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New Biomarkers for Diagnosing Inflammatory Bowel Disease and Assessing Treatment Outcomes

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Abstract

Despite advances in our understanding of the pathophysiology underlying Inflammatory Bowel Disease (IBD), there remains a significant need for biomarkers that can differentiate between Crohn's Disease (CD) and Ulcerative Colitis (UC) with high sensitivity and specificity, in a cost-efficient manner. As the focus on personalized approaches to the delivery of medical treatment increases, new biomarkers are being developed to predict an individual's response to therapy as well as their overall disease course. In this review, we will outline many of the existing and recently developed biomarkers, detailing their role in the assessment of patients with IBD. We will identify opportunities for improvement in our biomarkers, including better differentiation between the subtypes of IBD. We will also discuss new targets and strategies in biomarker development, including combining modalities to create biomarker signatures to improve the ability to predict disease courses and response to therapy among individual patients.

Introduction

Although great strides have occurred in our understanding of the epidemiology and pathophysiology of Inflammatory Bowel Disease (IBD) in recent years, we continue to seek a set of ideal biomarkers that would allow us to improve our diagnostic and therapeutic approaches in assessing and treating patients with Ulcerative Colitis (UC) and Crohn's Disease (CD). The initial diagnosis of UC or CD can be made utilizing a combination of phenotypic and serologic information,[1–3] however distinguishing the initial presentation of an IBD from an acute colitis of another etiology, or even distinguishing between UC and CD can at times be difficult. Furthermore, monitoring patients over time and potentially predicting clinical outcomes among individual patients requires a more nuanced and personalized approach.

The ideal biomarker is readily available, non-invasive, accurate, sensitive, specific, and affordable such that it can be used in clinical settings. Traditionally, the assessment of patients with IBD has been somewhat complicated by the necessary, but rather invasive nature of evaluation, including endoscopic procedures with biopsies. This has prompted

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investigators to seek non-invasive biomarkers that can be used in both the initial diagnosis of IBD and in monitoring the disease course. These efforts have led to the emergence of multiple serologic and stool biomarkers of varying degrees of utility, though many of these biomarkers still have underlying weaknesses that limit their widespread use.

To date, no ideal biomarker for the assessment and management of IBD has been identified. However, the newer biomarkers that have been developed in recent years have several strengths that should be noted. In this review we will outline many of the existing biomarkers, including a more detailed analysis of the recently developed biomarkers and their role in the assessment of patients with IBD. We will also identify opportunities for improvement in our biomarkers, including better differentiation between subtypes of IBD, and improvements in predictions of disease course and response to therapy among individual patients. Finally, we will discuss novel approaches to biomarker development and what targets biomarkers may focus on in the coming years.

Current Use of Biomarkers

Markers of Inflammation

Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) are two non-specific markers of inflammation that can be elevated in patients with active UC and CD. Under normal circumstances, hepatocyte production of CRP is low. CRP has demonstrated utility in differentiating IBD from other non-inflammatory gastrointestinal conditions,[4] however both ESR and CRP can be elevated in other conditions,[5–8] and thus reliance on these biomarkers alone in the evaluation of a patient with suspected or established IBD can be challenging. While CRP is thought to increase in the vast majority of patients with active CD, up to 50% of patients with an active flare of UC can demonstrate normal CRP levels.[9] Even among a subset of patients with endoscopically active CD, normal CRP levels can be noted,[10] as biomarker levels are not necessarily correlated with mucosal lesions noted on endoscopy. Additionally, some patients with CD can demonstrate persistently low CRP levels despite active disease, including patients with a low BMI or a purely ileal disease distribution.[11]

In contrast to serologic biomarkers, fecal biomarkers such as fecal calprotectin (FC) and fecal lactoferrin (FL) are more specific for intestinal inflammation. FC is released by activated neutrophils, and thus serves as an indirect estimate of the neutrophil infiltrate in the gastrointestinal tract. In the initial evaluation of a patient with suspected IBD, FC can be used as a screening tool for identifying patients who are likely to need endoscopy for further evaluation.[12] Among patients established IBD, FC serves as a reliable indicator of disease activity,[13–19] can serve as a marker of mucosal healing,[16,20,21] can predict relapse of disease,[22–25] and among patients with CD, can predict endoscopic recurrence after intestinal resection.[26] While FC has demonstrated significant utility in differentiating IBD from other chronic abdominal syndromes such as Irritable Bowel Syndrome,[4,27] FC does not reliably differentiate between UC and CD.[28] Recent studies have also demonstrated that intra-individual variability of FC can occur throughout the day, which may indicate that the time of assessment is also critical.[29]

Lactoferrin, a sensitive and specific marker of inflammation among patients with IBD,[30] is a major component of granules of neutrophilic granulocytes and is released during the process of neutrophil degradation.[31] Levels of FL are typically elevated in patients with active IBD, and tend to correlate well with FC levels.[32] In addition to the identification of active disease,[15,16] similar to FC, FL can serve as a marker of mucosal healing.[14,21]

S100A12 is a calcium binding calgranulin protein that is expressed in activated neutrophils. The expression of S100A12 is more restricted to granulocytes, with release occurring at the site of inflammation among patients with IBD.[33–35] S100A12 is an attractive candidate as a diagnostic biomarker, given its high sensitivity and specificity in differentiating pediatric patients with CD from healthy controls.[36] However, despite these findings and the ability of S100A12 to distinguish IBD from IBS,[34] S100A12 is also elevated in other inflammatory conditions such as Kawasaki Disease[37] and inflammatory arthritis.[38]

Lipocalin-2 (Lcn-2), also referred to as neutrophil gelatinase-associated lipocalin (NGAL), is stored in neutrophil granules and released at sites of inflammation.[39] Lcn-2 has demonstrated utility as a biomarker of active UC,[39] and has been reported as upregulated in both feces[40] and colonic mucosa[41,42] of patients with UC. While Lcn-2 correlates with other markers of inflammation, it does not appear to significantly distinguish between UC and CD.[43] Furthermore, Lcn-2 can be elevated in other conditions such as kidney disease,[44] ovarian cancer,[45] acute pancreatitis,[46] Chronic Obstructive Pulmonary Disease (COPD),[47] and cardiovascular disease[48] which limits its utility as an IBD specific biomarker.

Biomarkers that differentiate CD from UC

Multiple serologic biomarkers have been evaluated for their association with CD, including Anti-Sacchromyces cerevisae Antibodies (ASCAs) and antibodies to bacterial proteins such as outer membrane protein C (OMP-C), I2, and flagellin (CBir1). Increased titers of ASCA have demonstrated high specificity, but low sensitivity in the evaluation of patients with suspected CD.[49] Perinuclear Antineutrophil Cytoplasmic Antibodies (pANCA) were first reported as present in the sera of patients with UC, but not CD.[50] However, later studies demonstrated that elevated levels of pANCA can be seen in patients with both UC and patients with CD who have colonic disease in a UC like presentation.[49]

While the combined use of pANCA and ASCA could be of benefit in the evaluation of patients with IBD,[51] low sensitivity limits their overall utility. When evaluated in a meta-analysis of 60 studies, the most sensitive combination of these two tests for the evaluation of CD was ASCA+/pANCA-, which was 55% sensitive and 93% specific.[52] Among patients with UC, a pANCA+/ASCA- combination demonstrated a sensitivity of 51.3% and a specificity of 94.3%.[52] The characteristics of many of the biomarkers currently being used in the care of patients with IBD is summarized in Table 1.

New Approaches to Biomarkers

Biomarker Signatures

Given that no single serologic or fecal biomarker has demonstrated the necessary sensitivity and specificity to operate as a stand-alone tool in the evaluation of suspected or established

IBD, recent attention has been focused on the potential for development of groups of biomarkers operating in a pattern or signature that may increase diagnostic utility.

Gene Expression Analysis—The use of whole blood mRNA gene expression techniques is one area where such biomarker signatures may be useful. Recent advances have allowed for the evaluation of mRNA extracted from whole blood.[53,54] Among patients with IBD, gene expression profiles obtained from whole blood have been utilized to differentiate active from inactive CD.[55] Additionally, gene expression profiles have demonstrated the ability to differentiate between CD, UC, and other non-inflammatory diarrheal conditions.[56] More recently, the Affymetrix GeneChip technology was utilized to generate genome-wide expression profiles to predict disease activity in patients with UC and CD.[57] In this study, whole blood gene panels determined the activity of disease with high sensitivity and specificity, while reliably distinguishing between UC and CD.[57] While these initial results are promising, the majority of studies evaluating the utility of whole blood gene expression analysis have been performed in small populations, and thus larger studies remain necessary for further evaluation of this modality.[58]

An earlier study demonstrated high accuracy in distinguishing UC from CD when utilizing transcriptional profiling of peripheral blood mononuclear cell RNA.[59] In a separate study of 58 patients, peripheral blood mononuclear mRNA expression levels were used to reliably differentiate patients with IBD, rheumatoid arthritis, and psoriasis from healthy controls.[60] Similarly, in a comparison to healthy controls, patients with IBD in clinical remission demonstrated distinct gene expression profiles obtained from peripheral blood leukocytes.[61]

Gene expression profiling from mucosal biopsies has also stimulated interest as a potentially attractive means of identifying new biomarkers in the evaluation of IBD. Gene expression profiles obtained from mucosal biopsies have been utilized to differentiate patients with UC from healthy controls[62] and to differentiate patients with both subtypes of IBD from infectious colitis[63] and normal controls.[64] Another prior study utilized gene expression profiling from mucosal biopsies to identify discriminative signatures to differentiate between colon adenoma, colorectal cancer, and IBD.[65] While each of these studies is indicative of the significant promise for gene expression analysis as a tool in differentiating IBD from other colonic diseases and potentially predicting disease activity, the requirement of mucosal biopsy makes the non-invasive option of whole blood gene analysis potentially more attractive.

When evaluating specific patterns identified by gene expression profiling, trends along biological processes have been identified (Table 2a and 2b). In a study utilizing gene expression analysis of mucosal biopsies to evaluate response to infliximab among patients with UC, a specific gene profile involved in signaling along several pathways was identified, including the adaptive immune response, inflammation, and the TNF pathway.[66] In a separate evaluation comparing the gene sets utilized in this study to those identified in patients with the colitis subtype of CD, there was considerable overlap.[67] A similar focus around immune function has been demonstrated when analyzing those patterns identified by whole blood gene expression analysis. Among a four gene panel used to differentiate UC from CD, *CD300A* which potentially plays a role in modulating pro-inflammatory stimuli

among neutrophils and *IL1R2* which is involved in cytokine-cytokine receptor interactions were identified as potential markers.[56] In an evaluation of the prediction of disease activity among patients with UC and CD, a number of genes that were identified among patients with active disease had previously been associated with UC and CD in other studies.[39] These potential marker genes included *NLRP12* (a member of the Nod-like receptor family) and *TAGAP*, one of 22 genes previously identified as downregulated among responders to infliximab in the Active Ulcerative Colitis Trial 1 (ACT 1).[68]

microRNA—Circulating microRNA (miRNA) levels are another potential method of assessing disease activity among patients with IBD. In a comparison of patients with active and inactive UC and CD with controls, peripheral blood miRNAs were able to distinguish active UC and CD from healthy controls.[69] Although specific patterns were identified to allow for delineation between active UC and CD, in this evaluation there was significant overlap between several of the miRNAs in both CD and UC. The blood expression of miRs-199a-5p, -362- 3p, -340*, -532-3p, and miRplus-1271 were elevated in both subtypes of IBD as compared to healthy controls, which may indicate an overall inflammatory state found in both UC and CD.[69] In a similar evaluation, 11 miRNAs were elevated in pediatric patients with active CD when compared to healthy controls.[70] A later study suggested that several miRNAs could accurately distinguish UC from CD, in addition to differentiating both subtypes of IBD from controls.[71] Importantly, the authors of this study noted that among patients with CD, their miRNA profiles were consistent with the earlier patterns indicated by Wu, et al.[69] and Zahm, et al.[70] When patients with UC were compared to controls, a distinct signature consisting of 31 miRNAs were identified which could differentiate patients with UC from controls with high specificity, sensitivity, and accuracy.[72]

Tissue miRNA profiling has also been utilized to differentiate subtypes of IBD as well as to differentiate patients with IBD from controls.[73–79] Wu, et al. were among the first to analyze the potential role of miRNA obtained from colonic biopsies, in their description of the differential expression of 11 miRNAs among patients with active UC.[73] A separate study by Wu, et al. identified 5 miRNAs associated with active CD of the sigmoid colon and 4 miRNAs that were increased among patients with CD affecting the terminal ileum.[75] The 5 miRNAs associated with active colonic CD were later studied to assess their ability to differentiate CD from UC and indeterminate colitis. In this evaluation, all 5 miRNAs were statistically different when comparing patients with CD to those with indeterminate colitis, while no difference was noted when patients with UC were compared to those with indeterminate colitis.[80] The ability to identify similar miRNA expression profiles across multiple studies is encouraging, however the need for invasive testing with endoscopic examination and biopsy may limit the utility of colonic tissue miRNA profiling as a biomarker.

Future Directions for Biomarkers

In an era of increased focus on the potential for personalized medicine, the emphasis on strategies for the development of better biomarkers in IBD will continue to exist. In addition to the identification of specific disease subtypes within IBD, a renewed focus on predictors of the disease course is paramount. Improving the ability to not only diagnose patients with

IBD, but also to predict their disease activity and their response to therapy will significantly improve the care of patients with IBD. Additionally, by avoiding costly therapies that may be of minimal benefit, more precise therapy choices may lead to significant reductions in healthcare costs and resource utilization over time.

Novel Approaches to Biomarker Development

Given the lack of sensitivity and specificity associated with ESR and CRP, a significant opportunity exists for the development of disease specific serologic markers of inflammation. Further attention may be focused on specific genotypes associated with CD or UC as a means of identifying better targets for biomarker development. For example, defensins such as β-defensin 2 and antimicrobial peptides such as cathelicidin may be increased among patients with CD where bacterial DNA is present in blood samples, and mediated through a wildtype NOD2/CARD15 genotype.[81]

Metabolic profiling has been proposed as another area of great promise in the evaluation of patients with suspected IBD as well as in the differentiation of UC from CD.[82] Multiple specimen types can be analyzed via metabolomic methods, including mucosal biopsies, stool, and urine samples.[83–88] One of the more unique metabolomic profiles recently suggested is a breathprint that can differentiate children with IBD from healthy controls. In a study of 117 patients, the authors utilized selected ion flow tube mass spectrometry to identify patterns of volatile organic compounds in the exhaled breath of children with IBD, demonstrating the potential utility for breath testing as a non-invasive method of evaluating a patient with suspected IBD.[89]

Protein profiling of serum, plasma, and tissue samples may also reveal distinct patterns among those patients with IBD. A variety of techniques for proteomic analysis have been proposed,[90,91] with pilot studies indicating that proteomic profiling may be useful in the differentiation of IBD patients from healthy controls,[92,93] as well as in the differentiation of subtypes of IBD.[94] Early studies also suggest that protein profiling may also have a role in the prediction of response to biologic therapy among patients with IBD.[95]

Differentiation between Subtypes of IBD

There has been continued interest in the development of biomarkers to aid in the differentiation between subtypes of IBD given the low sensitivity associated with serologic tests such as pANCA and ASCA. Our ability to explore genetic associations with clinical presentations of disease has improved considerably over the past decade, holding great promise for such evaluations. Recently, the largest genotype-phenotype study of patients with IBD was published.[96] In an analysis of 29,838 patients with IBD, three gene loci (NOD2, MHC, and MST1 3p21) were identified which were associated with sub-phenotypes of IBD. These findings led to the recommendation that based on genetic factors, IBD may be better classified into three distinct sub-phenotypes (ileal CD, colonic CD, and UC).[96] In an accompanying editorial, more systematic evaluation of the gene-environment connections was suggested as one means of improving our understanding of disease pathogenesis.[97] Another recent genetic evaluation identified nearly 200 single nucleotide polymophisms

(SNPs) that were associated with IBD, many of which overlapped between patients with UC and CD.[98]

Other efforts have been focused on improving the sensitivity of more established tests with previously detailed high specificity. Given the inability of pANCA alone to distinguish UC from CD, combining pANCA with other biomarkers has been proposed as a means of better delineation of disease subtype. In a study of 484 patients, Targan et al. found anti-CBir1 positivity in 44% of pANCA positive patients with CD compared to 4% of pANCA positive patients with UC,[99] suggesting that the combination of these markers (pANCA+/anti-CBir1+) may be part of a biomarker signature suggestive of a specific, perhaps more complicated or UC-like phenotype of CD. In another approach, the genetic marker TNFSF15 was combined with ASCA IgA to increase the power of predicting a stenosing or perforating phenotype of CD.[100]

Perhaps most indicative of the potential power of utilizing a multi-faceted biomarker signature or panel was the comparison by Plevy, et al. of a panel of serological markers (ASCA-IgA, ASCA-IgG, ANCA, pANCA, OmpC, CBir1) to a panel that included the same serological markers as well as inflammatory markers (including CRP), gene variants, and 2 additional serological markers (A4-Fla2 and FlaX).[101] In this evaluation, the larger panel improved both the ability to differentiate IBD from non-IBD as well as the discrimination between CD and UC.[102] As the utilization of serological biomarkers, genetic analysis, inflammatory and potentially environmental factors would seem to offer the greatest hope for increasing the ability to differentiate patients with IBD from those without IBD as well as to differentiate UC from CD, the creation of multi-faceted biomarker signatures is an area that will likely continue to expand in the near future.

Predicting Disease Course

While complicated due to the inherent multi-factorial nature, the prediction of an individual patient's disease course is one area where improvement in biomarker performance is most desired. The potential use of biomarkers in the prediction of disease course has been demonstrated for over 15 years, beginning with the association of high ASCA levels with fibrostenosing and penetrating disease among patients with CD.[103] Other studies have suggested that the sum of antibodies is an important factor in the evaluation of disease progression among patients with CD.[104] Early prospective studies by Dubinsky et al, demonstrated that the frequency of internal penetrating or stricturing disease increased as the presence of immune response to microbial antigens such as I2, OmpC, CBir1, and ASCA increased.[105] In a larger study of 796 pediatric patients with CD, Dubinsky et al. demonstrated that the rate of complicated CD (penetrating, stricturing, or surgery requiring disease) increased as the number and magnitude of reactivity to antibodies increased, with those patients expressing immune reactivity demonstrating a significantly faster disease progression.[106] In a study of sera from 100 military personnel with CD, 65 patients were positive for at least one CD associated anti-microbial antibody (ASCA-IgA, ASCA-IgG, anti-OmpC, anti-CBir1, anti-A4-Fla2 or anti-FlaX) at a median of 6 years prior to a diagnosis of CD.[107] Additionally, the proportion of positive antimicrobial antibodies prior to diagnosis was higher among patients who developed complicated CD when compared to

those who developed non-complicated CD.[107] Genotyping may also suggest the potential for a more severe disease course, as the NOD2 genotype has been associated with stricturing small bowel disease among patients with CD and more rapid disease progression.[108]

Following the initial success in identifying serologic and genotypic predictors of disease course, more recent efforts have been focused on combining methods to create even stronger predictive models. In an evaluation of 1721 patients with CD, Kaur, et al. demonstrated that combining clinical and genetic data led to improved performance in determining an association with perianal CD.[109] Additionally, the development of models incorporating genotype, serologic, and clinical information into a multivariable model for prediction of disease progression offers great promise for better predictions of the disease course of patients with CD.[110,111] These models are particularly attractive given their web-based nature allowing for real time discussions of predictions of disease prognosis with individual patients.

In addition to the demonstrated abilities to assess inflammation and mucosal healing, FC has also emerged as a non-invasive assessment of prediction of disease relapse among patients with UC.[112] In a study of 70 patients in remission at study entry, an elevated FC was associated with an increased risk of relapse at both 6 and 12 months, while histologic inflammation, CRP, and length of remission were not predictive of relapse.[112] In patients with severe UC, multiple methods have been proposed for the identification of patients at greatest risk of colectomy. In one study, an elevated CRP alone was associated with an increased likelihood of colectomy.[113] However, a more recent study used a risk matrix model to identify extent of disease, age, need for systemic steroids, and CRP or ESR at diagnosis as reliable predictors of need for colectomy both individually and in combination.[114]

Predicting Response to Therapy

Given the success of combination approaches to predicting the disease course of patients with both CD[111] and UC,[115] it would appear that further development and refining of these prediction models holds the greatest potential for better identification of patients at risk for a more severe disease course, allowing for an earlier and more personalized approach to therapy.

Ideally, biomarkers would be utilized as a predictive means to guide the initial decisions regarding the initiation of one therapeutic agent over another among patients with active CD and UC. However, to this point, many biomarkers have demonstrated utility in predicting response or remission only after initiation of an agent, which may lead to trials of multiple therapies before a successful maintenance regimen is established. In addition to an increasing focus on the utility of pharmacodynamic and pharmacokinetic monitoring of patients being treated with biologic therapy,[116–120] multiple other biomarkers have been identified (Table 3).

CRP has been used in a variety of studies to predict response to biologic therapy[121–124] The overall importance of CRP in the prediction of response to biologic therapy has been discussed in many scenarios, with particular questions centered around CRP's role as an

independent biomarker predicting clinical response or remission to therapy as opposed to a more general indicator of inflammation.[125] CRP has also been described as a predictor of low IFX level, and subsequent loss of response among patients with CD being treated with IFX.[126] Among patients being treated with thiopurines, CRP can also serve as a predictor of relapse.[127,128] Elevated CRP has also served as a predictor of relapse after withdrawal of IFX therapy in patients being treated with combination therapy.[129]

Other serologic measures such as mean platelet volume[130] and erythrocyte mean corpuscular volume[131] have also demonstrated utility in predicting response to therapy. More recently, Arias et al. utilized a risk panel to predict long-term relapse free or colectomy free survival among patients with UC. This risk panel incorporated 5 factors including baseline CRP and albumin, pANCA, and clinical factors manifested as absence of short-term clinical response and absence of short-term mucosal healing.[132]

Given concerns that blood based tests such as CRP might reflect an overall state of inflammation, there has been continued interest in the role of fecal tests that may be more directly associated with mucosal inflammation. High FC at baseline have been associated with increased risk of disease relapse among patients with CD,[24] while FC levels that normalize after induction therapy have been associated with sustained clinical remission among patients with CD and UC.[133,134] Lower FC levels have been associated with response to biologic therapy and clinical outcomes including clinical remission and mucosal healing.[135,136] Perhaps most useful, among patients in remission, FC has been reported to increase earlier and remain elevated prior to clinical or endoscopic relapse of disease,[137] which may indicate a role for prospective or routine monitoring with FC to identify those patients at greatest risk of relapse.

Genome Wide Association Studies (GWAS) have been used to identify predictors of response to anti-TNF therapy among patients with IBD. In an evaluation of 94 patients with IBD, Dubinsky et al. found an association between six known susceptibility loci and primary non-response to an anti-TNF therapy.[138] In the final predictive model used in this study, only the 21q22.2/BRWDI loci demonstrated a significant association, along with pANCA and a diagnosis of UC.[138]

Gene expression analysis has also been utilized as a predictor of response to anti-TNF therapy in patients with both UC[66] and CD.[139,140] Gene expression analysis offers a particularly attractive tool, as it could be performed prior to initiation of therapy and thus offers a prediction of response prior to use of a therapy that may ultimately provide a less than desirable treatment effect. Techniques utilizing analysis of “metagenes,” transcript sets that have been derived to reflect ongoing biologic change within a mucosal biopsy, have also demonstrated utility in the identification of predictors of the response to IFX therapy among patients with UC.[141] Whole blood gene expression analysis techniques are perhaps more attractive, as they allow for prediction of response utilizing a minimally invasive approach as compared to the need for biopsies for gene expression analysis of mucosal tissue. Given the preference for a less invasive, blood based predictor of response, there are ongoing studies of whole blood gene expression analysis to identify predictors of response to therapy with IFX and ADA.

Conclusion

Further development of biomarkers to assist in the care of patients with UC and CD is an area that is primed for progression in the near future. As we move towards an ultimate goal of precision medicine, where treatment decisions can be individualized through the use of clinical, genetic, and phenotypic information, there will be further emphasis on the initial identification of patients with IBD, as well as predictors of disease course and responses to individual treatment regimens. Given the initial successes in combining multiple testing modalities, there is hope that the ultimate development of a biomarker signature may yield significant advances in our ability to identify those patients with the greatest risk for severe disease, and thus would benefit most from aggressive and individualized therapies. While the ideal biomarker for the care of patients with UC and CD does not exist at this point, there is hope that we can build on the initial foundations of serologic and stool tests to identify a more sensitive and specific biomarker or biomarker signature with low cost and increased availability.

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Table 1

Biomarkers that are currently being used in the assessment of patients with suspected or established Inflammatory Bowel Disease

Biomarker	Specific for IBD	Distinguish UC from CD	Predictive of Disease Course	Predictive of Response to Therapy
CRP	No	No	Yes	Yes
Fecal Calprotectin	Yes	No	Yes	Yes
Fecal Lactoferrin	Yes	No	Yes	Likely
S100A12	No	No	No	Yes
Lipocalin-2	No	No	No	Unknown
pANCA	Yes	Yes	Yes	Yes
ASCA	Yes	Yes	Yes	No

Table 2a

Whole Blood Gene Expression Analysis to Predict Disease Activity in Patients with Crohn's Disease

	Individual Gene	Gene Function/Association
Crohn's Disease with Mild Severity	**TAP2** (Transporter 2, ATP-Binding Cassettte, Sub-Family B)	Several autoimmune diseases including Rheumatoid Arthritis and Systemic Lupus Erythematosus
	ZFAS1 (ZNFX1 Antisense RNA 1)	Breast cancer and intrahepatic cholangiocarcinoma
	SIAH1 (E3 Ubiquitin Protein Ligase 1)	Induced at the tip of intestinal villi, upregulated during physiologic apoptosis
	GMPR2 (Guanosine Monophosphate Reductase)	Gastric adenocarcinoma
	WAPAL (Wings Apart-Like Homolog)	Promotes release of cohesin from chromosomes, involved in mitotic prophase
	ZNF45 (Zinc Finger Protein 45)	Multiple sclerosis, may be involved DNA-dependent in transcriptional regulation
Crohn's Disease with Moderate to Severe Disease	**KANSL1** (KAT8 Regulatory NSL Complex Subunit1)	May be involved in the regulation of transciption; involved in the acetylation of nucleosomal histone H4 on lysine residues
	PPP6C (Protein Phosphatase 6, Catalytic Subunit)	Regulates cell cycle progression in response to IL2 receptor stimulation
	LEPROTL1 (Leptin Receptor Overlapping Transcript-Like 1)	Believed to regulate the expression of growth hormone receptor cell surface in the liver
	MAP3K3 (Mitogen Activated Protein Kinase Kinase Kinase 3)	Component of a protein kinase signal transduction cascade. Mediates activation of the NF-kappa-B, AP1 and DDIT3 transcriptional regulators.
	SRA1 (Steroid receptor RNA activator 1)	A non-coding RNA that is able to co-activate steroid nuclear receptors
	ZNF45 (Zinc Finger Protein 45)	Multiple sclerosis, may be involved in DNA-dependent transcriptional regulation

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Table 2b

Whole Blood Gene Expression Analysis to Predict Disease Activity in Patients with Ulcerative Colitis

	Individual Gene	Gene Function/Association
Ulcerative Colitis with Mild Severity	**NLRP12** (Nucleotide-binding and oligomerization domain NOD-like receptors)	One of the members of the NOD-like receptor family of pattern recognition receptors. Plays a role in the production of IL-1β and IL-18
	TNFRSF10C (Tumor necrosis factor receptor super family, member 10c, decoy without an intracellular domain)	Functions as an antagonistic receptor that protects cells from TRAIL-induced apoptosis
	SRA1 (Steroid receptor RNA activator 1)	A non-coding RNA that is able to co-activate steroid nuclear receptors
	TAGAP (T-Cell Activation RhoGTPase Activating)	Plays a role in T-cell activation and migration
	PDE7A (Phosphodiesterase 7A)	A high-affinity cyclic AMP phosphodiesterase that is expressed in immune and pro-inflammatory cells
	ROPN1L (Rhophilin associated tail protein 1-like)	A protein-coding gene; elevated in breast cancer
Ulcerative Colitis with Moderate to Severe Disease	**CD24** (CD24 Molecule)	Modulates B-cell activation responses; CD24 C170T polymorphism is associated with IBD risk
	HIST1H3H (Histone Cluster 1, H3h)	Plays a central role in transcription regulation, DNA repair, DNA replication and chromosomal stability
	FDFT1 (Farnesyl-Diphosphate Farnesyltransferase)	Genetic factor associated with progression to NASH in patients with non-alcoholic steatosis
	PGM1 (Phosphoglucomutas 1)	Participates in both the breakdown and synthesis of glucose
	C14orf119 (Chromosome 14 Open Reading Frame 119)	Unknown
	RTFDC1 (Replication termination factor 2 domain containing 1)	Unknown

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Table 3

Prediction of Response to Therapy using Novel and Established Biomarkers

Biomarker	Therapy Evaluated	References
CRP	Infliximab, Thiopurines	121-124
pANCA	Infliximab	132
Mean Platelet Volume	Infliximab	130
Erythrocyte Mean Corpuscular Volume	Combination therapy with Infliximab and Azathioprine	131
Fecal Calprotectin	Infliximab, Adalimumab	135, 136
Genome Wide Association Studies	Infliximab	138
Gene Expression Analysis	Infliximab	66, 139, 140
Protein Profiling	Infliximab	95