REVIEW

Genetics and Therapeutics in Pediatric Ulcerative Colitis: the Past, Present and Future [version 1; peer review: 2 approved]

Luis Sifuentes-Dominguez, Ashish S. Patel

Children's Health, UT Southwestern Medical Center, Dallas, Texas, USA

V1 First published: 29 Feb 2016, 5(F1000 Faculty Rev):240
<https://doi.org/10.12688/f1000research.7440.1>

Latest published: 29 Feb 2016, 5(F1000 Faculty Rev):240
<https://doi.org/10.12688/f1000research.7440.1>

Abstract

Ulcerative colitis (UC) is a relapsing and remitting disease with significant phenotypic and genotypic variability. Though more common in adults, UC is being increasingly diagnosed in childhood. The subsequent lifelong course of disease results in challenges for the patient and physician. Currently, there is no medical cure for UC. Even though surgical removal of the colon can be curative, complications including infertility in females make colectomy an option often considered only when the disease presents with life-threatening complications or when medical management fails. One of the greatest challenges the clinician faces in the care of patients with UC is the inability to predict at diagnosis which patient is going to respond to a specific therapy or will eventually require surgery. This therapeutic conundrum frames the discussion to follow, specifically the concept of individualized or personalized treatment strategies based on genetic risk factors. As we move to therapeutics, we will elucidate traditional approaches and discuss known and novel agents. As we look to the future, we can expect increasing integrated approaches using several scientific disciplines to inform how genetic interactions shape and mold the pathogenesis and therapeutics of UC.

Keywords

Ulcerative colitis, genetic risk factors, therapeutics, personalized treatment strategies

Open Peer Review

Approval Status

	1	2
version 1 29 Feb 2016

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Jeffrey Hyams**, University of Connecticut School of Medicine, Hartford, USA
2. **Francisco Sylvester**, The University of North Carolina at Chapel Hill, Chapel Hill, USA

Any comments on the article can be found at the end of the article.

Corresponding author: Ashish S. Patel (Ashish.patel@childrens.com)

Competing interests: The authors declare that they have no competing interests.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2016 Sifuentes-Dominguez L and Patel AS. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Sifuentes-Dominguez L and Patel AS. **Genetics and Therapeutics in Pediatric Ulcerative Colitis: the Past, Present and Future [version 1; peer review: 2 approved]** F1000Research 2016, 5(F1000 Faculty Rev):240 <https://doi.org/10.12688/f1000research.7440.1>

First published: 29 Feb 2016, 5(F1000 Faculty Rev):240 <https://doi.org/10.12688/f1000research.7440.1>

Ulcerative colitis (UC) is a chronic relapsing and remitting disease characterized by inflammation, ulceration, and bleeding in the large intestine. UC can present with significant phenotypic and genetic variability. This variability results in substantial difficulty as it relates to the appropriate therapeutic approach for an individual patient. We will first investigate the concept of individualized or personalized treatment strategies by describing the current understanding of genetics in pediatric UC. We will then move to the therapeutic discussion, focusing on traditional approaches, known agents in new roles, and novel agents and targets. Our intent will be to frame the therapeutic discoveries of the past, present, and future on the timeline of genetic discovery.

Genetics of pediatric ulcerative colitis

Evolving technologies are allowing us to dissect the genetic architecture of inflammatory bowel disease (IBD) (Figure 1). Early epidemiological observations served as the basis for a genetic model of IBD, and a growing body of evidence continues to support and strengthen this notion. Genetic discoveries over the past century have greatly advanced our understanding of UC pathogenesis. These discoveries have provided great insight into disease-associated pathways and have had a dramatic influence over drug discovery and development.

Interestingly, Crohn's disease (CD) and UC share a large number of the described susceptibility loci, suggesting that they may share a common genetic background. Clinical differences, however, would suggest that different genes and pathways are involved in each disease and thus these differences may explain the discrepant phenotypes and may certainly provide the basis for targeted drug development.

Genetic epidemiology

Clinical recognition of disease clustering in select families has long been appreciated^{1,2}. Estimated IBD prevalence among family members of patients with UC is 7.9% to 12%^{3,4}, with high concordance for disease type. Although these observations may be explained by shared environmental factors in family members, further proof of genetic involvement has come from twin studies that show higher concordance rates of IBD among monozygotic twins. A recent analysis of available twin studies showed a 15.4% concordance rate for UC among monozygotic twins compared to 3.9% in dizygotic counterparts⁵. Yet UC does not exhibit traditional Mendelian inheritance and thus is a complex polygenic disease.

IBD clusters not only in families but also among populations. IBD prevalence is significantly higher in whites than in non-whites, notably in those of European ancestry⁶. Ethnic aggregation is particularly seen in Ashkenazi Jews in whom disease prevalence is highest^{7,8}. On the other hand, disease incidence continues to increase worldwide⁹, particularly in westernized societies, enforcing the concept that gene-environment interactions are at the core of IBD pathogenesis.

Linkage studies

In the latter part of the 20th century, association and linkage disequilibrium studies yielded fruitful evidence of loci associated with IBD susceptibility. The first IBD susceptibility locus was described in 1996¹⁰ and mapped to chromosome 16, where *NOD2* would later be identified as a candidate CD-associated gene^{11,12}. Similar studies followed and genetic heterogeneity of both CD and UC was quickly appreciated. It became apparent that many genes may also participate in the phenotypic expression of UC.

Figure 1. Timeline of genetic discoveries and recent drug developments in IBD. Adapted from Expert Rev Gastroenterol Hepatol. 2009 513–34.

To overcome the limitations of narrow genome coverage of linkage disequilibrium studies in the analysis of polygenic diseases, several key developments would have to occur. As pointed out by Mathew¹³, the creation of dense single nucleotide polymorphism (SNP) libraries, the development of a high-resolution genetic map that allowed measurement of association between SNPs (HapMap), and the advent of high-throughput genotyping methods provided the necessary tools for further discovery of IBD susceptibility loci through genome-wide association studies (GWAS).

The Genome-Wide Association Study era

To study polygenic diseases, GWAS rely on the premise that genome-wide genetic variations that may be associated with a specific disease will occur with greater frequency in subjects with the disease when compared to healthy controls. These associations must withstand rigorous statistical methods. Because signals from individual loci may be very small, GWAS require large patient and control cohorts to establish significance.

More than any other complex polygenic disease, IBD has been the subject of numerous GWAS and meta-analyses^{14–24}. Results from these studies have helped unravel the inner workings of IBD pathophysiology and numerous genes affecting key pathways have been described (relevant pathways discussed below). More recently, meta-analyses combining GWAS and Immunochip data (genotyping chip containing >196,000 polymorphisms)²⁵ have dramatically increased the number of IBD-associated loci.

The first publication using this strategy combined data from 75,000 samples²⁶. This study expanded the known IBD susceptibility loci to 163, with 23 of them UC specific and 110 (67%) shared by both CD and UC. Three important observations were also made by this study. First, IBD shows overlap with other immune-related diseases such as primary immunodeficiencies, spondyloarthropathies, and psoriasis, suggesting a common origin and pathophysiological basis. Second, IBD loci were significantly enriched in genes implicated in susceptibility to mycobacterial diseases, perhaps conserved by evolutionary pressure. Third, a large proportion of loci were found in non-coding regions, adding fuel to the idea that non-coding variation may be responsible for differential expression of complex traits.

A follow-up study using a similar approach incorporated more than 96,000 samples from European, East Asian, Indian, and Iranian populations, increasing the number of susceptibility loci to 200²⁷. Of notable interest was the finding that most loci were shared by all populations studied, implying that causal variants are common, even in ethnically diverse individuals. Admixed populations, such as African-Americans, have also recently been scrutinized using the Immunochip, and previously established loci were replicated in this population as well²⁸.

Current state of ulcerative colitis genetics

A common finding among GWAS and meta-analyses is increased signal enrichment in regions that participate in intestinal immune homeostasis. Functional characterization of genes found in these loci has led to important discoveries in the pathways involved in disease. Below, we describe relevant genes implicated in pathways associated with UC.

HLA genes

Because of their roles in antigen presentation and T-cell priming, HLA gene variants have long been considered prime candidates for IBD susceptibility^{29,30}. Indeed, pre-GWAS era linkage disequilibrium studies first described genetic association of IBD susceptibility to major histocompatibility complex (MHC) regions. Hampered by difficulties inherent to the linkage disequilibrium architecture of the area, susceptibility loci identification was slow³¹. However, all GWAS to date have continued to report a strong association between HLA loci and UC. A recent study performed high-density mapping of the MHC region in over 32,000 patients with IBD³². This study found significant enrichment in MHC class II alleles: HLA DRB1, HLA DQA1, and HLA-DRB1*01:03 in particular were strongly associated with UC. The HLA-DRB1*01:03 allele is of particular interest as it also showed a strong association with CD colitis and other studies have linked it to pancolitic phenotype in UC³³. Goyette also found decreased class II HLA heterozygosity, suggesting that broader colonic antigen recognition is important in protection against UC development.

These associations are especially intriguing for pediatric IBD, since young patients, in particular those less than 8 years of age, are more prone to developing extensive colonic disease³⁴. Two pediatric IBD GWAS studies have replicated findings of HLA polymorphisms with UC susceptibility^{17,18}.

Barrier function

Immune tolerance to food and the normal intestinal microbiota is crucial for the control of intestinal homeostasis. A critical element in maintaining intestinal immune homeostasis is epithelial integrity. In addition, the observation that *MUC2*^{-/-} deficient mice develop spontaneous colitis³⁵ suggests that the intestinal mucus layer contributes to barrier function and colonic immune homeostasis. Epithelial barrier function in UC is impaired³⁶ and active UC is characterized by mucin depletion.

Not surprisingly, polymorphisms associated with UC have been found in genes controlling key aspects of barrier function. These include polymorphisms in *ECM1*, believed to control epithelial basement membrane integrity^{37,38}. SNPs in the *CDH1* locus, encoding the adherens junction protein E-cadherin required for tight junction formation, *HNF4a*, responsible for epithelial differentiation, and *LAMB1*, encoding the β 1 subunit of basement membrane laminin, have also been identified¹⁴ and replicated³⁹. Finally, polymorphisms in *GNAI2*, associated with tight junction assembly via interactions with Zo-1 and Src, have recently been described⁴⁰.

Unfolded protein response

The unfolded protein response (UPR) is a stress response of the endoplasmic reticulum (ER) aimed at maintaining cellular homeostasis, especially in highly secretory cells such as Paneth cells and goblet cells. ER stress has been linked to environmental influences and loss or dysregulation of the UPR leads to activation of apoptotic pathways. The intestinal surface is the largest epithelium in contact with the environment, so it is not surprising that genes controlling the UPR pathway have been associated with IBD pathogenesis. Bertolotti *et al.* reported that mice lacking IRE1 β expression, a component of the UPR, develop exacerbated dextran sulfate sodium

(DSS)-induced colitis⁴¹. Human UPR-associated polymorphisms have also been described. Kaser *et al.* reported associations of *XBPI* variants, a transcription factor involved in the UPR, with development of UC⁴². Similarly, susceptibility-associated variants in *PTPN2*, a protein tyrosine phosphatase linked to UPR and autophagosome formation^{43,44}, have also been described^{40,45}.

Interleukin-23

The interleukin (IL)-23 pathway plays a key role in expansion and differentiation of T helper (T_H) and innate immune cells. Abnormalities in the IL-23 signaling pathway have been linked to development of UC in several cohorts²³. Other components of the pathway such as JAK2 and TYK2 have also been linked to disease pathogenesis³⁷. The importance of this pathway in regulating pro-inflammatory effects seen in IBD is highlighted by the clinical improvement seen in patients with CD when treated with ustekinumab, a monoclonal antibody directed against the p40 subunit shared by IL-12 and IL-23⁴⁶. The ongoing phase 3 international multicenter study UNIFI aims to evaluate this monoclonal antibody in maintenance and induction of patients with moderate to severe UC⁴⁷.

Other T_H17-centric polymorphisms have been associated with UC, including those in *NFKB1Z*, a regulator of T_H17 cell development, and *AHR*, a transcription factor involved in T_H17 cytokine expansion²⁷. Additional important polymorphisms in blocks containing immune regulatory genes have been described. For a detailed review please refer to the article by Khor *et al.*⁴⁸.

Genome-Wide Association Study limitations and missing heritability

Results from meta-analyses employing Immunochip indicate that the expected UC disease variance from susceptibility loci is only 8.2%. Therefore, there is a wide gap in the expected disease heritability, a problem termed “missing heritability”. One approach to tackling the missing heritability problem in IBD is the study of patients with single gene disorders with large effects. These monogenic forms of IBD are highly penetrant and cluster in young children, the very early onset IBD group (VEOIBD). Indeed, numerous single gene disorders have been recently described and include mutations in *ADAM17*, *NCF2*, *NCF4*, *TTC7A*, *IL-10*, and *XIAP*^{49–54}.

Next-generation sequencing

Although GWAS have dramatically influenced our understanding of complex diseases, one limitation of such studies is that they neglect contribution from rare variants, those with minor allele frequencies less than 5%. High effect rare risk variants missed by GWAS may be contained within known IBD susceptibility loci. Two studies have sought to identify causal functionally relevant genetic variants contained within IBD susceptibility loci by employing deep next-generation sequencing. Results from these studies pointed to three new mutations associated with UC. While variants in *CARD9* and *IL23R* were protective, a variant in *RNF186*, a RING ubiquitin ligase, was found to confer risk^{55,56}. In addition to reporting novel associations with IBD risk, these studies provide new insight into future methodological strategies for gene discovery in IBD.

Implications for translation

One of the most promising aspects of genetics is the use of genetic markers to help inform clinical decision-making. In this regard, IBD genetics has made significant strides.

Diagnosis

Currently, pediatric UC diagnosis is based on aggregate clinical, endoscopic, imaging, and histopathological findings as suggested by North American and European working groups^{57,58}. The rapid pace of discovery of UC-associated genetic variants suggests that genetic diagnosis is quickly unfolding. To date, UC-specific diagnostic approaches utilizing genetic expression analysis from colonic biopsies^{59,60}, composite genetic risk scores⁶¹, and combined serological and genetic markers⁶² have shown promise, yet application of these tools has yet to invade day-to-day clinical practice. The VEOIBD age group is an exception. As monogenic forms of IBD cluster in this age group, exome and targeted gene chips are increasingly being suggested and used in the genetic diagnosis of VEOIBD^{63,64}.

Genotype-phenotype correlations

The best-described genotype-phenotype associations in IBD are *NOD2* variants and ileal CD^{65–67}. Recent evidence has also pointed to UC-associated polymorphisms and phenotype associations. MHC-associated variants are of notable interest. As mentioned earlier, polymorphisms in the MHC region have been associated with extensive colonic involvement and colectomy^{33,68}. Recently, the international IBD Genetics Consortium (IIBDGC) reported the results of the largest genotype-phenotype study to date, incorporating data from more than 34,000 IBD patients. Results pointed to three loci associated with disease subphenotype: *NOD2*, MHC, and 3p21. MHC loci were again associated with extensive colonic involvement⁶⁹.

Prognosis

The ability to predict disease course at diagnosis as well as early identification of patients who will develop severe and medically refractory UC may result in changes in treatment algorithms.

Haritunians *et al.* developed a risk score utilizing a GWAS approach in a well-characterized cohort of patients with medically refractory UC. A modeled risk score using 46 SNPs explained 48% of the variance for colectomy risk in the population studied, with a sensitivity of 79% and a specificity of 86%. Further, this study confirmed associations of severe UC with SNPs within the MHC region, as well as SNPs in *TNFSF15*, *IL-10*, *IL-12B*, 12q15, *ZPF90*, *KIF1A*, and *GSDML/ORMDL3*⁷⁰. A study using the same strategy incorporated data from 703 UC patients from 40 sites within the IIBDGC. This study replicated an association between rs2403456 (11p15.3) with medically refractory, severe UC⁷¹.

In order to identify genetic predictors of response to biologic therapy, Arijs *et al.* studied colonic mucosal gene expression signatures from two cohorts of anti-tumor necrosis factor (anti-TNF)-naïve UC patients receiving biologic induction with infliximab.

Microarray-based colonic biopsy profiling was used to develop a prediction response probe set. Five genes – osteoprotegerin, stanniocalcin-1, prostaglandin-endoperoxide synthase 2, IL-13 receptor alpha-2, and IL-11 – were found to be differentially expressed in responders versus non-responders. The genes identified are involved in adaptive immune response signaling and TNF pathways⁷². Of note, osteoprotegerin has been suggested as a stool marker for diagnosis and assessment of treatment response in pediatric UC^{73,74}.

Therapeutics

The intent of our discussion previously on genetics and UC is seeded in the hope that personalization of therapies based on genetics will change disease outcomes and potentially lead us to a cure of UC in the future. Though corticosteroids and mesalamine remain the mainstays of current therapy, the following sections will outline other options within our armamentarium with a special focus on the resurgence of drugs like methotrexate, the debate around antibiotics, and a brief look at potential newcomers.

Methotrexate, an immunosuppressant developed in 1948, has been widely used initially in leukemia and now in oncologic, rheumatologic, and autoimmune diseases. Methotrexate inhibits lymphocyte proliferation as a folate antagonist⁷⁵. Methotrexate has recently garnered attention as an alternative oral or subcutaneous agent in the treatment of UC, particularly in patients who have failed or become intolerant to 6-mercaptopurine (6-MP) or infliximab therapy. Two Cochrane reviews from 2014 and 2015, assessing induction and remission success, respectively, showed no significant difference between methotrexate and placebo in patients with UC^{76,77}. Currently there are two large prospective trials evaluating the potential of methotrexate in UC. The Comparison of Methotrexate versus Placebo in Corticosteroid-dependent UC (METEOR) trial has completed enrollment and is closed. The Methotrexate Response In the Treatment of UC (MERIT-UC) trial is currently recruiting as multicenter prospective trials comparing methotrexate to placebo in patients who are steroid dependent or who failed 6-MP or infliximab therapy.

Antibiotics present an interesting clinical discussion in the setting of UC. Dysbiosis is present in patients with IBD, even at diagnosis. Previous work has shown that in patients with acute severe colitis, those with a more diverse microbiome at diagnosis respond better to steroid therapy versus those with a less diverse microbiome needing salvage medical therapy⁷⁸. A recent paper by Turner *et al.* described the use of an oral broad-spectrum antibiotic cocktail (metronidazole, amoxicillin, doxycycline, and vancomycin [MADOV]) in pediatric UC patients who had failed other traditional therapies (steroids, oral immunosuppressants including azathioprine and tacrolimus, and anti-TNF agents, both infliximab and adalimumab). A total of 7 out of 15 patients achieved complete short-term remission with the antibiotic cocktail. A larger pediatric randomized controlled trial to assess this intervention is underway⁷⁹. Additionally, in the discussion of dysbiosis, fecal microbial transplantation (FMT) has been proposed in the treatment of UC. There are several active recruiting studies ongoing; however, the only published data on the subject by Kunde *et al.* suggested a promising response in a pilot study of 10 children over 1 month⁸⁰.

The latest treatment for UC is a humanized monoclonal antibody named vedolizumab. An $\alpha 4\beta 7$ integrin blocker, the medication targets inflammation by blocking the recruitment of lymphocytes specifically to the gut without interfering with trafficking to the central nervous system. This gut-specific feature makes it unique to the current group of therapeutics by isolating the affected area of involvement and subsequently decreasing the systemic effects⁸¹.

Novel therapeutic targets continue to be developed and there are multiple drugs in different phases of development (Figure 2).

Treatment algorithms continue to evolve in UC and are increasingly utilizing predictive models to determine the best potential therapies for an individual patient. An integral part of the predictive model will be our continued advancement of the understanding of genetic data. Additionally, clinical variables have been recognized to impact the determination of initial therapy and as a predictive

Figure 2. New therapeutic agents for ulcerative colitis. New therapeutic agents for ulcerative colitis with drug targets in parenthesis^{47,83–90}.

tool for choosing a more aggressive therapy in patients at risk for a poor outcome. Schechter *et al.* described the importance of the PUCAI score at baseline and moreover at the 3-month mark. The 3-month PUCAI was most predictive of sustained response and steroid-free remission at 1 year. Several other variables, including elevated C-reactive protein (CRP), hypoalbuminemia, and anemia have also been described in other studies, though not found to be significant in the Schechter model⁵².

Cure

Although a cure for polygenic complex diseases is still a hope, lessons from VEOIBD provide proof of principle that, indeed, certain well-characterized monogenic forms of IBD may be amenable to cure. Glocker *et al.* described a series of patients with infantile fistulizing enterocolitis resulting from mutations in *IL-10RA* and *IL-10RB*. Allogeneic stem cell transplantation in one of the patients resulted in complete resolution of gastrointestinal symptoms⁵⁰. Similarly, Worthey *et al.* described a patient with onset of fistulizing colonic disease at 15 months of age. Exome sequencing of this patient pointed to hemizygous missense mutation affecting *XIAP*; cord blood hematopoietic stem cell transplantation led to disease remission⁵².

Conclusions

The future of UC genetics looks bright, but there are a few hurdles to overcome. Current GWAS/ImmunoChip approaches are likely to have exhausted loci discovery in European ancestry populations;

further multi-ethnic studies might lead to fruitful discoveries. Fine mapping and next-generation sequencing will provide additional tools for IBD-associated gene discoveries and may help explain some of the missing heritability in IBD, as well as provide a basis for functional studies that will in turn pave the way for targeted drug development.

Lastly, it is important to consider how genetics will influence daily clinical practice in the years to come and how clinicians will choose to adopt newer technologies. Certainly, the large amount of data associated with genetic information may be daunting to the general gastroenterology practitioner, and it is the job of researchers, IBD specialists, and working guideline groups to provide tools for daily clinical use.

As we look to the future, we can expect increasing integrated approaches using several biological disciplines to inform how genetic interactions shape and mold the pathogenesis and therapeutics of UC.

Competing interests

The authors declare that they have no competing interests.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

- Allchin WH: **A Discussion on "Ulcerative Colitis.": Introductory Address.** *Med Sect.* 1909; 2(Med Sect): 59–75.
[PubMed Abstract](#) | [Free Full Text](#)
- Kirsner JB, Spencer JA: **Family Occurrences of Ulcerative Colitis, Regional Enteritis, and Ileocolitis.** *Ann Intern Med.* 1963; 59(2): 133–144.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Childers RE, Eluri S, Vazquez C, *et al.*: **Family history of inflammatory bowel disease among patients with ulcerative colitis: a systematic review and meta-analysis.** *J Crohns Colitis.* 2014; 8(11): 1480–1497.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Monsén U, Broström O, Nordenvall B, *et al.*: **Prevalence of inflammatory bowel disease among relatives of patients with ulcerative colitis.** *Scand J Gastroenterol.* 1987; 22(2): 214–218.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Brant SR: **Update on the heritability of inflammatory bowel disease: the importance of twin studies.** *Inflamm Bowel Dis.* 2011; 17(1): 1–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Ahmad T, Satsangi J, McGovern D, *et al.*: **Review article: the genetics of inflammatory bowel disease.** *Aliment Pharmacol Ther.* 2001; 15(6): 731–748.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Roth MP, Petersen GM, McElree C, *et al.*: **Geographic origins of Jewish patients with inflammatory bowel disease.** *Gastroenterology.* 1989; 97(4): 900–904.
[PubMed Abstract](#)
- Yang H, McElree C, Roth MP, *et al.*: **Familial empirical risks for inflammatory bowel disease: differences between Jews and non-Jews.** *Gut.* 1993; 34(4): 517–524.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Molodecky NA, Soon IS, Rabi DM, *et al.*: **Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review.** *Gastroenterology.* 2012; 142(1): 46–54.e42; quiz e30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Hugot JP, Laurent-Puig P, Gower-Rousseau C, *et al.*: **Mapping of a susceptibility locus for Crohn's disease on chromosome 16.** *Nature.* 1996; 379(6568): 821–823.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Ogura Y, Bonen DK, Inohara N, *et al.*: **A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease.** *Nature.* 2001; 411(6837): 603–606.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Hugot JP, Chamaillard M, Zouali H, *et al.*: **Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease.** *Nature.* 2001; 411(6837): 599–603.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Mathew CG: **New links to the pathogenesis of Crohn disease provided by genome-wide association scans.** *Nat Rev Genet.* 2008; 9(1): 9–14.
[PubMed Abstract](#) | [Publisher Full Text](#)
- UK IBD Genetics Consortium, Barrett JC, Lee JC, *et al.*: **Genome-wide association study of ulcerative colitis identifies three new susceptibility loci, including the HNF4A region.** *Nat Genet.* 2009; 41(12): 1330–1334.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Duerr RH, Taylor KD, Brant SR, *et al.*: **A genome-wide association study identifies IL23R as an inflammatory bowel disease gene.** *Science.* 2006; 314(5804): 1461–1463.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Franke A, Balschun T, Sina C, *et al.*: **Genome-wide association study for ulcerative colitis identifies risk loci at 7q22 and 22q13 (IL17REL).** *Nat Genet.* 2010; 42(4): 292–294.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Imielinski M, Baldassano RN, Griffiths A, *et al.*: **Common variants at five new loci associated with early-onset inflammatory bowel disease.** *Nat Genet.* 2009; 41(12): 1335–1340.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kugathasan S, Baldassano RN, Bradfield JP, *et al.*: **Loci on 20q13 and 21q22 are**

- associated with pediatric-onset inflammatory bowel disease. *Nat Genet.* 2008; 40(10): 1211–1215.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
19. **F** Libioulle C, Louis E, Hansoul S, *et al.*: Novel Crohn disease locus identified by genome-wide association maps to a gene desert on 5p13.1 and modulates expression of *PTGER4*. *PLoS Genet.* 2007; 3(4): e58.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 20. **F** McGovern DP, Gardet A, Törkvi L, *et al.*: Genome-wide association identifies multiple ulcerative colitis susceptibility loci. *Nat Genet.* 2010; 42(4): 332–337.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 21. McGovern DP, Jones MR, Taylor KD, *et al.*: *Fucosyltransferase 2 (FUT2)* non-secretor status is associated with Crohn's disease. *Hum Mol Genet.* 2010; 19(17): 3468–3476.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 22. **F** Rioux JD, Xavier RJ, Taylor KD, *et al.*: Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. *Nat Genet.* 2007; 39(5): 596–604.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 23. Silverberg MS, Cho JH, Rioux JD, *et al.*: Ulcerative colitis-risk loci on chromosomes 1p36 and 12q15 found by genome-wide association study. *Nat Genet.* 2009; 41(2): 216–220.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 24. **F** Wellcome Trust Case Control Consortium: Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature.* 2007; 447(7145): 661–678.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 25. Cortes A, Brown MA: Promise and pitfalls of the Immunochip. *Arthritis Res Ther.* 2011; 13(1): 101.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 26. **F** Jostins L, Ripke S, Weersma RK, *et al.*: Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature.* 2012; 491(7422): 119–124.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 27. **F** Liu JZ, van Sommeren S, Huang H, *et al.*: Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet.* 2015; 47(9): 979–986.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 28. Huang C, Haritunians T, Okou DT, *et al.*: Characterization of genetic loci that affect susceptibility to inflammatory bowel diseases in African Americans. *Gastroenterology.* 2015; 149(6): 1575–1586.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 29. Asakura H, Tsuchiya M, Aiso S, *et al.*: Association of the human lymphocyte-DR2 antigen with Japanese ulcerative colitis. *Gastroenterology.* 1982; 82(3): 413–418.
[PubMed Abstract](#)
 30. Bergman L, Lindblom JB, Säfwenberg J, *et al.*: HL-A frequencies in Crohn's disease and ulcerative colitis. *Tissue Antigens.* 1976; 7(3): 145–150.
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. Stokkers PC, Reitsma PH, Tytgat GN, *et al.*: HLA-DR and -DQ phenotypes in inflammatory bowel disease: a meta-analysis. *Gut.* 1999; 45(3): 395–401.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 32. **F** Goyette P, Boucher G, Mallon D, *et al.*: High-density mapping of the MHC identifies a shared role for *HLA-DRB1*01:03* in inflammatory bowel diseases and heterozygous advantage in ulcerative colitis. *Nat Genet.* 2015; 47(2): 172–179.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 33. Satsangi J, Welsh KI, Bunce M, *et al.*: Contribution of genes of the major histocompatibility complex to susceptibility and disease phenotype in inflammatory bowel disease. *Lancet.* 1996; 347(9010): 1212–1217.
[PubMed Abstract](#) | [Publisher Full Text](#)
 34. Biank V, Broeckel U, Kugathasan S: Pediatric inflammatory bowel disease: clinical and molecular genetics. *Inflamm Bowel Dis.* 2007; 13(11): 1430–1438.
[PubMed Abstract](#) | [Publisher Full Text](#)
 35. **F** Van der Sluis M, De Koning BA, De Bruijn AC, *et al.*: Muc2-deficient mice spontaneously develop colitis, indicating that MUC2 is critical for colonic protection. *Gastroenterology.* 2006; 131(1): 117–129.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 36. Schmitz H, Barmeyer C, Fromm M, *et al.*: Altered tight junction structure contributes to the impaired epithelial barrier function in ulcerative colitis. *Gastroenterology.* 1999; 116(2): 301–309.
[PubMed Abstract](#) | [Publisher Full Text](#)
 37. Anderson CA, Massey DC, Barrett JC, *et al.*: Investigation of Crohn's disease risk loci in ulcerative colitis further defines their molecular relationship. *Gastroenterology.* 2009; 136(2): 523–9.e3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 38. **F** Fisher SA, Tremelling M, Anderson CA, *et al.*: Genetic determinants of ulcerative colitis include the *ECM1* locus and five loci implicated in Crohn's disease. *Nat Genet.* 2008; 40(6): 710–712.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 39. van Sommeren S, Visschedijk MC, Festen EA, *et al.*: HNF4 α and CDH1 are associated with ulcerative colitis in a Dutch cohort. *Inflamm Bowel Dis.* 2011; 17(8): 1714–1718.
[PubMed Abstract](#) | [Publisher Full Text](#)
 40. **F** Anderson CA, Boucher G, Lees CW, *et al.*: Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nat Genet.* 2011; 43(3): 246–252.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 41. **F** Bertolotti A, Wang X, Novoa I, *et al.*: Increased sensitivity to dextran sodium sulfate colitis in IRE1 β -deficient mice. *J Clin Invest.* 2001; 107(5): 585–593.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 42. **F** Kaser A, Lee AH, Franke A, *et al.*: *XBP1* links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease. *Cell.* 2008; 134(5): 743–756.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 43. Bettaieb A, Liu S, Xi Y, *et al.*: Differential regulation of endoplasmic reticulum stress by protein tyrosine phosphatase 1B and T cell protein tyrosine phosphatase. *J Biol Chem.* 2011; 286(11): 9225–9235.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 44. Scharl M, Wójcik KA, Becker HM, *et al.*: Protein tyrosine phosphatase nonreceptor type 2 regulates autophagosome formation in human intestinal cells. *Inflamm Bowel Dis.* 2012; 18(7): 1287–1302.
[PubMed Abstract](#) | [Publisher Full Text](#)
 45. **F** Franke A, Balschun T, Karlens TH, *et al.*: Replication of signals from recent studies of Crohn's disease identifies previously unknown disease loci for ulcerative colitis. *Nat Genet.* 2008; 40(6): 713–715.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 46. **F** Sandborn WJ, Gasink C, Gao LL, *et al.*: Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med.* 2012; 367(16): 1519–1528.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 47. Janssen Research & Development, LLC: A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Participants With Moderately to Severely Active Ulcerative Colitis (UNIFI). In: Vol In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US), NLM Identifier: NCT02407236. 2000.
[Reference Source](#)
 48. Khor B, Gardet A, Xavier RJ: Genetics and pathogenesis of inflammatory bowel disease. *Nature.* 2011; 474(7351): 307–317.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 49. Matute JD, Arias AA, Wright NA, *et al.*: A new genetic subgroup of chronic granulomatous disease with autosomal recessive mutations in p40^{phox} and selective defects in neutrophil NADPH oxidase activity. *Blood.* 2009; 114(15): 3309–3315.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 50. **F** Glocker EO, Kotlarz D, Boztug K, *et al.*: Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N Engl J Med.* 2009; 361(21): 2033–2045.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 51. Blaydon DC, Biancheri P, Di WL, *et al.*: Inflammatory skin and bowel disease linked to *ADAM17* deletion. *N Engl J Med.* 2011; 365(16): 1502–1508.
[PubMed Abstract](#) | [Publisher Full Text](#)
 52. **F** Worthey EA, Mayer AN, Syverson GD, *et al.*: Making a definitive diagnosis: successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. *Genet Med.* 2011; 13(3): 255–262.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 53. Avitzur Y, Guo C, Mastropalo LA, *et al.*: Mutations in tetratricopeptide repeat domain 7A result in a severe form of very early onset inflammatory bowel disease. *Gastroenterology.* 2014; 146(4): 1028–1039.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 54. **F** Muise AM, Xu W, Guo CH, *et al.*: NADPH oxidase complex and IBD candidate gene studies: identification of a rare variant in *NCF2* that results in reduced binding to RAC2. *Gut.* 2012; 61(7): 1028–1035.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 55. **F** Beaudoin M, Goyette P, Boucher G, *et al.*: Deep resequencing of GWAS loci identifies rare variants in *CARD9*, *IL23R* and *RNF186* that are associated with ulcerative colitis. *PLoS Genet.* 2013; 9(9): e1003723.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 56. **F** Rivas MA, Beaudoin M, Gardet A, *et al.*: Deep resequencing of GWAS loci identifies independent rare variants associated with inflammatory bowel disease. *Nat Genet.* 2011; 43(11): 1066–1073.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 57. Levine A, Koletzko S, Turner D, *et al.*: ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr.* 2014; 58(6): 795–806.
[PubMed Abstract](#)
 58. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; Colitis Foundation of America, Bousvaros A, *et al.*: Differentiating ulcerative colitis from Crohn disease in children and young adults: report of a working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America. *J Pediatr Gastroenterol Nutr.* 2007; 44(5): 653–674.
[PubMed Abstract](#) | [Publisher Full Text](#)
 59. von Stein P, Lofberg R, Kuznetsov NV, *et al.*: Multigene analysis can discriminate between ulcerative colitis, Crohn's disease, and irritable bowel syndrome.

- Gastroenterology*. 2008; **134**(7): 1869–81; quiz 2153–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
60. Janczewska I, Kapraali M, Saboonchi F, *et al.*: Clinical application of the multigene analysis test in discriminating between ulcerative colitis and Crohn's disease: a retrospective study. *Scand J Gastroenterol*. 2012; **47**(2): 162–169.
[PubMed Abstract](#) | [Publisher Full Text](#)
 61. Ananthakrishnan AN, Huang H, Nguyen DD, *et al.*: Differential effect of genetic burden on disease phenotypes in Crohn's disease and ulcerative colitis: analysis of a North American cohort. *Am J Gastroenterol*. 2014; **109**(3): 395–400.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 62. Plevy S, Silverberg MS, Lockton S, *et al.*: Combined serological, genetic, and inflammatory markers differentiate non-IBD, Crohn's disease, and ulcerative colitis patients. *Inflamm Bowel Dis*. 2013; **19**(6): 1139–1148.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 63. Kammermeier J, Drury S, James CT, *et al.*: Targeted gene panel sequencing in children with very early onset inflammatory bowel disease—evaluation and prospective analysis. *J Med Genet*. 2014; **51**(11): 748–755.
[PubMed Abstract](#) | [Publisher Full Text](#)
 64. Uhlig HH, Schwerdt T, Koletzko S, *et al.*: The diagnostic approach to monogenic very early onset inflammatory bowel disease. *Gastroenterology*. 2014; **147**(5): 990–1007.e3.
[PubMed Abstract](#) | [Publisher Full Text](#)
 65. Abreu MT, Taylor KD, Lin YC, *et al.*: Mutations in *NOD2* are associated with fibrostenosing disease in patients with Crohn's disease. *Gastroenterology*. 2002; **123**(3): 679–688.
[PubMed Abstract](#) | [Publisher Full Text](#)
 66. Brant SR, Picco MF, Achkar JP, *et al.*: Defining complex contributions of *NOD2/CARD15* gene mutations, age at onset, and tobacco use on Crohn's disease phenotypes. *Inflamm Bowel Dis*. 2003; **9**(5): 281–289.
[PubMed Abstract](#) | [Publisher Full Text](#)
 67. Newman B, Silverberg MS, Gu X, *et al.*: *CARD15* and *HLA DRB1* alleles influence susceptibility and disease localization in Crohn's disease. *Am J Gastroenterol*. 2004; **99**(2): 306–315.
[PubMed Abstract](#) | [Publisher Full Text](#)
 68. de la Concha EG, Fernandez-Arquero M, Lopez-Nava G, *et al.*: Susceptibility to severe ulcerative colitis is associated with polymorphism in the central MHC gene *IKBL*. *Gastroenterology*. 2000; **119**(6): 1491–1495.
[PubMed Abstract](#) | [Publisher Full Text](#)
 69. **F** Cleyneen I, Boucher G, Jostins L, *et al.*: Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study. *Lancet*. 2016; **387**(10014): 156–67.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 70. **F** Haritunians T, Taylor KD, Targan SR, *et al.*: Genetic predictors of medically refractory ulcerative colitis. *Inflamm Bowel Dis*. 2010; **16**(11): 1830–1840.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 71. Radford-Smith G, Doecke JD, Lees CW, *et al.*: Su1762 Clinical and Molecular Characterization of Medically Refractory Acute, Severe Colitis: Preliminary Results From the International Inflammatory Bowel Disease Genetics Consortium (IBDGC) Immunochip Study. *Gastroenterology*. 2015; **144**(5, Supplement 1): S-470.
[Publisher Full Text](#)
 72. **F** Arijis I, Li K, Toedter G, *et al.*: Mucosal gene signatures to predict response to infliximab in patients with ulcerative colitis. *Gut*. 2009; **58**(12): 1612–1619.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 73. **F** Sylvester FA, Turner D, Draghi A 2nd, *et al.*: Fecal osteoprotegerin may guide the introduction of second-line therapy in hospitalized children with ulcerative colitis. *Inflamm Bowel Dis*. 2011; **17**(8): 1726–1730.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 74. **F** Skinner A, Lerer T, Wyzga N, *et al.*: S1225 Fecal Osteoprotegerin: A Marker for Pediatric Ulcerative Colitis At Diagnosis - a Pilot Study. *Gastroenterology*. 2008; **134**(4, Supplement 1): A-205.
[Publisher Full Text](#) | [F1000 Recommendation](#)
 75. Herfarth HH, Osterman MT, Isaacs KL, *et al.*: Efficacy of methotrexate in ulcerative colitis: failure or promise. *Inflamm Bowel Dis*. 2010; **16**(8): 1421–1430.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 76. **F** Chande N, MacDonald JK, McDonald JW: Methotrexate for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2007; **4**: CD006618.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 77. **F** Wang Y, MacDonald JK, Vandermeer B, *et al.*: Methotrexate for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2015; **8**: CD007560.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 78. **F** Michail S, Durbin M, Turner D, *et al.*: Alterations in the gut microbiome of children with severe ulcerative colitis. *Inflamm Bowel Dis*. 2012; **18**(10): 1799–1808.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 79. **F** Turner D, Levine A, Kolho KL, *et al.*: Combination of oral antibiotics may be effective in severe pediatric ulcerative colitis: a preliminary report. *J Crohns Colitis*. 2014; **8**(11): 1464–1470.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 80. **F** Kunde S, Pham A, Bonczyk S, *et al.*: Safety, tolerability, and clinical response after fecal transplantation in children and young adults with ulcerative colitis. *J Pediatr Gastroenterol Nutr*. 2013; **56**(6): 597–601.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 81. **F** Feagan BG, Rutgeerts P, Sands BE, *et al.*: Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013; **369**(8): 699–710.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 82. **F** Schechter A, Griffiths C, Gana JC, *et al.*: Early endoscopic, laboratory and clinical predictors of poor disease course in paediatric ulcerative colitis. *Gut*. 2015; **64**(4): 580–588.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 83. Snapper SB: Low Dose IL-2 for Ulcerative Colitis. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US), NLM Identifier: NCT02200445. 2000.
[Reference Source](#)
 84. Kyowa Hakkō Kirin Pharma, Inc: Study of a Monoclonal Antibody KHK4083 in Moderate Ulcerative Colitis. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US), NLM Identifier: NCT02647866. 2000.
[Reference Source](#)
 85. Mayer L, Sandborn WJ, Stepanov Y, *et al.*: Anti-IP-10 antibody (BMS-936557) for ulcerative colitis: a phase II randomised study. *Gut*. 2014; **63**(3): 442–450.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 86. Pfizer: Long-Term Safety Of PF-00547659 In Ulcerative Colitis (TURANDOT II). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US), NLM Identifier: NCT01771809. 2000.
[Reference Source](#)
 87. Celgene Corporation: Efficacy and Safety Study of Apremilast to Treat Active Ulcerative Colitis (UC). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US), NLM Identifier: NCT02289417. 2000.
[Reference Source](#)
 88. Danese S, Rudziński J, Brandt W, *et al.*: Tralokinumab for moderate-to-severe UC: a randomised, double-blind, placebo-controlled, phase IIa study. *Gut*. 2015; **64**(2): 243–249.
[PubMed Abstract](#) | [Publisher Full Text](#)
 89. Herrlinger KR, Diculescu M, Fellermann K, *et al.*: Efficacy, safety and tolerability of vidofludimus in patients with inflammatory bowel disease: the ENTRANCE study. *J Crohns Colitis*. 2013; **7**(8): 636–643.
[PubMed Abstract](#) | [Publisher Full Text](#)
 90. Pfizer: Long-Term Study Of CP-690,550 In Subjects With Ulcerative Colitis (OCTAVE). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US), NLM Identifier: NCT01470612. 2000.
[Reference Source](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. Francisco Sylvester

Department of Pediatrics, Division of Gastroenterology, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Competing Interests: No competing interests were disclosed.

2. Jeffrey Hyams

Division of Pediatric Gastroenterology, University of Connecticut School of Medicine, Hartford, CT, 06106, USA

Competing Interests: Advisory Board: Janssen, AbbVie, Celgene. Consultant: Takeda, Astra Zeneca, Genentech, Lilly, UCB.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research