. Scatter plot with line at median and interquartile range, Mann-Whitney U test.

[Spearman correlation coefficient = 0.17,  $p = 0.02$ ] and none with CRP or TNF load. We observed a similar moderate correlation for BMI and albumin in patients who were underweight [Spearman correlation coefficient = 0.44,  $p = 0.03$ ] indicating that the most lean patients did not simply have a more severe disease.

We could not observe any differences in concentrations of serological markers between responders and PNR. An elevated CRP has

been identified as a predictor of good response to IFX in CD.<sup>20,21</sup> Except for ASCA IgG, antimicrobial antibodies have not been investigated as possible markers for response to IFX in CD. In UC however, anti-OmpC antibodies have recently been associated with a lack of response to anti-TNF therapy at 1 year of treatment.<sup>22</sup> Our findings suggest that neither the individual nor the cumulative immune response against these microbial antigens [measured by ASCA IgA, ASCA IgG, anti-OmpC, CBir1, Fla2, and Fla-X] influence primary response to IFX in CD. In addition, serum TNF load before start of IFX did not seem to affect primary response to IFX in our cohort, and this is in line with previous reports.<sup>20</sup>

The majority of pharmacogenetic studies looking at TNF response attempted to identify a single gene [*TNF*, *NOD2*, *FCGR3A*, *IL-23R*]<sup>20,23,24,25</sup> or gene groups [apoptosis genes]<sup>26</sup> of interest. As this approach has not yet proven to be very successful, it is very probable that single nucleotide polymorphisms [SNPs] do not sufficiently explain genetic contribution to PNR. We therefore calculated a total genetic risk score for each patient, based on the 140 validated risk loci for CD and IBD, but show that this does not impact on a person's ability to respond to anti-TNF therapy. Although our sample size might have been too small to detect any difference and no other studies have investigated this total genetic risk, we believe that future pharmacogenetic attempts should focus on loci other than the disease loci.

**Table 3.** Colour-coded matrix-based prediction model showing the predicted probabilities for an individual Crohn's disease patient to be a primary non-responder to infliximab according to the different categories for age [years] at first infliximab, body mass index [BMI] [kg/m<sup>2</sup>] and previous surgery status.

BMI (kg/m <sup>2</sup> )						Age (years)	
≥ 25	18.5-24.9	< 18.5	≥ 25	18.5-24.9	< 18.5		
2.5%	8.9%	21.5%	9.4%	28.6%	53.0%	≥ 65	Age (years)
2.0%	7.4%	18.3%	7.8%	24.7%	48.0%	41-64	
0.7%	2.8%	7.4%	2.9%	10.5%	24.8%	26-40	
0.2%	0.9%	2.5%	0.9%	3.6%	9.4%	≤ 25	
No			Yes				
Prior Surgery							

The strength of this study lies in the construction of a prediction matrix which combines results into a visually informative tool that shows the probability of primary response to IFX in CD patients. The categories for BMI were determined according to the WHO definitions of underweight, normal range, and overweight. The categories for age were based on the Montreal disease classification for CD [A1, ≤ 16 years; A2, 17–40 years; A3, > 40 years].<sup>27</sup> As we had no patients aged < 16 years at start of IFX in this cohort, we arbitrarily chose < 25 years to be the cut-off for the youngest patients. We also created a category for the elderly [> 65 years] as it is now more and more being recognised that these are a distinct group of patients who require special attention.<sup>28</sup> This prediction tool may be useful in explaining therapeutic choices to patients and an increased understanding may result in better adherence to therapy.

Our study has several shortcomings. The most obvious is the use of physician's global assessment for primary [non-]response instead of clinically validated scoring systems such as the Crohn's Disease Activity Index [CDAI] or Harvey-Bradshaw Index [HBI].<sup>29</sup> Ideally a more objective endpoint such as mucosal healing, assessed by endoscopy, should be used in future studies investigating prediction of response to TNF inhibitors. However, in real-life clinical practice, early response to anti-TNF therapy in CD is still evaluated using a combination of clinical and biological markers, as early repeated ileocolonoscopy are difficult to defend or justify.

Our results are furthermore based on a small number of primary non-responders [ $n = 16$ , 8%] and we acknowledge that this study might be underpowered to yield conclusive data. However, this model is an initial exploratory effort and clearly requires further development, optimisation, and confirmation in larger independent cohorts.

Another drawback is the retrospective nature of our study. This could introduce heterogeneity in therapeutic decisions. However, since 1999 all IBD patients were carefully evaluated for primary response by the same staff of physicians at fixed clinical visits, and we excluded those in whom there was any doubt regarding indication or response so that the cohort was as homogeneous as possible.

In brief, we have demonstrated that simple clinical factors [older age at first IFX, lower BMI, and previous surgery] outperform serological and IBD-related genetic risk markers in prediction of primary non-response to infliximab in this real-life cohort of CD patients. This matrix-based prediction model could be a clinically useful tool that has the potential of aiding physicians in making well-considered therapeutic decisions when treating refractory CD patients, and a first step towards personalised medicine, although further external prospective validation is warranted.

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## Conflicts of Interest

KP received a consultancy fee from MSD Hellas. FP and SS are employees of Prometheus Laboratories. MF received financial support for research from Janssen Biologics, lecture fees from MSD, Ferring Pharmaceuticals Inc., Chiesi, MSD, Tillotts, Janssen Biologics, Abbott Laboratories, and Abbvie, and consultancy fees from Abbott Laboratories, Abbvie, MSD, and Janssen Biologics. GVA received financial support for research from Abbott and Ferring Pharmaceuticals, lecture fees from Janssen, MSD, and Abbott, and consultancy fees from PDL BioPharma, UCB Pharma, Sanofi-Aventis, Abbott, Abbvie, Ferring, Novartis, Biogen Idec, Janssen Biologics, NovoNordisk, Zealand Pharma A/S, Millenium/Takeda, Shire, Novartis, and Bristol Mayer Squibb. SV received financial support for research from MSD, Abbvie, and UCB Pharma, lecture fees from Abbott, Abbvie, MSD, Ferring Pharmaceuticals, and UCB Pharma, and consultancy fees from Pfizer, Ferring Pharmaceuticals, Shire Pharmaceuticals Group, MSD, and AstraZeneca Pharmaceuticals. TB, MdB, BV and IC disclose no conflicts of interest.

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## Author Contributions

TB: data acquisition and interpretation, statistical analysis and drafting of the manuscript; KP: data acquisition and interpretation, critical revision of the manuscript; MdB: statistical analysis and critical revision of the manuscript; BV, IC, MF, GVA: critical revision of the manuscript; SV: study concept, design and supervision, critical revision of the manuscript; FP and SS: technical support

## Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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