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Inflammatory Bowel Disease: Historical Perspective, Current Management Strategies & Future Therapeutic Horizons

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Abstract
The two main types of inflammatory bowel disease (IBD), which are defined by persistent gastrointestinal inflammation, are Crohn's disease (CD) and ulcerative colitis (UC). In addition to discussing current management approaches, such as corticosteroids, immunosuppressants, biologics, and surgery intended to achieve mucosal repair and modify disease progression, this study offers a historical perspective on IBD. Problems like adverse effects and therapeutic non-response still exist despite improvements. Precision medicine, which uses genetics, transcriptomics, and gut microbiome studies to predict individual therapy responses, is the way of the future for IBD care. In the upcoming years, more individualized, efficient, and secure patient care may be possible because of new treatments, innovative drug delivery methods, and the incorporation of artificial intelligence and digital health tools.

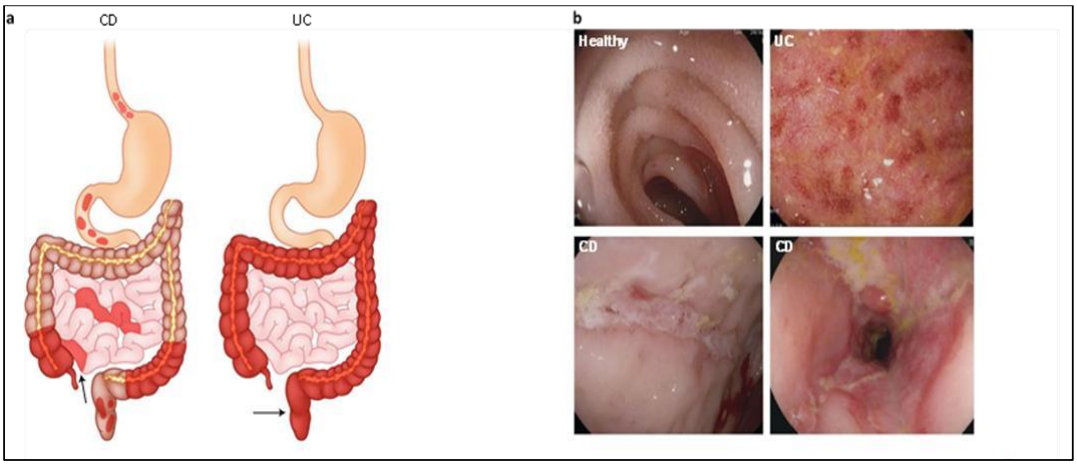
Keywords: Inflammatory Bowel Disease, Crohn's Disease, Ulcerative Colitis, Intestinal Microbiota, Immune Dysregulation, Biologic Therapy, Precision Medicine, Artificial Intelligence

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two most prevalent inflammatory gastrointestinal (GI) illnesses that are classified as inflammatory bowel diseases (IBDs). Mucosal inflammation that begins in the rectum and spreads to the proximal sections of the colon is its defining feature. [1] [2] The existence of 47 loci linked to ulcerative colitis was recently verified by a meta-analysis of six such studies; of these, 19 are unique to ulcerative colitis and 28 are shared with Crohn's disease. [3] In the majority of the world's areas, Crohn's disease has been continuously rising [appendix]. [4] A family history of Crohn's disease is present in about 12% of patients. [5] The most researched environmental factor is cigarette smoking, which is linked to a two-fold increased incidence of Crohn's disease [odds ratio [OR] 1.76; 95% CI 1.40-2.22]. [6] The incidence of Crohn's disease is increased by childhood antibiotic exposure (OR 1.74; 95% CI 1.35-2.23). [7] aspirin, as well as nonsteroidal anti-inflammatory medications, along with aspirin. [8] Oral contraceptives are among the other drugs that may be linked to an elevated risk. [9] Higher intakes of saturated fat and lower intakes of dietary fiber have also been linked to increased risk. [10]

An overview of IBD's history is given in this study, along with a discussion of contemporary treatment approaches and potential future paths, such as precision medicine and new therapeutic developments that could revolutionize IBD care in the years to come.

Fig. 1 Clinical Features of IBD. A) Clinical features of IBD. A. Inflammation in CD (left) has a segmented pattern and frequently affects the terminal ileum [arrow]; in contrast, inflammation in UC (right) usually affects the rectum [arrow] and sometimes the entire colon. b] Endoscopic features of CD (bottom row) and UC (top right) versus those of unaffected intestine (top left): erosions and bleeding (top right), large ulcers (bottom left), and ulcers with stenosis (bottom right) are visible.



HISTORICAL PERSPECTIVE:

The intestinal inflammation that we now know as Crohn's disease was first documented by Morgagni in 1761. [11] It became evident after Koch identified the causal agent of tuberculosis in 1882 that some people had a condition that resembled intestinal tuberculosis but did not have the tubercle bacillus. Reports by Moschowitz and Wilensky (1923 and 1927), Fenwick (1889), Dalziel (1913), Weiner (1914), Goldfarb and Suissman (1931), and others were published before the seminal work of Crohn, Ginzburg, and Oppenheimer [1932] on terminal ileitis. [11, 12] A further description of granulomatous colitis was provided by Lockhart-Mummery and Morson [13]. The first pathologic description of what was then known as simple ulcerative colitis was attributed to Wilkes in 1859. Later, in 1875, Wilkes and Moxon provided a more thorough description of a basic ulcerative colitis condition. [11] IBD prevalence statistics are displayed in Table 2, while incidence rates from a few global geographic locations are displayed in Table 1. Geographical locations historically associated with IBD, such as northern Europe [14,15], the United Kingdom [16,17], and North America [18,19], have generally recorded the greatest incidence rates and prevalence for both Crohn's disease and ulcerative colitis. Nonetheless, studies of rising incidence and prevalence from other parts of the world, including Southern or Central Europe [21, 22], Asia [22, 23], Africa [24], and Latin America [25], highlight that IBD is a dynamic phenomenon. According to Table 1, the incidence rates of Crohn's disease and ulcerative colitis in North America range from 3.1 to 14.6 cases per 100,000 person-years and 2.2 to 14.3 cases per 100,000 person-years, respectively. The prevalence of Crohn's disease varies from 26 to 199 cases per 100,000 people, while that of ulcerative colitis ranges from 37 to 246 cases per 100,000 people (Table 2). IBD was uncommon on other continents in the past, except for South Africa, Australia, and Israel.

Table 1. Incidence Rates of Ulcerative Colitis and Crohn's Disease from Selected Registries

Author[s][reference]	Setting	Case ascertainment	Incidence dates	Incidence of UC	Incidence of CD
North America Pinchbeck *et al.* [18]	Northern Alberta	Population	1981	6	10
Hiatt *et al.* [33]	Northern California	HMO	1980-1981	10.9	7.0
Stowe *et al*. [34]	Monroe County, NY	Hospital	1980-1989	2.3	3.9
Kurata *et al*. [35]	Southern California	HMO, Outpatient HMO, Outpatient	1987-1988 1988	NA NA	3.6 5.4
Loftus *et al*. [36, 37]	Olmsted County, MN	Population	1984-1993	8.3	6.9
Bernstein *et al*. [38]	Manitoba	Population	1989-1994	14.3	14.6
Blanchard *et al*. [39]	Manitoba	Population	1987-1996	15.6	15.6
Europe Shivananda *et al*. [40]	8 N. European cities	Population	1991-1993	11.8	7.0
Shivananda *et al*. [40]	12 S. European cities	Population	1991-1993	8.7	3.9
Scandinavia Bjornsson *et al*. [15]	Iceland	Population	1990-1994	16.5	5.5
Munkholm *et al*. [41]	Copenhagen County	Population	1980-1987	9.2	4.1
Moum *et al*. [43, 44]	S.E. Norway	Population	1990-1993	13.6	5.8
Roin *et al*. [45]	Faroe Isles, Denmark	Population	1981-1999	20.3	3.6
Lapidus *et al*. [46]	Stockholm County	Population	1985-1989	NA	4.9
United Kingdom Rubin *et al*. [17]	North Tees	Population	1985-1994	13.9	8.3
Yapp *et al*. [47]	Cardiff, Wales	Population	1991-1995	NA	5.6
Kyle [16]	N.E. Scotland	Population	1985-1987	NA	9.8

Table 2. Prevalence of Ulcerative Colitis and Crohn's Disease from Selected Registries

Author[s] [reference]	Setting	Case ascertainment	Prevalence date	Prevalence of UC[a]	Prevalence of CD[a]
North-America Pinchbeck *et al*. [18]	Northern Alberta	Population	12/31/1981	37.5	44.4
Kurata *et al*. [35]	Southern California	HMO	1988	NA	26.0
Loftus *et al*. [36, 37]	Olmsted County, MN	Population	1/1/1991	229	144.1
Loftus *et al*. [19]	Olmsted County, MN	Population	1/1/2001	246	162
Bernstein *et al*. [38]	Manitoba	Population	12/31/1994	169.7	198.5
Europe Langholz *et al*. [42]	Copenhagen	Population	12/31/1987	161.2	54
Munkholm *et al*. [41]	N.E. Scotland, United Kingdom	Population	12/31/1988	NA	147
Mate´-Jiminez *et al*. [50]	2 Spanish regions	Hospital	12/31/1988	43.4	19.8
Vucelic *et al*. [20, 53]	Zagreb, Croatia	Population	12/31/1989	21.4	8.3
Trallori *et al*. [54]	Florence, Italy	Population	12/31/1992	121	40
Rubin *et al*. [17]	North Tees, United Kingdom	Population	1/1/1995	243	144
Daiss *et al*. [14]	Tubingen, Germany	Population	12/31/1984	24.8	54.6
Montgomery *et al*. [58]	United Kingdom	Survey	1996	122	214
Asia Fireman *et al*. [59]	Central Israel	Population	1980	55.2	19.5
Grossman *et al*. [60]	Southern Israel	Population	12/31/1985	70.6	NA
Odes *et al*. [55]	Southern Israel	Population	12/31/1992	NA	50.6

Sood *et al*. [23]	Punjab, India	Survey	1999	44.3	NA
Morita *et al*. [57]	Japan	Survey	1991	18.1	5.8
Lee *et al*. [61]	Singapore	Hospital	1985–1996	6.0	3.6
Yang *et al*. [56]	Seoul, Korea	Population	12/31/1997	7.6	NA

IBD's descriptive histology implied that treatment drugs might also target immune activation. Finally, the use of adrenocorticotropic hormone was brought about by the discovery of both acute and chronic inflammatory cells as well as the frequent occurrence of extraintestinal immune-mediated symptoms. corticosteroids [26, 27]. However, the use of corticosteroids to treat IBD has been shown to be a double-edged sword. Research from population-based cohorts indicates that while fewer than half of IBD patients need to be treated with these medications, the requirement for corticosteroids is linked to a worse prognosis, which includes a higher chance of surgery and disability. [28] Mercaptopurine and Azathioprine become part of the IBD arsenal, mostly used to treat steroid-dependent or steroid-refractory patients. Additionally, these substances are believed to be useful in fistulizing Crohn's illness. [29] Methotrexate is a second-line medication that has been demonstrated to be successful in treating steroid-dependent Crohn's disease. Additionally, these substances are believed to be useful in fistulizing Crohn's illness. [29] Methotrexate is a second-line medication that has been demonstrated to be successful in treating steroid-dependent Crohn's disease. This medication is useful for both short-term steroid-free remission induction and long-term remission maintenance. [30] Significant progress has also been made in the realm of surgery. Instead of doing resection, the earliest procedures for Crohn's disease frequently aimed to redirect the fecal stream. Since most Crohn's disease patients may undergo primary anastomosis and resection, this method has long been out of favor despite its effectiveness. The understanding that large margins of resection were ineffective in avoiding disease recurrence was more directly related to providing patients with the best treatment possible. [31] Last but not least, ileal pouch-anal anastomosis, a groundbreaking surgical advancement that offered a much-needed substitute for permanent endileostomy, was developed in the 1980s for patients with ulcerative colitis who needed total proctocolectomy. [32]

CURRENT MANAGEMENT STRATEGIES:

Depending on the disease's phenotype, severity, and patient characteristics, current therapies include pharmaceutical, surgical, nutritional, and supportive approaches. Immunomodulators (thiopurines, methotrexate), TNF-α antagonists, anti-integrin agents (vedolizumab), Janus kinase inhibitors (tofacitinib), and interleukin 12/23 antagonists (ustekinumab). [62] The medical management of adult outpatients with moderate to severe UC is the subject of the first seven questions. The next four questions are about adult patients hospitalized with ASUC, with an emphasis on initial management and rescue medication in situations of corticosteroid-refractory disease. Reading the AGA guideline on the management of mild to moderate UC may help you better understand this concept, which we agree is difficult to define due to inconsistent definitions in clinical practice. [63], The diagnosis of Crohn's disease is based on a mix of endoscopy, radiography, and symptoms. Patients were previously begun on steroids, aminosalicylates, or thiopurines, and only when these treatment modalities had failed [step-up therapy] were they moved on to more effective ones. High rates of surgery indicate that this approach was ineffective in altering the course of the condition. Thus, the approach to treatment changed from only

managing symptoms to halting the disease's course, which causes complications, intestinal damage, and incapacity. Since it is associated with lower rates of relapse and surgical necessity as well as less intestinal damage, endoscopic healing—generally defined as the absence of ulcerations—has become a key treatment target in IBD. [64]

TREATMENT OF IBD

1. Corticosteroids

Guidelines state that steroids [budesonide or prednisone] should be used to treat mild to moderately active illness [65]. Despite being less effective than prednisone, budesonide, a locally active glucocorticosteroid, should be used to reduce systemic adverse effects in cases of localized ileal or ileocecal illness. [66] For all other disease sites, systemic steroids [prednisolone] should be administered. Around 28% of patients develop steroid dependence [67]; budesonide and prednisolone are ineffective at sustaining remission, and given the negative effects of long-term use (such as infections, diabetes, bone loss, and hypertension), steroid withdrawal with a steroid-sparing agent ought to be a primary therapeutic objective. [66, 68, 69]

2. Immunosuppressants

Only for maintenance treatment should thiopurines and methotrexate be taken into consideration. [70, 71] A number of trials have shown that thiopurine use in Crohn's disease has a moderate benefit in maintaining remission and is linked to a decreased requirement for surgery [72, 73] There was no evidence of azathioprine's ability to modify the course of early Crohn's disease in two controlled trials. [75, 74] Additionally, these medications are linked to an elevated risk of non-melanoma skin cancers, lymphoma, myeloid diseases, and urinary tract cancers. [76, 77] Young men [less than 35 years old] and elderly individuals who are more likely to acquire cancer should use thiopurines with caution. Monitoring thiopurine metabolites may be useful in identifying overdose or refractoriness to thiopurine, preferential 6-MMP metabolism, resistance to thiopurines, underdosing, and poor treatment compliance. [78] Methotrexate has been underutilized in IBD despite some indications of efficacy [79, 80], most likely because IBD primarily affects young individuals and is contraindicated in pregnant women. Despite the need for more research to determine its effectiveness in combination therapy, methotrexate is being used more and more to treat Crohn's disease due to a good risk-benefit ratio [81, 82].

3. Nutritional therapy:

In the treatment of Crohn's disease patients who are malnourished or have lost weight, as well as prior to surgery, nutritional support is essential. While there is not enough evidence to support nutrition as a major therapy for adults with Crohn's disease, exclusive enteral nutrition is advised as the first-line treatment for children with the condition in order to induce remission [83, 84]. Research is required; however, interest in dietary therapies is growing.

4. Surgery:

Surgery is an option for patients with refractory medical conditions who either do not tolerate medical therapy, develop problems [such as abscesses or cancer], or both. Similar to this, patients who have obstructive symptoms but no signs of inflammation do not respond well to anti-inflammatory drugs and may require surgical resection. In certain cases, colonic diversion is necessary for symptom control prior to the safe use of anti-TNF medication when severe colonic illness and perianal sepsis coexist. [85]. The choice to use inflammatory drugs may require surgical resection as a result. When perianal sepsis and severe colonic illness coexist, colonic diversion may be necessary to treat symptoms before anti-TNF therapy may be utilized safely. [85] A multidisciplinary team should review the decision to operate and

cover topics such as prophylactic measures against thromboembolic events, optimal nutritional status, patient counselling, and adequate preoperative imaging. [86] The treatment of Crohn's disease is incorporating advances in minimally invasive surgery, which provide better cosmetic results, quicker recovery periods, and shorter hospital stays. [87]

FUTURE THERAPEUTIC HORIZONS IN IBD:

Not with standing notable progress in the treatment of inflammatory bowel disease (IBD), issues like treatment-averse events, lack of response to existing treatments, and variability in disease behavior still exist. As a result, future therapeutic approaches are increasingly concentrated on:

1. Genetics

In CD or UC, more than 250 different single nucleotide polymorphisms have been linked. Only a tiny number of NOD2 variations have been strongly and reliably linked to disease phenotype, including responsiveness to therapy, aside from the link between NOD2 mutations and the emergence of structuring or piercing small-bowel CD-related sequelae. Although individual research has found single gene variations or employed polygenic risk scores to forecast anti-TNF medication response, these findings have not been confirmed in separate cohorts. [88, 89]

2. Serum Biomarkers and Transcriptomics

In order to determine if particular expression patterns predict response or nonresponse, numerous studies have looked at gene expression in tissue or serologic markers. Microarray data was used for colonic samples from two cohorts of UC patients on infliximab treatment by Arijs *et al*. [90]. 53 genes were identified as having differing baseline expressions in the two cohorts between treatment responders and non-responders. Osteoprotegerin (TNFRSF11B), stanniocalcin-1 (STC1), prostaglandin endoperoxide synthase 2 (PTGS2), interleukin-13 receptor alpha 2 (IL-13Rα2), and IL-11 were the top 5 differentially elevated genes. In ileal CD, gene expression data had a worse predictive value when using a similar methodology. [91]. West and associates [92] used a step-by-step method to analyze transcriptome data in order to find treatment response signatures. They found 16 genes that were differentially expressed when comparing intestinal tissue from healthy controls and patients with IBD. Of these, four genes—oncostatin M (OSM), IL-1A, IL-1B, and IL-6—showed at least a two-fold difference and were shared by CD and UC. On endoscopy and histopathology, the expression of both OSM and OSM receptors showed a dose-dependent relationship, gradually rising with the severity of the disease. Compared to 15% of patients in a cluster with low expression, over 90% of individuals in a cluster with high OSM expression at baseline were infliximab refractory. Two other clinical trial cohorts independently confirmed this connection Verstockt *et al*. [93] TREM1 expression in the mucosa and whole blood triggering receptor expressed on myeloid cells 1 (TREM1) was shown to be downregulated in patients who were likely to respond to anti-TNF medication in both CD and UC, with an AUC of around 0.77 to 0.78. TREM1 expression and serum TREM1 levels did not change across vedolizumab or ustekinumab responders and non-responders, indicating that this expression was unique to anti-TNF therapy. On colon biopsies from patients receiving vedolizumab or anti-TNF medication, the same group also did RNA-seq. They discovered that baseline expression of four genes (PIWIL1, MAATS1, RGS13, and DCHS2) may predict endoscopic remission with vedolizumab (with an AUC of 0.79), but not with anti-TNF therapy. [94] In isolated investigations, deeper single-cell transcriptional profiling has also provided useful information for predicting therapy response. Single-cell transcriptomics was used by Martin and associates to analyze ileal samples from CD patients. [95] They discovered that the likelihood of responding to anti-TNF medication was linked to a

cellular module comprised of activated T cells, inflammatory mononuclear phagocytes, stromal cells, and IgG plasma cells [referred to as GIMATS]. Higher GIMATS module expression was found in patients who were resistant to anti-TNF treatment (P=0.02). [95] In a similar vein, Smillie *et al*. [96] showed that UC associated with IL-13Rα2+IL-11+ inflammatory fibroblasts was linked to anti-TNF therapy resistance.

3. Microbiome

An important factor in the pathophysiology of IBD is the gut microbiota. Therefore, it is conceivable that the baseline microbial composition affects the course of the disease, including how well it responds to treatment. Fewer studies have examined many treatment pathways, but a number of studies have shown that the gut microbiota can predict response to each one. Kolho *et al*. [97], in one of the first studies to look at this relationship, showed that faecal calprotectin levels three months after starting anti-TNF treatment were predicted by baseline microbial diversity or resemblance to healthy controls. Sanchis-Artero *et al*.'s study [98]. Faecal bacterium to Escherichia coli ratios were more accurate than calprotectin or symptom-based disease activity assessments at predicting treatment response (AUC, 0.87). Zhou *et al*. [99], in a Chinese cohort of 16 patients treated with infliximab and monitored for 30 weeks, discovered that a number of species differed between treatment responders and non-responders. Predicting response to infliximab was most accurately done by a model that was trained on both faecal calprotectin levels and microbial composition using 16S rRNA sequencing [AUC, 0.92]. We showed that the abundance of two butyrate-producing species, Burkholder ales and Roseburia inulinivorans, differed between participants who responded to therapy and those who did not in a prospective cohort of patients starting vedolizumab treatment at a single establishment. [100] Crucially, at the functional level, responders and non-responders to therapy had different baseline distributions for a number of pathways (13 in CD, 5 in UC). With an AUC of 0.87, an artificial neural network-based model that took into account both functional and compositional alterations in the microbiome predicted early treatment response. An additional independent cohort of 100 patients starting anti-cytokine medication [either anti-TNF or anti-IL-12/23] was then included in this research. [101]. Two separate groups of microorganisms could be identified at baseline. Compared to anti-integrin treatment (41% and 26%, respectively), the response rates to anti-TNF medication at week 14 (72%) or week 52 (65%) were significantly greater among patients assigned to cluster 1. There was no discernible difference between the two treatment arms for cluster 2 individuals. In patients whose microbiome resembled cluster 1, a higher Bai+ operon positivity was linked to higher baseline serum secondary bile acid concentrations, which were associated with a higher likelihood of response to anti-TNF medication. [102]

4. Novel Drug Delivery and Small Molecules

To get around the present administration and toxicity restrictions, research is being done on safer small-molecule medicines (JAK inhibitors, S1P modulators), oral biologic formulations, and targeted delivery systems based on nanomedicine.

5. Artificial Intelligence and Digital Health

AI and machine learning are transforming the treatment of IBD, from guiding endoscopic evaluation and therapy response to forecasting recurrence utilizing biomarkers (such as faecal calprotectin and CRP). Utilizing mobile applications and wearable technology for remote monitoring improves patient-centered care.

CONCLUSION:

Crohn's disease and ulcerative colitis are included in the category of inflammatory bowel disease (IBD),

which has undergone substantial treatment advancements from a poorly understood condition. Although corticosteroids, immunosuppressants, biologics, and surgery are used in contemporary therapeutic strategies to promote mucosal healing and change the course of the disease, problems such as treatment non-response and side effects continue to exist.

Precision medicine is the way of the future for treating IBD, going beyond a one-size-fits-all strategy. Promising indicators to predict individual responses to treatments like vedolizumab and anti-TNF medications are emerging from research into transcriptome signatures, genetic markers, and the gut flora. New hope is also provided by advancements in stem cell therapy, small-molecule medications, and innovative drug delivery methods. Personalized treatment planning and remote patient monitoring could be revolutionized by the combination of digital health tools and artificial intelligence.

In the end, a new era of IBD management one that is safer, more efficient, and highly customized for better patient outcomes is being ushered in by the convergence of these cutting-edge diagnostic and therapeutic approaches.

Abbreviations

1. IBD – Inflammatory Bowel Disease
2. CD – Crohn's Disease
3. UC – Ulcerative Colitis
4. GI – Gastrointestinal
5. OR – Odds Ratio
6. CI – Confidence Interval
7. TNF – Tumor Necrosis Factor
8. JAK – Janus Kinase
9. HMO – Health Maintenance Organization
10. NA – Not Available / Not Applicable
11. AUC – Area Under the Curve
12. OSM – Oncostatin M
13. IL – Interleukin
14. TREM1 – Triggering Receptor Expressed on Myeloid Cells 1
15. RNA-seq – RNA Sequencing
16. GIMATS- (Acronym from the text, refers to a cellular module: activated T cells, inflammatory mononuclear phagocytes, stromal cells, and IgG plasma cells)
17. CRP – C-Reactive Protein
18. S1P – Sphingosine-1-Phosphate
19. AI – Artificial Intelligence
20. ECCO – European Crohn’s and Colitis Organisation
21. ESPGHAN—European Society for Paediatric Gastroenterology, Hepatology and Nutrition
22. HLA – Human Leukocyte Antigen
23. 6-MMP – 6-Methylmercaptopurine (a thiopurine metabolite)
24. STC1 – Stanniocalcin-1
25. PTGS2 – Prostaglandin-Endoperoxide Synthase 2
26. NOD2 – Nucleotide-Binding Oligomerization Domain Containing 2
27. SNP – Single Nucleotide Polymorphism

28. TNFRSF11B – Tumor Necrosis Factor Receptor Superfamily Member 11b (Osteoprotegerin)
29. rRNA – Ribosomal RNA
30. AGA – American Gastroenterological Association
31. ASUC – Acute Severe Ulcerative Colitis
32. MRI – (Implied in context of imaging, not explicitly abbreviated)
33. CT – (Implied in context of imaging, not explicitly abbreviated)

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