# Novel Diagnostic and Prognostic Modalities in Inflammatory Bowel Disease

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**KEYWORDS**

• Inflammatory bowel disease • Diagnosis • Prognosis
• Serologies • Imaging • Fecal biomarkers

Inflammatory bowel disease (IBD) is a heterogenous group of diseases that can be broadly classified into Crohn disease and ulcerative colitis (UC). The term IBD-unclassified (IBDU) applies to the subset of 10% to 15% of patients with IBD in whom this subcategorization is not possible. There is no gold standard single test that provides the diagnosis of IBD, so assigning a diagnosis of IBD is often not straightforward and involves integration of historical factors, physical examination findings, and evidence of inflammation on endoscopic, histologic, and radiologic evaluations. Consequently, there is significant uncertainty both in establishing the initial diagnosis and, importantly, in assessing for disease relapse after a period of remission. These challenges are compounded by the increased appreciation of the importance of an accurate and timely diagnosis. Delay in diagnosis can result in complications of stricturing or penetrating disease, whereas an incorrect diagnosis has emotional and insurance implications and can expose patients to the modest but nonetheless real risks of medical therapy. The uncertainty in diagnosing IBD and the need to get the diagnosis right has fueled improvements in techniques to assess bowel inflammation, including serologic and fecal markers and novel endoscopic and radiologic tools for imaging the entire bowel. These new techniques for evaluating patients with IBD are developed with the goals of improving early and accurate diagnosis, clarifying disease type and distribution in order to select optimal therapy, identifying patients at high risk

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for aggressive disease, and detecting complications such as abscess or malignancy. The past decade has seen a dramatic advancement in diagnostic and prognostic modalities in IBD, and these novel instruments are reviewed in this article.

## SEROLOGIC BIOMARKERS

Serologic biomarkers in IBD include an enlarging panel of antibodies directed against microbial and self-antigens and acute phase reactants. It is unclear whether these antimicrobial antibodies are mechanistically related to the pathogenesis of IBD. They may represent a loss of immune tolerance to commensal organisms, or they may simply be an indicator of increased bowel permeability with consequent exposure to luminal antigens. A variety of uses for these markers have been explored in IBD patients, including as potential diagnostic tools, follow-up parameters, prognostic indicators for phenotypic stratification, or subclinical disease markers in IBD patients or their family members. Serologic tests have several advantages in that they are easy to obtain, noninvasive, and objectively quantified.

### *Antineutrophil Cytoplasmic Antibodies*

Antineutrophil cytoplasmic antibodies (ANCA) are detected on peripheral blood neutrophils by indirect immunofluorescence (IIF) techniques. Two major staining patterns have been described. A cytoplasmic (c-ANCA) staining pattern characterized by diffuse granularity of the cytoplasm is classically seen in patients with Wegener granulomatosis. These c-ANCA antibodies typically recognize proteinase-3 on enzyme-linked immunosorbent assay (ELISA) testing. By contrast, a thin homogeneous rim-like staining of the perinuclear cytoplasm (p-ANCA) is associated with microscopic polyangiitis and antibodies directed against myeloperoxidase. A third pattern exists, often referred to as atypical p-ANCA, that appears as a broad heterogeneous staining of the nuclear periphery, often with intranuclear inclusions to suggest that the antigen may be in the periphery of the nucleus rather than in the perinuclear cytoplasm. This atypical p-ANCA is associated with IBD[1] and primary sclerosing cholangitis[2] and autoimmune hepatitis type I.[3] Atypical p-ANCA is present in 40% to 80% of patients with UC [4,5] and 5% to 25% of patients with Crohn disease.[1] The target antigens of atypical p-ANCA have not been identified, but several have been explored, including cathepsin G, elastase, β-glucuronidase, lactoferrin, and the natural antibiotic bactericidal permeability increasing protein. Myeloperoxidase and proteinase-3, the antigens recognized by typical p-ANCA and c-ANCA, respectively, are not autoantigens in IBD. Because the target antigens of atypical p-ANCA have not been identified, there is no ELISA test to distinguish these antibodies from typical p-ANCA. Rather one must rely on IIF, which has drawbacks, including differences in methodology and subjective interpretation of staining pattern that result in substantial variability of results among laboratories.[6,7] Consequently, the numerous studies describing the performance characteristics of atypical p-ANCA in the detection of IBD have yielded heterogeneous and discrepant results.[1] Given this variability, an alternative methodology was developed by Targan and colleagues[8] to distinguish atypical p-ANCA from the typical vasculitis-associated p-ANCA by a 3-step process that involves IIF staining before and after treatment of neutrophils with deoxyribonuclease (DNase). Addition of DNase abolishes the fluorescent staining of atypical, UC-associated p-ANCA, allowing distinction from the typical p-ANCA pattern. In a large meta-analysis, the overall sensitivity of atypical p-ANCA for detecting UC was 55%, with a specificity of 89%, a positive likelihood ratio of 4.5, and a negative likelihood ratio of −0.5.[9]