



Beyond Diagnostic Labels: Why Pre-IPAA Biomarker Stratification Optimizes Surgical Decision-Making in Colorectal Inflammatory Bowel Disease

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Introduction

A Diagnostic Problem with Surgical Consequences

Despite substantial advances in the diagnosis and treatment of Colonic Inflammatory Bowel Disease (cIBD), distinguishing Ulcerative Colitis (UC) from Crohn's Colitis (CC) remains a significant clinical challenge [1-13]. The clinical, endoscopic, histologic, radiologic, and laboratory features of these diseases may overlap considerably. As a result, some patients cannot be definitively classified at the time of their initial evaluation and may be categorized as having Indeterminate Colitis (IC) [14-17]. In our opinion, the importance of this diagnostic uncertainty changes fundamentally when restorative surgery is being considered. During medical management, continued observation and reassessment may allow the disease phenotype to become clearer over time. However, when a patient is being considered for restorative proctocolectomy with Ileal Pouch–Anal Anastomosis (IPAA), uncertainty about the underlying disease phenotype becomes a potentially irreversible

surgical problem. We argue that the most important unmet need is not simply to improve the diagnostic distinction between UC and CC, but to improve preoperative disease stratification before IPAA is performed. This distinction matters because the consequences of diagnostic uncertainty are not equivalent before and after pouch construction.

The Pre-IPAA Diagnostic Dilemma

IPAA remains an established restorative surgical procedure for appropriately selected patients with medically refractory UC [18-21]. In contrast, IPAA is generally avoided in patients with established Crohn's disease because of the increased risk of pouch-related complications and pouch failure [1,3,7,22,23]. Patients initially believed to have UC who subsequently develop Crohn's disease after IPAA, (Figure 1) may experience fistula formation, chronic pouchitis, Crohn's disease of the pouch, and pouch failure [3,7,24-34]. In severe cases, pouch failure may require pouch excision and permanent ileostomy, with substantial

consequences for quality of life, healthcare utilization, and costs [35-37]. For this reason, we believe that the key question before IPAA should not be limited to: **“Does this patient currently meet the diagnostic criteria for UC?”** A more clinically meaningful question may be: **“Is the available evidence sufficiently reliable to support proceeding with irreversible pouch construction?”** his reframing places the emphasis on the decision that matters most to the patient. A degree of diagnostic uncertainty that may be acceptable during medical management may be unacceptable when the next step is irreversible anatomical reconstruction.

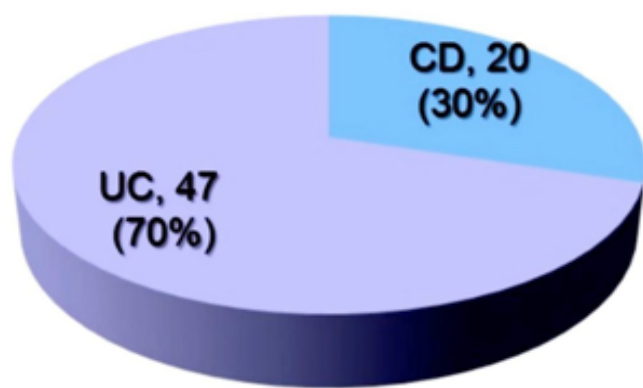


Figure 1: IPAA Crohn’s colitis misdiagnosed as ulcerative colitis.

One hundred twenty (120) patients with refractory UC underwent IPAA surgery between 2001 and 2008. Of these, 67 patients had their diagnosis re-evaluated after a mean follow-up of 9.4 years (range, 6–13 years) and had functionally acceptable pouches. A review of the medical records allowed us to evaluate the clinical course of patients initially diagnosed with UC who subsequently developed Crohn’s Disease of the Ileal Pouch (CDP) following IPAA. Clinical information for each patient was available in the IBD Medical Records Registry database at VUMC. The aim was to re-evaluate the definitive diagnosis of UC in patients who underwent IPAA and subsequently developed clinical features characteristic of Crohn’s disease. In these patients, the change in diagnosis was supported by clinical findings consistent with Crohn’s disease. Our biomarker-based test, performed on their pre-IPAA biopsy specimens, distinguished Crohn’s Colitis (CC) from UC based on DEFA5 levels, with a positive predictive value of 96% and an overall diagnostic accuracy of 76.9% [14,15]. Reproduced with permission from Williams AD, et al., PLoS One. 2017 Dec 6;12(12).

DEFA5 as a Potential Tool for Preoperative Risk Stratification

Investigators at Meharry Medical College (MMC) and Vanderbilt University Medical Center (VUMC) are pursuing a translational

strategy centered on human alpha-defensin 5 (DEFA5; also known as HD5) to improve the distinction between UC and CC and address the persistent challenge of IC [14,15,38,39]. DEFA5 can be detected in tissue and serum from patients with cIBD. Early studies have demonstrated promising diagnostic performance, including a reported positive predictive value of 96% and an overall diagnostic accuracy of 76.9% for differentiating CC from UC [14,15]. These findings suggest that DEFA5 may also help reclassify patients initially categorized as having IC [14,15,40,41]. In our view, the potential value of DEFA5 extends beyond its performance as a diagnostic biomarker. Its most important clinical application may be as an additional objective component of preoperative risk assessment. If validated in larger and more diverse populations, a rapid DEFA5-based assay could provide additional information when conventional clinical, endoscopic, histologic, radiologic, and laboratory assessments remain inconclusive. Such information could help identify patients for whom IPAA is appropriate, patients who require further diagnostic evaluation, and patients in whom alternative surgical strategies should be considered. Importantly, we do not suggest that a biomarker should replace multidisciplinary clinical assessment. Rather, DEFA5 should be considered as a potential complement to existing diagnostic pathways.

From Diagnostic Accuracy to Pre-surgical Decision Accuracy

In our opinion, biomarker research in cIBD should move beyond the traditional objective of improving diagnostic accuracy alone. A biomarker may demonstrate excellent sensitivity, specificity, or predictive value without necessarily improving patient outcomes. The more important question is whether the information generated by the biomarker changes a clinically meaningful decision. For patients being considered for IPAA, the relevant outcome is therefore not simply whether DEFA5 improves the classification of UC and CC. The more important question is whether it improves **pre-surgical decision accuracy**.

A clinically useful biomarker could potentially support three different preoperative pathways:

1. Greater confidence in proceeding with IPAA when the overall clinical and biomarker profile supports UC;
2. Additional diagnostic evaluation when the available information remains inconclusive; or
3. Considerations of an alternative surgical strategy when findings raise substantial concern for occult CC.

For appropriately selected patients without significant rectal involvement or active rectal disease, alternatives such as ileorectal anastomosis may be considered. The purpose of improved stratification is not to deny patients restorative surgery, but to better match the surgical procedure to the underlying disease phenotype and associated risks.

Translating DEFA5 from Discovery to Clinical Practice

The translational program involving MMC and VUMC seeks to move DEFA5 from biomarker discovery toward practical clinical application [42-45]. This work has resulted in patented diagnostic methodologies and tools and provides a foundation for the development of an accessible diagnostic platform [42-45]. Ongoing validation of anti-DEFA5 monoclonal antibodies, including clones 1A8 and 4F5, using biopsy specimens obtained during diagnostic endoscopy from a clinical cohort of 230 patient samples, is intended to determine whether these reagents can reliably distinguish UC from CC and improves the classification of patients currently diagnosed with IC [42-46]. The development strategy is guided by the ASSURED framework: Affordable, Sensitive, Specific, User-friendly, Rapid, Robust, Equipment-free, and Deliverable. In our view, this translational emphasis is essential. A clinically important biomarker must ultimately be available in a form that can realistically be incorporated into patient care. Scientific discovery alone is insufficient if the resulting technology cannot be implemented where and when important clinical decisions are made.

The Biological Context: Colonic Ileal Metaplasia

The investigation of colonic ileal metaplasia provides an additional biological context for understanding DEFA5 expression. This metaplastic phenotype has been associated with DEFA5 expression and may represent a histopathology feature associated with CC [15,47]. Further investigation of the relationship among colonic ileal metaplasia, DEFA5 expression, and Crohn’s disease may provide important insight into the biological basis for disease classification. We believe that this biological context is particularly relevant to biomarker development. The most useful clinical biomarkers may emerge when a measurable biological phenomenon can be connected directly to a clearly defined clinical decision. In this setting, that decision is whether sufficient evidence exists to proceed with IPAA.

Diagnostic Epitopes and the Emerging Translational Framework

A new diagnostic epitope associated with cIBD has been officially registered in the international Immune Epitope Database (IEDB) under Reference Number 1047508 [40,45]. This development adds another molecular component to the emerging translational framework for cIBD stratification. In our opinion, the identification of disease-associated epitopes may ultimately contribute to more precise approaches to disease classification, early diagnostic testing and personalized therapeutic monitoring. However, the discovery of a molecular marker should not itself be interpreted as proof of clinical utility. Rigorous validation remains essential.

What Should Be the Next Step?

The most important next phase of DEFA5 research should be prospective clinical validation in the patients for whom diagnostic uncertainty has the greatest consequences. Larger and more diverse cohorts are needed to establish reproducibility and generalizability. The relationship between tissue and circulating DEFA5 levels requires further characterization. Particular attention should be given to patients with IC and patients whose disease phenotype changes over time. However, we believe that future studies should not stop at diagnostic endpoints.

The critical questions are:

- Does DEFA5-based stratification change preoperative decision-making?
- Does it identify patients at increased risk of poor outcomes following IPAA?
- Does it reduce inappropriate pouch construction?
- Does it reduce pouch-related complications and pouch failure?
- Does it improve long-term quality of life?

These outcomes should ultimately determine the clinical value of DEFA5.

Conclusions

The distinction between UC and CC remains one of the most important diagnostic challenges in cIBD. However, its greatest clinical significance may arise when a patient is being considered for IPAA. Our opinion is that the field should move beyond the narrow objective of diagnostic classification and toward a broader objective of risk-informed preoperative decision-making. DEFA5 represents a promising candidate for this approach. Its potential importance lies not simply in its ability to distinguish UC from CC, but in the possibility that it could provide additional objective information before an irreversible surgical pathway is chosen. The ongoing translational work involving biomarker discovery, histopathology, colonic ileal metaplasia, monoclonal antibody development, diagnostic epitope identification, and clinical validation provides a promising framework for addressing this problem. Nevertheless, promising biomarkers must ultimately be judged by their clinical consequences. The most meaningful measure of success will not simply be whether DEFA5 improves diagnostic accuracy. It will be whether it helps surgeons and patients avoid the wrong operation in the wrong patient. If validated through rigorous prospective studies, DEFA5-based testing could become an important component of personalized, risk-informed surgical decision-making in cIBD. The ultimate goal should be

straightforward: to provide better information before IPAA is performed and, in doing so, improve the likelihood that the right operation is selected for the right patient.

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