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Molecular Predictors of Biologic Therapy Response in Mucosal Biopsies from Patients with Crohn's Disease: A Review

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Abstract

Roughly two in five patients with Crohn's disease do not respond to anti-tumour necrosis factor therapy, and at present there is no way to identify them before treatment begins. Mucosal biopsies taken at diagnosis contain signals that separate responders from non-responders, and the question is whether any of them is reliable enough to act on.

Objectives: To review the published evidence on molecular markers measured in mucosal biopsies that predict response to biologic therapy in Crohn's disease: which markers have been reported for each drug class, how accurate they are, how well they replicate, and why so few have entered practice.

Material and Methods: Narrative review of transcriptomic profiling studies, single-cell analyses, prospective cohorts and meta-analyses indexed in PubMed and the major gastroenterology and immunology journals. Studies were eligible if they reported the association between a molecular measurement in intestinal tissue and subsequent response to a biologic agent. No new patient data were generated; every accuracy estimate and effect size quoted is one published by the original investigators.

Results: High mucosal oncostatin M expression separated patients sharply: complete mucosal healing on infliximab was achieved by 85 per cent of those with low expression against 10 to 15 per cent of those with high expression. A five-gene mucosal panel comprising TNFRSF11B, STC1, PTGS2, IL13RA2 and IL11 predicted endoscopic remission after infliximab with 95 per cent sensitivity and 85 per cent specificity, and in Crohn's colitis a related five-gene signature separated responders from non-responders completely. Single-cell analysis of ileal lesions identified a cellular module of IgG plasma cells, inflammatory mononuclear phagocytes, activated T cells and stromal cells whose presence at diagnosis, confirmed across four independent cohorts totalling 441 patients, correlated with failure to achieve durable corticosteroid-free remission on anti-TNF therapy. Markers for other classes are more preliminary: a four-gene colonic panel for vedolizumab and mucosal IL23A expression for ustekinumab.

Conclusion: The signal is real and reproducible in direction, but the reported accuracy figures come from small derivation cohorts with cut-offs set in the same data, and the gene sets identified in different studies barely overlap. The obstacle is not the absence of a marker but the absence of a common endpoint and of independent prospective validation.

Abbreviations: CD – Crohn's Disease, UC – Ulcerative Colitis, IBD – Inflammatory Bowel Disease, TNF – Tumour Necrosis Factor, OSM – Oncostatin M, OSMR – Oncostatin M Receptor, TREM1 – Triggering Receptor Expressed on Myeloid Cells 1, GIMATS – IgG Plasma Cells, Inflammatory Mononuclear Phagocytes, Activated T and Stromal Cells, SES-CD – Simple Endoscopic Score for Crohn's Disease, scRNA-seq – Single-Cell RNA Sequencing, mRNA – Messenger Ribonucleic Acid, qPCR – Quantitative Polymerase Chain Reaction.

Keywords: Crohn's Disease; Anti-TNF Therapy; Oncostatin M; Mucosal Transcriptomics; Predictive Biomarkers

Introduction

Anti-tumour necrosis factor antibodies remain the mainstay of biologic treatment in Crohn's disease, and up to 40 per cent of patients derive no benefit from them [1]. Those patients are identified retrospectively, after months of exposure, incurring the cost of the drug, the delay before an effective alternative is started, and the disease progression that occurs meanwhile [2,3].

The appeal of a predictive marker is therefore obvious, and the mucosal biopsy is the natural place to look for one. Biopsies are taken at diagnostic endoscopy in essentially every patient, they sample the tissue in which the disease actually occurs, and transcriptional profiling of them is now routine in research settings [4,5]. Unlike serum markers, which reflect systemic inflammation, mucosal measurements report the local immune environment that the

drug is meant to modify.

Two decades of profiling studies have produced a long list of candidate markers. Some are cytokines with a plausible mechanistic link to treatment failure, notably oncostatin M [1] and interleukin 13 receptor alpha 2 [6]. Others are multi-gene signatures identified by microarray or sequencing without a prior hypothesis [7,8,9]. More recently, single-cell methods have shifted attention from individual transcripts to the cellular composition of the lesion [10].

What has not happened is adoption. No mucosal molecular marker is in routine use for choosing a biologic in Crohn's disease, despite reported accuracy figures that in some studies approach perfect discrimination [8,11]. The aim of this review is to set out what has been reported for each drug class, how strong that evidence is, and to be specific about why the gap between reported accuracy and clinical adoption is as wide as it is.

Material and Methods

Search strategy: PubMed and the archives of the major gastroenterology and immunology journals were searched for studies of molecular prediction of biologic response in inflammatory bowel disease. Search terms combined Crohn's disease and inflammatory bowel disease with mucosal gene expression, transcriptomics, single-cell, biopsy, predictive biomarker, anti-TNF, infliximab, adalimumab, vedolizumab, ustekinumab, primary non-response and mucosal healing. Reference lists of retrieved reviews and meta-analyses were screened by hand for primary sources.

Eligibility: Studies were included if they reported an association between a molecular measurement made in intestinal tissue and subsequent clinical, endoscopic or histological response to a biologic agent in inflammatory bowel disease. Studies in ulcerative colitis are included where the marker has also been examined in Crohn's disease or where they established the method, and are identified as such. Studies reporting only blood-based measurement are cited for comparison but not counted as mucosal evidence.

Data extraction and handling: Design, sample size, tissue sampled, assay platform, definition of response and reported accuracy or effect estimates were extracted as published. The response endpoint is reported alongside every accuracy figure, because studies in this field use clinical remission, endoscopic response, mucosal healing and corticosteroid-free remission interchangeably and the choice materially changes the result. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 3 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The size of the problem: Anti-TNF agents remain effective in the majority of patients, but non-response is common enough to be a routine clinical event rather than an exception. Up to 40 per cent of patients with inflammatory bowel disease are non-responsive to anti-TNF therapy (Figure 3) [1], and comparative meta-analysis of biologics for induction and maintenance of mucosal healing shows that no available class resolves the problem [3]. Loss of response after initial benefit adds a further layer [2].

Oncostatin M is the best-characterised single marker: Screening mucosal expression of 64 candidate cytokines against healthy tissue identified only four consistently upregulated in both Crohn's disease and ulcerative colitis, among them oncostatin M [1]. Mucosal expression of the cytokine and its receptor correlated closely with histopathological severity, and the prognostic finding was striking:

complete mucosal healing following infliximab was achieved by 85 per cent of patients with low mucosal oncostatin M expression, against only 10 to 15 per cent of those with high expression (Figure 1) [1].

That result has partly replicated in blood. Pre-treatment plasma concentrations were higher in patients who subsequently lost response to infliximab in adult and paediatric cohorts [12], and low baseline serum oncostatin M was significantly associated with mucosal healing at 54 weeks in patients treated with anti-TNF, though notably not in those treated with vedolizumab [13]. A separate prospective study found that whole blood oncostatin M expression did not differ significantly between remitters and non-remitters, with the difference falling short of conventional significance [14]. The mucosal signal is therefore stronger and more consistent than the circulating one.

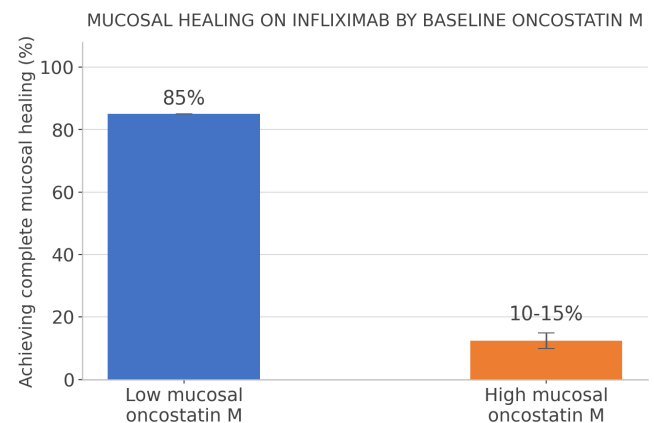


Figure 1: Complete mucosal healing on infliximab stratified by baseline mucosal oncostatin M expression [1]

Multi-gene mucosal panels: The alternative approach has been hypothesis-free profiling. Microarray analysis of mucosal biopsies in ulcerative colitis identified gene signatures separating infliximab responders from non-responders [7], and a related analysis reported response signatures for differential infliximab response in the same disease [15]. In Crohn's disease, a five-gene epithelial panel comprising TNFRSF11B, STC1, PTGS2, IL13RA2 and IL11 predicted endoscopic remission after infliximab with sensitivity of 95 per cent and specificity of 85 per cent (Figure 2) [8].

In Crohn's colitis specifically, a five-gene panel comprising S100A8, S100A9, G0S2, TNFAIP6 and IL11 was reported to separate responders from non-responders completely, and a subsequent genetic association study examined whether the polymorphisms underlying those genes carried the same signal [11]. A figure of complete separation in a derivation cohort should be read as a description of that cohort rather than as an accuracy estimate, a point returned to below.

One marker from these panels has been examined on its own. Mucosal IL13RA2 expression was reported to predict non-response to anti-TNF therapy in Crohn's disease [6], which is notable because the same transcript appears in the five-gene epithelial signature [8]. Overlap of that kind is uncommon in this literature.

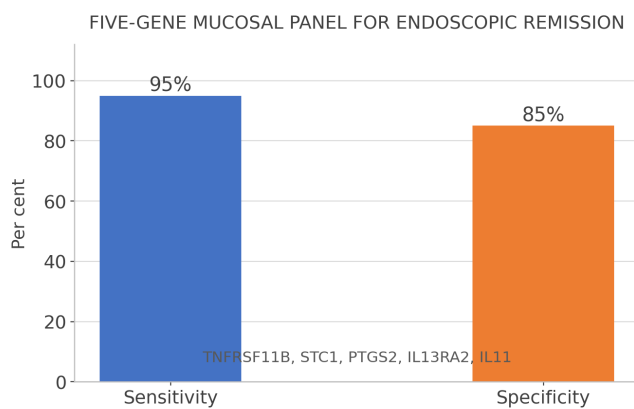


Figure 2: Accuracy of a five-gene mucosal panel for endoscopic remission after infliximab in Crohn's disease [8]

Study	n	Agent	Principal reported finding
Arijs et al. 2009 [7]	—	Infliximab	Mucosal signatures separate responders in colitis
Arijs et al. 2010 [8]	—	Infliximab	Five-gene panel, 95% sensitivity and 85% specificity
West et al. 2017 [1]	—	Anti-TNF	Mucosal healing 85% with low OSM against 10-15% with high
Verstockt et al. 2019 [6]	—	Anti-TNF	Mucosal IL13RA2 predicts non-response
Martin et al. 2019 [10]	441	Anti-TNF	GIMATS module at diagnosis predicts treatment failure
Verstockt et al. 2020 [16]	—	Vedolizumab	Four colonic genes predict endoscopic remission
Nishioka et al. 2021 [17]	—	Ustekinumab	Mucosal IL23A expression predicts response

Table 1: Principal studies reviewed, with the agent studied and the finding as reported by the original investigators

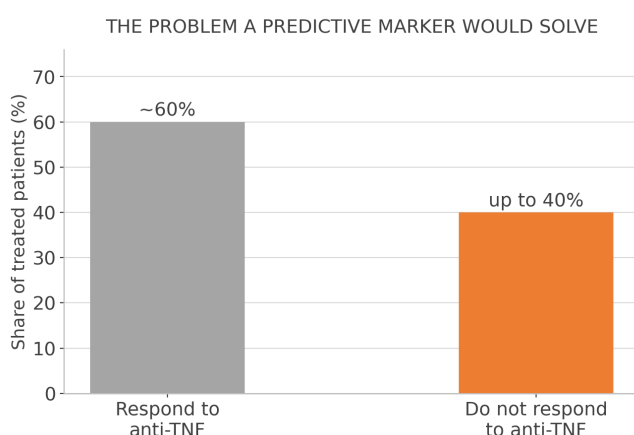


Figure 3: Reported proportion of patients not responding to anti-TNF therapy, the population a predictive marker would identify [1]

From transcripts to cellular composition: The most conceptually different contribution applied single-cell RNA sequencing, mass cytometry and multiplex tissue imaging to inflamed and uninfamed ileal tissue with matched blood. A subset of patients was found to carry a distinct cellular module in inflamed tissue, consisting of IgG plasma cells, inflammatory mononuclear phagocytes, activated T cells and stromal cells, termed the GIMATS module [10].

The clinical finding is what matters here. The module was present in a subset of patients across four independent cohorts totalling 441 patients, and its presence at diagnosis correlated with

failure to achieve durable corticosteroid-free remission on anti-TNF therapy. It was independent of systemic inflammatory markers and of disease severity and duration [10,18]. Analysis of ligand-receptor interaction pairs placed inflammatory macrophages and mature dendritic cells at the centre of the network, and tumour necrosis factor was produced mainly by T cells in patients with low module scores but by both T cells and inflammatory phagocytes in those with high scores, which offers a mechanistic account of why blocking the cytokine alone would work less well in the latter group [10].

A cell-centred meta-analysis reached compatible conclusions by computational deconvolution of bulk biopsy and blood data, identifying baseline cellular predictors of anti-TNF non-response [19,20].

Markers for the newer classes: Evidence for agents other than anti-TNF is thinner but follows the same pattern. Expression levels of four genes in colonic tissue were reported to predict which patients enter endoscopic remission after vedolizumab [16], and vedolizumab's effect on histological healing and mucosal gene expression has been characterised directly [21]. For ustekinumab, mucosal IL23A expression predicted response [17], and interleukin 22 has been linked to resistance in ulcerative colitis [22]. Intestinal transcriptomic profiles associated with mucosal healing on ustekinumab have been examined with prospective cohort validation [23].

Notably, serum oncostatin M predicted mucosal healing under anti-TNF but not under vedolizumab in the same study [13], which is what a genuinely mechanism-specific marker should do and is an encouraging sign that these markers reflect pathway biology rather than disease severity alone.

Drug class	Reported mucosal marker	Strength of evidence
Anti-TNF	Oncostatin M and its receptor	Largest effect size; replicated in blood with less consistency [1,12,13,14]
Anti-TNF	Five-gene epithelial panel	High reported accuracy from a derivation cohort [8,11]
Anti-TNF	IL13RA2	Single marker; overlaps the five-gene panel [6,8]
Anti-TNF	GIMATS cellular module	Confirmed across four cohorts, n = 441 [10]
Vedolizumab	Four-gene colonic panel	Single study; no independent validation [16,21]
Ustekinumab	IL23A expression	Single study; mechanistically plausible [17,23]

Table 2: Reported mucosal markers by drug class, with the strength of the evidence behind each

A different kind of predictor: genotype and drug handling:

Running alongside the mucosal literature is a second strand that predicts not whether the tissue will respond but whether the drug will survive long enough to act. A prospective multicentre cohort of anti-TNF-naïve patients with active luminal Crohn's disease examined predictors of treatment failure directly and found drug concentration and immunogenicity central to it [26].

The genetic finding from that programme is the most clinically advanced predictor in the field. Carriage of HLA-DQA1*05, present in roughly 40 per cent of Europeans, significantly increased the rate of anti-drug antibody development, with a hazard ratio of 1.90 overall and consistent effects for adalimumab (HR 1.89, 95% CI 1.32-2.70) and infliximab (HR 1.92, 95% CI 1.57-2.33). The extremes are striking: immunogenicity at one year reached 92 per cent in patients on infliximab monotherapy who carried the allele,

against 10 per cent in those on adalimumab with an immunomodulator who did not (Figure 4) [27].

That result has been contested in detail. A reanalysis argued for drug-specific association of two distinct HLA class II haplotypes rather than a single shared one [28], and the original investigators responded that the reanalysis was underpowered [29]. Independent confirmation has since come from trial cohorts [30], from a Chinese population in whom the allele also correlated with reduced infliximab response [31], and from pooled analysis [32,33]. A separate line of work shows that anti-drug antibodies accelerate drug clearance and that dose intensification can reverse immunogenicity and recapture response [34], which is what makes the genotype actionable rather than merely prognostic.

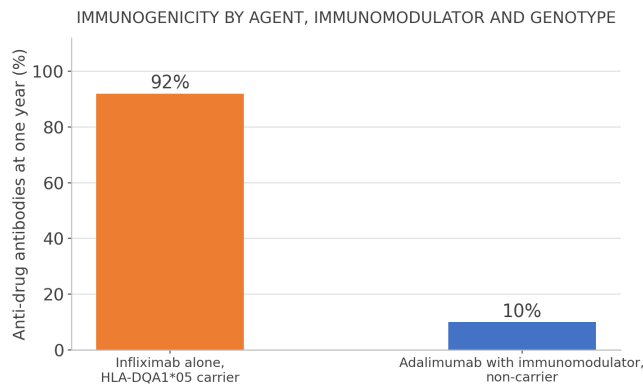


Figure 4: Anti-drug antibody development at one year by agent, immunomodulator use and HLA-DQA1*05 carriage [27]

The contrast with the mucosal markers is instructive. The genotype predicts pharmacokinetic failure rather than tissue biology, it requires only a blood sample, it has replicated across independent cohorts and populations, and a commercial test already exists. None of those things is true of the mucosal signatures, which predict a different failure mode and remain confined to research use [26,27,32]. The two are complementary rather than competing: a patient may fail because the drug never reaches an effective concentration, or because the inflammation is not driven by the pathway being blocked, and no single marker addresses both.

Discussion

The evidence supports a conclusion that is more encouraging about the biology than about the clinical readiness. Mucosal measurements do separate anti-TNF responders from non-responders, the separation is large where it has been measured, and at least three independent approaches, single cytokines, multi-gene panels and cellular composition, converge on the same conclusion that failure is written into the tissue before treatment starts [1,8,10].

The obstacle is methodological. Accuracy figures of 95 per cent sensitivity, or of complete separation between groups, come from cohorts in which the marker was discovered and the cut-off chosen [8,11]. Applied to new patients those figures will fall, and by how much is not known because the prospective studies have not been done. Reporting a derivation result as though it were a validation result is the most common overstatement in this field.

Why the gene sets do not agree

A more specific problem is that studies identify barely overlapping gene sets. Comparisons between Crohn's disease and ulcerative colitis cohorts have found almost no overlap in the genes identified, which has been attributed to heterogeneity in the diseases studied, the agents used and the endpoints chosen [6,8]. That last factor is

under investigators' control and deserves attention: studies in this field variously define response as clinical remission, endoscopic response, mucosal healing or durable corticosteroid-free remission, and a model derived against mucosal healing performs poorly when tested against clinical endpoints [23,24].

There is also a sampling question specific to mucosal work. Crohn's disease is patchy, expression differs between inflamed and uninflamed tissue in the same patient, and the ileal and colonic mucosa are immunologically distinct [4,10]. A marker measured in one biopsy from one site carries an unquantified sampling error that none of the reviewed studies addresses directly.

Study limitations

The limitations belong to the underlying literature. Derivation cohorts are small, frequently under a hundred patients, and cut-offs are typically set and tested within the same data, which inflates apparent accuracy [7,8,11]. Several key findings originate in ulcerative colitis and are extrapolated to Crohn's disease, where the mucosal immune environment differs [1,7,15]. Endpoint definitions are inconsistent across studies to a degree that prevents pooling [3,24]. Assay platforms range from microarray through quantitative polymerase chain reaction to single-cell sequencing, and results are not interchangeable between them [10,19]. Genetic association studies have not consistently supported the expression findings, which raises the possibility that some signatures reflect disease state rather than a causal predictor [11,25].

Two gaps deserve naming. No prospective trial has randomised patients to marker-guided against standard biologic selection with response as the primary endpoint, which is the design that would establish clinical utility rather than association. And no study reviewed here reports how much of the predictive signal survives when the marker is tested against established clinical predictors, or against genotype and drug concentration, rather than in isolation [10,24,26].

Conclusion

Mucosal biopsies taken before treatment contain information about whether a biologic will work. For anti-TNF therapy the evidence is strongest: high mucosal oncostatin M identifies a group in which mucosal healing falls from 85 to around 12 per cent, and a distinct cellular module present at diagnosis predicts failure to reach durable remission across four independent cohorts. Multi-gene panels report high accuracy but do so from the cohorts in which they were derived. For vedolizumab and ustekinumab the corresponding evidence rests on single studies. Genotype at HLA-DQA1*05 is further advanced than any of them, but predicts immunogenicity rather than tissue response, and the two failure modes are separate [27]. What is missing is not another candidate marker but agreement on the response endpoint and prospective validation of the markers already identified, in the population and at the decision point where they would actually be used.

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Conflict of Interest

No competing interest arises for any of the authors.

Ethics Statement

Only work that has already been published is reviewed here. Nothing was collected from patients afresh and no one was enrolled, so the study needed no ethical approval.

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