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Review

Molecular and cellular biomarkers in Crohn's disease: from pathogenesis to clinical application

Alexander Blagov[1*], Marina D. Sazonova[1], Anastasia I. Ryzhkova[1], Vasily P. Karagodin[1,5], Mikhail A. Popov[6], Egor Yu. Budnikov[1], Elizaveta R. Korchagina[4], Alexander N. Orekhov[1,4], Margarita A. Sazonova[1,2], Yuri V. Arkhipenko[1,3]

[1] Laboratory of angiopathology, Institute of General Pathology and Pathophysiology, 8, Baltiiskaya Street, 125315 Moscow, Russia
[2] Laboratory of Medical Genetics, Institute of Experimental Cardiology, National Medical Research Center for Cardiology named after academician Y.Chazov of the Ministry of Health of the Russian Federation, 15a, 3rd Cherepkovskaya Str., Moscow, 121552, Russia
[3] Faculty of Medicine, MSU, 31-5 Lomonosovsky Prospekt, Moscow, 117192, Russia
[4] R&D Lab, Institute for Atherosclerosis Research, Osennyaya Street 4-1-207, 121609 Moscow, Russia
[5] Plekhanov Russian University of Economics, Stremyanny lane, 36, Moscow, 117997, Russia
[6] Department of Cardiac Surgery, Moscow Regional Research and Clinical Institute ("MONIKI"), 61/2, Shchepkin St., Moscow, 129110, Russia

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Abstract

Crohn's disease (CD) is a chronic inflammatory bowel disease characterized by transmural inflammation that can affect any part of the gastrointestinal tract. Early and accurate diagnosis remains challenging due to the heterogeneous nature of the disease and overlapping symptoms with other gastrointestinal disorders. Current diagnostic approaches rely on a combination of clinical presentation, endoscopic findings, histological examination, and imaging studies, which can be invasive and time-consuming. The identification of reliable biomarkers could significantly improve diagnostic accuracy and reduce the need for invasive procedures. This review examines currently used biomarkers, including C-reactive protein, fecal calprotectin, and anti-Saccharomyces cerevisiae antibodies, while exploring emerging potential biomarkers such as microRNA panels, metabolomic signatures, and novel inflammatory mediators. Recent advances in genomics, proteomics, and metabolomics have revealed promising biomarker candidates that could enhance diagnostic precision and enable personalized treatment approaches. Understanding the performance characteristics and clinical utility of these biomarkers is crucial for their implementation in routine clinical practice and improved patient outcomes.

Keywords: Crohn's disease, Inflammatory bowel disease, Biomarkers, C-reactive protein, MicroRNA.

1. Introduction

Crohn's disease represents one of the two major forms of inflammatory bowel disease, affecting approximately 6.8 million people worldwide with increasing incidence rates globally [1]. The disease is characterized by chronic, relapsing inflammation that can involve any segment of the digestive tract from mouth to anus, with a predilection for the terminal ileum and colon [2]. The pathogenesis involves a complex interplay between genetic susceptibility, environmental factors, intestinal microbiota, and immune system dysfunction [3]. Over 200 genetic loci have been associated with CD susceptibility, highlighting the polygenic nature of the disease [4].

The clinical presentation of CD is highly variable, ranging from mild symptoms to severe complications including strictures, fistulas, and perforation [5]. Common symptoms include abdominal pain, diarrhea, weight loss, and fatigue, which often overlap with functional gastrointestinal disorders and other inflammatory conditions [6]. This symptomatic overlap, combined with the lack of pathognomonic features, makes early diagnosis challenging and often leads to diagnostic delays averaging 9-12 months from symptom onset [7].

Current diagnostic algorithms rely on the Montreal classification system and require integration of clinical, endoscopic, histological, and radiological findings [8]. Gold standard diagnostic procedures include ileocolonoscopy with biopsy and cross-sectional imaging, which are

* Corresponding author.
E-mail address: al.blagov2014@gmail.com (A. Blagov).
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invasive, expensive, and not always readily available [9]. The absence of a single definitive diagnostic test necessitates a comprehensive approach that can be time-consuming and stressful for patients [10].

The concept of biomarkers in CD diagnosis has evolved significantly over the past decades [11]. Biomarkers are defined as measurable indicators of biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions [12]. In the context of CD, biomarkers can serve multiple purposes, including diagnosis, disease activity monitoring, treatment response assessment, and prognosis prediction [13]. The ideal biomarker should be easily measurable, reproducible, cost-effective, and demonstrate high sensitivity and specificity for the target condition [14]. Despite extensive research, no single biomarker has achieved sufficient diagnostic accuracy to replace current diagnostic modalities, emphasizing the need for biomarker panels and multimodal approaches [15].

2. Stages of Crohn's disease

Crohn's disease exhibits a progressive nature with distinct stages that reflect the evolution of intestinal inflammation and structural damage over time [16]. Understanding these stages is crucial for biomarker development as different molecular signatures may characterize each phase of disease progression [17]. The staging systems have evolved from purely clinical classifications to more sophisticated frameworks incorporating molecular and imaging parameters [18].

The early inflammatory stage represents the initial phase of CD, characterized by mucosal inflammation without structural complications [19]. During this stage, the intestinal barrier function is compromised, leading to increased permeability and bacterial translocation [20]. Inflammatory mediators, including tumor necrosis factor-alpha, interleukin-1β, and interleukin-6, are elevated, creating a pro-inflammatory milieu [21]. Endoscopically, patients present with aphthous ulcerations, erythema, and edema of the mucosa [22]. Histological examination reveals focal chronic inflammation, along with cryptitis and crypt abscess formation [23]. At the molecular level, this stage is characterized by activation of the nuclear factor-κB (NF-κB) signaling pathways and upregulation of inflammatory genes [24].

The intermediate fibrostenotic stage develops as chronic inflammation triggers fibroblast activation and excessive collagen deposition [25]. This process involves transforming growth factor-β signaling and mechanical stress responses that promote extracellular matrix remodeling [26]. Clinically, patients may experience symptoms of partial intestinal obstruction with postprandial pain and bloating [27]. Endoscopically, luminal narrowing and stricture formation become apparent, while imaging studies reveal bowel wall thickening and upstream dilatation [28]. Key biomarkers during this stage include matrix metalloproteinases, tissue inhibitors of metalloproteinases, and fibrosis-related proteins such as hyaluronic acid and procollagen peptides [29,30].

Advanced penetrating disease represents the most severe form of CD with development of fistulas, abscesses, and perforations [31]. This stage involves complex interactions between inflammatory cells, tissue matrix, and bacterial components that promote tissue destruction and abnormal healing responses [32]. Neutrophil infiltration and release of proteolytic enzymes contribute to tissue damage and fistula tract formation [33]. Clinically, patients present with complications requiring surgical intervention and often experience reduced quality of life [34]. Biomarkers associated with this stage include neutrophil-derived proteins, complement activation products, and damage-associated molecular patterns [35,36].

The remission stage occurs when active inflammation subsides, either spontaneously or following therapeutic intervention [37]. However, complete histological healing is rare, and subclinical inflammation often persists [38]. During remission, anti-inflammatory mechanisms become predominant, including regulatory T-cell activation and production of anti-inflammatory cytokines such as interleukin-10 [39]. Mucosal healing, defined as absence of visible lesions on endoscopy, has emerged as an important therapeutic target associated with improved long-term outcomes [40]. Biomarkers of remission include normalization of inflammatory parameters and emergence of tissue repair markers such as vascular endothelial growth factor and epithelial growth factors [41].

Disease phenotype evolution is increasingly recognized as a dynamic process rather than static classification [42]. The Montreal classification system categorizes CD based on age at diagnosis, disease location, and behavior, but these characteristics can change over time [43]. Longitudinal studies demonstrate that up to 50% of patients with initially inflammatory disease develop complications within 10 years [44]. This phenotypic progression appears to be influenced by genetic factors, with certain polymorphisms predisposing to accelerated disease course [45]. Environmental factors, including smoking, medication adherence, and intestinal microbiota composition, also influence disease progression patterns [46,47].

Recent advances in molecular profiling have revealed stage-specific signatures that could guide personalized treatment approaches [48]. Transcriptomic studies have identified distinct gene expression patterns associated with different disease stages, while proteomics approaches have revealed stage-specific protein profiles [49,50]. These molecular insights are driving the development of precision medicine approaches that tailor treatment based on individual disease characteristics and predicted progression patterns [51].

3. Used biomarkers for the diagnosis of Crohn's disease

Current clinical practice employs several established biomarkers for CD diagnosis, each with distinct advantages and limitations [52]. These biomarkers span multiple biological matrices, including serum, feces, and tissue samples, providing complementary information about disease activity and extent [53].

C-reactive protein (CRP) remains the most widely used inflammatory biomarker in CD diagnosis and monitoring [54]. CRP is an acute-phase protein synthesized by hepatocytes in response to inflammatory cytokines, particularly interleukin-6 [55]. In CD patients, CRP levels correlate with disease activity and extent of inflammation, with elevated levels (>3.0 mg/L) observed in approximately 70% of patients with active disease [56]. However, CRP lacks specificity for intestinal inflammation and can be elevated in various infectious and inflammatory conditions [57]. Additionally, up to 25% of CD patients maintain nor-

mal CRP levels despite active disease, particularly those with isolated small bowel involvement [58]. The sensitivity of CRP for detecting CD ranges from 50-90%, while specificity ranges from 40-80% depending on the clinical context [59].

Erythrocyte sedimentation rate (ESR) represents another traditional inflammatory marker used in CD assessment [60]. ESR reflects the tendency of red blood cells to settle in plasma and correlates with plasma protein concentrations, particularly fibrinogen and immunoglobulins [61]. While ESR is less specific than CRP and slower to respond to changes in inflammatory activity, it provides complementary information and may remain elevated longer during recovery phases [62]. The diagnostic utility of ESR in CD is limited by its poor specificity and is influence by factors such as age, anemia, and other systemic conditions [63].

Fecal calprotectin has emerged as a valuable noninvasive biomarker for intestinal inflammation [64]. Calprotectin is a calcium-binding protein predominantly found in neutrophils and represents approximately 60% of neutrophil cytoplasmic proteins [65]. In CD, increased neutrophil migration into the intestinal lumen results in elevated fecal calprotectin concentrations [66]. The biomarker demonstrates excellent correlation with endoscopic disease activity and histological inflammation [67]. Fecal calprotectin levels >250 μg/g are considered indicative of organic intestinal disease with sensitivity ranging from 85-95% and specificity of 75-85% for CD diagnosis [68]. The biomarker is particularly useful for distinguishing inflammatory bowel diseases from functional disorders and monitoring treatment response [69].

Lactoferrin is another neutrophil-derived protein found in feces that serves as a marker of intestinal inflammation [70]. Similar to calprotectin, lactoferrin levels correlate with disease activity and endoscopic findings in CD patients [71]. However, lactoferrin appears less stable than calprotectin and may be more susceptible to degradation by intestinal bacteria [72]. The diagnostic performance of fecal lactoferrin is comparable to calprotectin but with slightly lower specificity [73].

Anti-Saccharomyces cerevisiae antibodies (ASCA) represent serological markers that demonstrate specificity for CD compared to ulcerative colitis [74]. ASCA-IgG and ASCA-IgA antibodies are directed against phosphopeptidomannan epitopes of the yeast cell wall [75]. Approximately 50-60% of CD patients test positive for ASCA compared to 10-15% of healthy controls and 2-8% of ulcerative colitis patients [76]. ASCA positivity is associated with ileal involvement, fibrostenotic behavior, and need for surgical intervention [77]. However, the relatively low sensitivity limits the utility of ASCA as a standalone diagnostic test [78].

Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) are more commonly associated with ulcerative colitis but can be found in a subset of CD patients [79]. Approximately 5-25% of CD patients test positive for pANCA, particularly those with colonic involvement [80]. The combination of ASCA positivity and pANCA negativity has been proposed as a serological signature favoring CD diagnosis [81].

Antibodies against outer membrane porin C (anti-OmpC) and flagellin (anti-CBir1) represent additional serological markers associated with CD [82,83]. Anti-OmpC antibodies are directed against bacterial outer membrane proteins and are found in approximately 30-55% of CD patients [84]. Anti-CBir1 antibodies target bacterial flagellin and are associated with small bowel CD and complicated disease behavior [85]. These antibodies may be particularly useful when combined in serological panels [86].

Genetic markers have provided insights into CD pathogenesis but have limited diagnostic utility due to incomplete penetrance [87]. The most significant genetic association involves variants in the NOD2/CARD15 gene, found in approximately 30-40% of CD patients compared to 10-15% of controls [88]. Other relevant genetic markers include ATG16L1, IRGM, and IL23R variants [89]. However, the low positive predictive value of genetic testing limits its clinical application for diagnosis [90].

Recent advances have led to the development of multi-biomarker panels that combine traditional markers with novel candidates [91]. Commercial panels such as the IBD differentiation panel combine multiple antibodies and inflammatory markers to improve diagnostic accuracy [92]. These panels typically achieve sensitivity and specificity rates of 80-90% for CD diagnosis when compared to clinical gold standards [93].

According to Table 1, fecal calprotectin demonstrates the highest sensitivity and specificity among noninvasive biomarkers, making it particularly useful for distinguishing inflammatory bowel disease from functional disorders.

4. Potential biomarkers for the diagnosis of Crohn's disease

The landscape of CD biomarker research is rapidly evolving with the emergence of novel candidates identified through advanced molecular techniques [94]. These potential biomarkers offer promise for improved diagnostic accuracy, earlier detection, and personalized treatment approaches [95].

MicroRNA (miRNA) biomarkers represent a promising class of regulatory molecules that control gene expres-

Table 1. Summary of currently used biomarkers for Crohn's disease.

Biomarker	Sample Type	Sensitivity (%)	Specificity (%)	Clinical Utility
C-reactive protein	Serum	50-90	40-80	Disease activity monitoring
Fecal calprotectin	Feces	85-95	75-85	IBD vs functional disorders
ASCA IgG/IgA	Serum	50-60	85-90	CD vs UC differentiation
pANCA	Serum	5-25	90-95	Combined with ASCA
Anti-OmpC	Serum	30-55	80-85	Disease behavior prediction
Anti-CBir1	Serum	40-60	70-80	Small bowel involvement
Lactoferrin	Feces	80-90	70-80	Alternative to calprotectin
NOD2 variants	Blood	30-40	85-90	Risk stratification

sion post-transcriptionally [96]. Several miRNAs have been identified as dysregulated in CD patients, including miR-155, miR-146a, and miR-21 [97]. These miRNAs play crucial roles in inflammatory pathways and immune cell differentiation [98]. Circulating miRNAs in serum and plasma demonstrate stability and can be easily measured using quantitative PCR techniques [99]. miR-155 is particularly notable as it promotes pro-inflammatory responses and is consistently upregulated in CD patients compared to healthy controls [100]. Fecal miRNAs, including miR-223 and miR-142-3p, have also shown potential as non-invasive biomarkers reflecting local intestinal inflammation [101]. Combined miRNA panels demonstrate superior diagnostic performance compared to individual miRNAs, with some studies reporting sensitivity and specificity rates exceeding 85% [102].

Long non-coding RNAs (lncRNAs) represent another class of regulatory molecules with biomarker potential [103]. Several lncRNAs, including ANRIL, MALAT1, and H19, are dysregulated in CD and participate in inflammatory signaling pathways [104]. These molecules are detectable in various biological samples and demonstrate tissue-specific expression patterns [105]. lncRNA signatures may provide insights into disease subtypes and progression patterns [106].

Metabolomic biomarkers offer a functional readout of disease processes and environmental influences [107]. Untargeted metabolomics studies have identified numerous metabolite alterations in CD patients, including changes in amino acid metabolism, lipid profiles, and microbial metabolites [108]. Tryptophan metabolism is particularly disrupted in CD, with decreased levels of tryptophan and increased kynurenine pathway metabolites [109]. Short-chain fatty acids, particularly butyrate, are decreased in CD patients due to altered microbial fermentation [110]. Bile acid metabolism is also significantly altered, with implications for intestinal barrier function and immune responses [111]. Metabolomic panels combining multiple pathways have demonstrated diagnostic accuracies comparable to or exceeding traditional biomarkers [112].

Proteomic biomarkers leverage advances in mass spectrometry and protein analysis techniques to identify disease-associated protein signatures [113]. Serum proteomic studies have identified altered levels of complement proteins, acute-phase reactants, and immune mediators in CD patients [114]. Fecal proteomics has revealed neutrophil-derived proteins, epithelial markers, and microbial proteins that distinguish CD from other conditions [115]. Tissue proteomics provides insights into local inflammatory processes and fibrotic changes [116]. Multi-protein panels demonstrate enhanced diagnostic performance compared to single protein markers [117].

Cytokine and chemokine profiles represent direct measures of inflammatory activity with biomarker potential [118]. Beyond traditional inflammatory markers, novel cytokines, including IL-17A, IL-22, and IL-23, are elevated in CD patients and correlate with disease activity [119]. Chemokines such as CCL2, CCL3, and CXCL10 demonstrate altered expression patterns and may predict treatment responses [120]. Th17-related cytokines are particularly prominent in CD and may serve as targets for therapeutic intervention [121]. Multiplex cytokine assays enable simultaneous measurement of multiple mediators, providing comprehensive inflammatory profiles [122].

Microbiome-derived biomarkers reflect the altered gut microbial composition characteristic of CD [123]. Specific bacterial taxa, including Faecalibacterium prausnitzii and Roseburia species, are consistently decreased in CD patients [124]. Conversely, potentially pathogenic bacteria such as adherent-invasive E. coli are increased [125]. Microbial diversity indices and functional pathway analyses provide additional biomarker candidates [126]. Microbial metabolites, including trimethylamine N-oxide and indole derivatives, demonstrate altered levels in CD patients [127]. Host-microbiome interaction markers, such as anti-microbial antibodies and microbial sensing receptor expression, offer insights into disease pathogenesis [128].

Extracellular vesicle biomarkers represent a novel frontier in biomarker research [129]. Extracellular vesicles carry molecular cargo including proteins, lipids, and nucleic acids that reflect their cellular origin [130]. Circulating extracellular vesicles from immune cells and intestinal epithelial cells are altered in CD patients [131]. These vesicles can be isolated from various body fluids and analyzed for their molecular content [132]. miRNA profiles within extracellular vesicles may provide more stable and specific biomarkers compared to free-circulating miRNAs [133].

Epigenetic biomarkers, including DNA methylation patterns and histone modifications, are increasingly recognized as disease-associated markers [134]. CpG methylation studies have identified differentially methylated regions in CD patients affecting genes involved in immune responses and barrier function [135]. Histone modifications, including H3K4me3 and H3K27me3, are altered in CD intestinal tissues [136]. These epigenetic marks can be detected in circulating cell-free DNA and may function as liquid biopsy markers with diagnostic potential comparable to, or surpassing, that of traditional biomarkers [137].

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According to Table 2, a wide range of molecular entities, such as microRNAs, metabolites, and extracellular vesicles, show promise as potential biomarkers, although most remain in early research or validation stages.

5. Discussion

The quest for reliable biomarkers in Crohn's disease diagnosis reflects the complex and heterogeneous nature of this inflammatory condition [138]. While current biomarkers provide valuable clinical information, their individual limitations highlight the need for more sophisticated approaches combining multiple molecular signatures [139]. The integration of traditional inflammatory markers with emerging molecular biomarkers represents a promising strategy for improving diagnostic accuracy and enabling personalized medicine approaches [140].

The transition from single biomarker approaches to multi-parametric panels aligns with our growing understanding of CD as a multifaceted disease involving genetic, environmental, microbial, and immunological factors [141]. Machine learning and artificial intelligence applications are increasingly being applied to biomarker data to identify complex patterns that may not be apparent through traditional statistical approaches [142]. By integrating multiple layers of information, including genomic, proteomic, metabolomic, and clinical data, these computational methods enable the development of comprehensive and data-driven diagnostic algorithms [143].

The clinical implementation of novel biomarkers faces several challenges, including standardization of measurement techniques, establishment of reference ranges, and validation across diverse populations [144]. Regulatory approval processes require extensive validation studies demonstrating clinical utility and cost-effectiveness [145]. The development of point-of-care testing platforms could facilitate widespread adoption of biomarker-based diagnostics in routine clinical practice [146].

Economic considerations play a crucial role in biomarker adoption, with healthcare systems requiring evidence of improved outcomes and cost-effectiveness [147]. The potential for biomarkers to reduce the need for invasive procedures and enable earlier diagnosis could provide significant economic benefits [148]. However, the initial costs of implementing new biomarker technologies must be balanced against long-term healthcare savings [149].

Future directions in CD biomarker research include the development of predictive models for disease progression, treatment response, and complication risk [150]. Longitudinal studies tracking biomarker changes over time will provide insights into disease evolution and therapeutic monitoring [151]. The integration of digital health technologies, including wearable devices and smartphone applications, could enable continuous biomarker monitoring and real-time disease assessment [152].

6. Conclusions

The landscape of biomarkers for Crohn's disease diagnosis is rapidly evolving, with traditional inflammatory markers being complemented by sophisticated molecular signatures derived from genomics, proteomics, and metabolomics approaches. While current biomarkers, including C-reactive protein, fecal calprotectin, and serological markers, provide valuable clinical information, their individual limitations necessitate the development of multi-biomarker panels with enhanced diagnostic performance. Emerging biomarker candidates, including microRNAs, metabolomic profiles, microbiome signatures, and extracellular vesicle markers, demonstrate promising potential for improving diagnostic accuracy and enabling personalized treatment approaches. The successful clinical implementation of these novel biomarkers will require extensive validation studies, standardization of measurement techniques, and demonstration of clinical utility and cost-effectiveness. The integration of advanced computational methods and artificial intelligence approaches offers opportunities to harness the complexity of multi-dimensional

Table 2. Summary of potential biomarkers for Crohn's disease.

Biomarker Category	Examples	Sample Type	Advantages	Current Status
microRNAs	miR-155, miR-146a, miR-21	Serum, feces	Stable, specific	Research phase
Metabolites	Tryptophan, SCFA, bile acids	Serum, urine, feces	Functional readout	Validation studies
Proteins	Complement, cytokines	Serum, tissue	Direct measurement	Clinical trials
Microbiome	F. prausnitzii, diversity	Feces	Non-invasive	Development phase
Extracellular vesicles	miRNA cargo, proteins	Serum, urine	Protected cargo	Early research
Epigenetic marks	DNA methylation	Blood, tissue	Stable modifications	Proof of concept
lncRNAs	ANRIL, MALAT1	Tissue, blood	Regulatory function	Research phase

biomarker data for improved diagnostic algorithms. Future research should focus on longitudinal validation studies, development of point-of-care testing platforms, and integration of biomarker-guided approaches into clinical decision-making algorithms. The ultimate goal remains the development of precise, non-invasive, and cost-effective diagnostic tools that can facilitate early detection, accurate diagnosis, and personalized management of Crohn's disease patients.

Author contributions
AB and AO designed the review plan. MS, AR, VK, MP, EB, EK, YA performed the data analyses. All authors wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

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Conflict of interest
The authors declare no conflict of interest.

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