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(54) **Title:** ILEAL POUCH-ANAL ANASTOMOSIS (IPAA) FACTORS IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

(57) **Abstract:** A common long term problem after Ileal Pouch-Anal Anastomosis (IPAA) is the inflammation of the pouch, called pouchitis. Additionally, about 5-10% of patients undergoing IPAA with a diagnosis of ulcerative colitis at the time of surgery are subsequently diagnosed with Crohn's disease. In one embodiment, the present invention provides methods of diagnosing and predicting susceptibility to pouchitis after IPAA by detecting the presence or absence of pANCA and/or Cbir1 Flagellin expression.

ILEAL POUCH-ANAL ANASTOMOSIS (IPAA) FACTORS IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

FIELD OF THE INVENTION

The invention relates generally to the fields of inflammation and autoimmunity and autoimmune disease and, more specifically, to ileal pouch-anal anastomosis and genetic methods for diagnosing and treating Inflammatory Bowel Disease.

BACKGROUND

All publications herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

Crohn's disease (CD) and ulcerative colitis (UC), the two common forms of idiopathic inflammatory bowel disease (IBD), are chronic, relapsing inflammatory disorders of the gastrointestinal tract. Each has a peak age of onset in the second to fourth decades of life and prevalences in European ancestry populations that average approximately 100-150 per 100,000 (D.K. Podolsky, N Engl J Med 347, 417 (2002); E.V. Loftus, Jr., Gastroenterology 126, 1504 (2004)). Although the precise etiology of IBD remains to be elucidated, a widely accepted hypothesis is that ubiquitous, commensal intestinal bacteria trigger an inappropriate, overactive, and ongoing mucosal immune response that mediates intestinal tissue damage in genetically susceptible individuals (D.K. Podolsky, N Engl J Med 347, 417 (2002)). Genetic factors play an important role in IBD pathogenesis, as evidenced by the increased rates of IBD in Ashkenazi Jews, familial aggregation of IBD, and increased concordance for IBD in monozygotic compared to dizygotic twin pairs (S. Vermeire, P. Rutgeerts, Genes Immun 6, 637 (2005)). Moreover, genetic analyses have linked IBD to specific genetic variants,

especially CARD15 variants on chromosome 16q12 and the IBD5 haplotype (spanning the organic cation transporters, SLC22A4 and SLC22A5, and other genes) on chromosome 5q31 (S. Vermeire, P. Rutgeerts, Genes Immun 6, 637 (2005); J.P. Hugot et al., Nature 411, 599 (2001); Y. Ogura et al., Nature 411, 603 (2001); J.D. Rioux et al., Nat Genet 29, 223 (2001); V.D. Peltekova et al., Nat Genet 36, 471 (2004)). CD and UC are thought to be related disorders that share some genetic susceptibility loci but differ at others.

A procedure used to treat patients with chronic ulcerative colitis is the ileal pouch-anal anastomosis (IPAA). This is a surgical procedure designed for instances where the entire colon and rectum needs to be removed so that a permanent stoma, opening for collecting waste, can be avoided. Specifically, a pouch is made out of remaining small intestine, which is then pulled through the rectal muscle and sewn to the skin around the anus. After the procedure, when the patient feels the urge to defecate, the rectal muscle contracts and the pouch empties through the anal sphincter.

A common long term problem after IPAA is the inflammation of the pouch, called pouchitis. Additionally, about 5-10% of patients undergoing IPAA with a diagnosis of UC at the time of surgery are subsequently diagnosed with CD. Thus, there is a need in the art to develop predictors of outcome after IPAA.

SUMMARY OF THE INVENTION

Various embodiments provide methods of diagnosing susceptibility to acute pouchitis after ileal pouch anal anastomois for ulcerative colitis in an individual, comprising determining the presence or absence of positive antibody expression of pANCA and Cbir1 in the individual, determining the presence or absence of a low immune reactivity of pANCA and Cbir1, where a low immune reactivity is less than 100 EU/ml in a serum sample taken from the individual, and diagnosing susceptibility to acute pouchitis after ileal pouch anal anastomosis for ulcerative colitis in an individual based upon the presence of a positive antibody expression of pANCA and Cbir1 and the presence of a low immune reactivity of pANCA and Cbir1.

Other embodiments provide methods of diagnosing susceptibility to chronic pouchitis after ileal pouch anal anastomosis for ulcerative colitis in an individual, comprising determining the presence or absence of positive antibody expression of pANCA in the individual, determining the presence or absence of a high immune reactivity of pANCA, where a high immune reactivity is more than 100 EU/ml in a serum sample taken from the individual, and diagnosing susceptibility to chronic pouchitis after ileal pouch anal anastomosis for ulcerative colitis in an individual based upon the presence of a positive antibody expression of pANCA and the presence of a high immune reactivity of pANCA.

Other embodiments provide methods of diagnosing susceptibility to Crohn's Disease after ileal pouch anal anastomosis for ulcerative colitis in an individual, comprising determining the presence or absence of a high immune reactivity of ASCA relative to a healthy subject, determining the presence or absence of a family history of Crohn's Disease, and diagnosing susceptibility to Crohn's Disease after ileal pouch anal anastomosis for ulcerative colitis based upon the presence of a high immune reactivity of ASCA and the presence of a family history of Crohn's Disease.

Other embodiments provide methods of treating pouchitis in an individual, comprising determining the presence of positive antibody expression of pANCA and Cbir1 in the individual, determining the presence of a low immune reactivity of pANCA and Cbir1, where a low immune reactivity is less than 100 EU/ml in a serum sample taken from the individual, and treating the pouchitis in the individual.

Additional embodiments provide methods of treating pouchitis in an individual, comprising determining the presence of positive antibody expression of pANCA in the individual, determining the presence of a high immune reactivity of pANCA, wherein a high immune reactivity is more than 100 EU/ml in a serum sample taken from the individual, and treating the pouchitis in the individual.

Various embodiments also provide methods of treating Crohn's Disease after ileal pouch anal anastomosis for ulcerative colitis in an individual, comprising determining the presence of ASCA sero-positivity, and determining the presence of a

family history of Crohn's Disease, and treating the Crohn's Disease after ileal pouch anal anastomosis for ulcerative colitis.

Other embodiments provide methods of determining the prognosis of ulcerative colitis after ileal pouch anal anastomosis ("IPAA") for ulcerative colitis in an individual, comprising, after IPAA, determining the presence or absence of positive antibody expression of pANCA and Cbir1 in the individual, determining the presence or absence of a low immune reactivity of pANCA and Cbir1, where a low immune reactivity is less than 100 EU/ml in a serum sample taken from the individual, and prognosing a complicated case of ulcerative colitis if the individual demonstrates the presence of positive antibody expression of pANCA and Cbir1 and the presence of a low immune reactivity of pANCA and Cbir1. In other embodiments, the complicated case of ulcerative colitis further comprises acute pouchitis.

Various embodiments also provide methods of determining the prognosis of ulcerative colitis after ileal pouch anal anastomosis ("IPAA") for ulcerative colitis in an individual, comprising, after IPAA, determining the presence or absence of positive antibody expression of pANCA in the individual, determining the presence or absence of a high immune reactivity of pANCA in the individual, where a high immune reactivity is more than 100 EU/ml in a serum sample taken from the individual, and prognosing a complicated case of ulcerative colitis if the individual demonstrates the presence of positive antibody expression of pANCA and the presence of a high immunity of pANCA. In other embodiments, the complicated case further comprises chronic pouchitis.

Other features and advantages of the invention will become apparent from the following detailed description, taken in conjunction with the accompanying drawing, which illustrate, by way of example, various embodiments of the invention.

DESCRIPTION OF THE INVENTION

All references cited herein are incorporated by reference in their entirety as though fully set forth. Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Singleton *et al.*, *Dictionary of Microbiology and*

Molecular Biology 3rd ed., J. Wiley & Sons (New York, NY 2001); March, *Advanced Organic Chemistry Reactions, Mechanisms and Structure 5th ed.*, J. Wiley & Sons (New York, NY 2001); and Sambrook and Russel, *Molecular Cloning: A Laboratory Manual 3rd ed.*, Cold Spring Harbor Laboratory Press (Cold Spring Harbor, NY 2001), provide one skilled in the art with a general guide to many of the terms used in the present application.

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described.

"SNP" as used herein means single nucleotide polymorphism.

"Haplotype" as used herein refers to a set of single nucleotide polymorphisms (SNPs) on a gene or chromatid that are statistically associated.

As used herein, the term "biological sample" means any biological material from which nucleic acid molecules can be prepared. As non-limiting examples, the term material encompasses whole blood, plasma, saliva, cheek swab, or other bodily fluid or tissue that contains nucleic acid.

As used herein, a "family history" means information concerning disorders of those individuals who are direct relatives of a patient, evaluated in an attempt to find out if the patient has hereditary tendencies toward particular diseases. As an example, a family history of Crohn's Disease may be evaluated by multivariate Cox proportional hazards model.

I. Both Preoperative pANCA and Cbir1 Flagellin Expression in Ulcerative Colitis (UC) Patients Influence Pouchitis Development After Ileal Pouch-Anal Anastomosis (IPAA)

As disclosed herein, the inventors assessed the association of preoperative Cbir1 flagellin and pANCA expression on AP or CP development after IPAA for UC. Patients were prospectively assessed for the development of clinically and

endoscopically proven AP (antibiotic responsive) or CP (antibiotic dependent or refractory to antibiotic therapy). Sera obtained at time of colectomy in 238 colitis patients were analyzed for ANCA and Cbir using ELISA. pANCA+ patients were substratified into high-level (>100 EU/ml) and lower-level (<100 EU/ml) groups.

As further disclosed herein, there were 171 pANCA+ patients (72%) and 46 Cbir1+ patients (19%). After a median follow-up of 47 months (range, 3-153 mos), 72 patients (30%) developed pouchitis. Median time to diagnosis of pouchitis was 7 months (range, 1-116 mos). Pouchitis developed in 36% of pANCA+ patients vs. 16% of pANCA- patients (p=0.005), 46% of Cbir1+ patients vs. 26% of Cbir1- patients (p=0.02), and 54% of 35 pANCA +/Cbir1+ patients vs. 31% of 136 pANCA+/Cbir1- patients (p=0.02). AP was seen in 43 patients (18%) and CP seen in 29 patients (12%). AP developed in 37 pANCA+ patients (22%) vs. 6 pANCA- patients (9%) (p=0.02), and 12 Cbir1+ patients (26%) vs. 31 Cbir1- patients (16%) (p=0.1). Overall pANCA and Cbir1 were not associated with CP development. Twenty-one patients (12%) were high-level (HL) pANCA+ and 150 patients (88%) were lower-level (LL) pANCA+. Although AP was not influenced by pANCA level, AP was seen in 38% of LL pANCA +/Cbir1+ patients vs. 18% LL pANCA +/Cbir- patients (p=0.03). CP was seen in 29% of HL pANCA+ patients vs. 11% of LL pANCA+ patients (p=0.03). There was no significant difference in CP incidence between HL pANCA+/Cbir+ patients (50%) and LL pANCA +/Cbir- patients (20%) (p=0.3).

As further disclosed herein, both pANCA and Cbir1 expression are associated with pouchitis after IPAA. AP is influenced by both lower-level pANCA+ expression and Cbir1, whereas CP appears to be linked solely to high-level pANCA+ expression. These unique serologic patterns suggest that changes in reactivity to microbial antigens may manifest as different forms of pouchitis after IPAA.

In one embodiment, the present invention provides a method of determining susceptibility to acute pouchitis after ileal pouch anal anastomois for ulcerative colitis in an individual, by determining the presence or absence of positive antibody expression of pANCA and Cbir1 in the individual, determining the presence or absence of a low immune reactivity of pANCA and Cbir1, and diagnosing susceptibility to acute pouchitis

after ileal pouch anal anastomosis for ulcerative colitis in an individual based upon the presence of a positive antibody expression of pANCA and Cbir1 and the presence of a low immune reactivity of pANCA and Cbir1. In another embodiment, the present invention provides a method of prognosing ulcerative colitis after ileal pouch anal anastomosis for ulcerative colitis in an individual, by determining the presence or absence of positive antibody expression of pANCA and Cbir1 in the individual, determining the presence or absence of a low immune reactivity of pANCA and Cbir1, and prognosing ulcerative colitis after ileal pouch anal anastomosis for ulcerative colitis, where the presence of a positive antibody expression of pANCA and Cbir1 and the presence of a low immune reactivity of pANCA and Cbir1 is indicative of acute pouchitis. In another embodiment, the present invention provides a method of treating ulcerative colitis by determining the determining the presence of positive antibody expression of pANCA and Cbir1 in the individual, determining the presence of a low immune reactivity of pANCA and Cbir1, and treating the ulcerative colitis.

II. A Prospective Analysis of Predictive Factors for the Diagnosis of Crohn's Disease After Ileal Pouch-Anal Anastomosis for Ulcerative Colitis

As disclosed herein, the inventors evaluated the association of preoperative clinical and serologic factors with CD after IPAA in UC. 238 consecutive patients with UC undergoing IPAA at a tertiary referral center were prospectively enrolled into a longitudinally updated database. Demographic and clinical factors were tabulated immediately after surgery. Serum drawn before surgery was assayed for the IBD-associated antibodies anti-Saccharomyces-cerevisiae (ASCA IgG and IgA), anti-outer membrane porin C (OmpC), anti-CBir1 flagellin, and perinuclear antineutrophil cytoplasmic antibody (pANCA) using ELISA. CD was defined by inflammation involving the small-bowel mucosa proximal to the ileal pouch or when a pouch fistula or other perianal complication developed more than 3 months after ileostomy closure. Clinical and serologic predictors were compared using univariate and time-dependent multivariate methods.

As further disclosed herein, sixteen of 238 patients (7%) were diagnosed with CD; 14 underwent IPAA for refractory disease and 2 had surgery for dysplasia. Median time to CD diagnosis was 5 months (range, 1-41 months); median follow-up was 41 months (1-153 months). CD was diagnosed on the basis of afferent ileal limb disease (n=12) and new perianal disease (n=4). Univariate predictors of CD with a p-value $\leq$0.15 used in the multivariate model included: family history of CD, pre-colectomy platelet count, sero-positivity for ASCA-IgA and pANCA. Multivariate Cox proportional hazards model identified family history of CD (hazard ratio 8.1, 95% confidence interval (CI) 2.6 – 24.9, p<0.001) and ASCA-IgA sero-positivity (hazard ratio 3.4, 95% CI 1.1 - 10.5, p=0.03) as the 2 significant factors predictive of CD after IPAA. CD developed in only 8 of 198 (4%) patients without these predictors versus 8 of 40 (20%) in those with at least one of these factors (p=0.002).

As further disclosed herein, patients with UC who have a family history of CD and/or are ASCA-IgA sero-positive before surgery are more likely to be diagnosed with CD after IPAA.

In one embodiment, the present invention provides methods of diagnosing and/or predicting susceptibility to Crohn's Disease in an individual after ileal pouch anal anastomosis by determining the presence or absence in the individual of a family history of Crohn's Disease and/or a high immune reactivity of ASCA relative to a healthy individual, where the presence of a family history of Crohn's Disease and/or a high immune reactivity of ASCA is indicative of susceptibility to Crohn's Disease. In another embodiment, the present invention provides methods of prognosis of ulcerative colitis in an individual by determining the presence or absence in the individual of a family history of Crohn's Disease and/or a high immune reactivity of ASCA relative to a healthy individual, where the presence of a family history of Crohn's Disease and/or a high immune reactivity is indicative of Crohn's Disease after ileal pouch anal anastomosis.

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and

materials described. For purposes of the present invention, the following terms are defined below.

EXAMPLES

The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. One skilled in the art may develop equivalent means or reactants without the exercise of inventive capacity and without departing from the scope of the invention.

Example 1

Both Preoperative pANCA and Cbir1 Flagellin Expression in Ulcerative Colitis (UC) Patients Influence Pouchitis Development After Ileal Pouch-Anal Anastomosis (IPAA)

Although most studies of pouchitis after IPAA for UC consider acute pouchitis (AP) and chronic pouchitis (CP) to be a single entity, several lines of evidence suggest that they are distinct disease processes. Antibody responses to microbial antigens define different groups of patients with IBD. Preoperative high-level pANCA (perinuclear antineutrophil cytoplasmic antibody) expression is associated with CP but not AP development. The association of serum responses to Cbir1 flagellin with AP or CP is unknown.

The inventors assessed the association of preoperative Cbir1 flagellin and pANCA expression on AP or CP development after IPAA for UC. Patients were prospectively assessed for the development of clinically and endoscopically proven AP (antibiotic responsive) or CP (antibiotic dependent or refractory to antibiotic therapy). Sera obtained at time of colectomy in 238 colitis patients were analyzed for ANCA and Cbir using ELISA. pANCA+ patients were substratified into high-level (>100 EU/ml) and lower-level (<100 EU/ml) groups.

There were 171 pANCA+ patients (72%) and 46 Cbir1+ patients (19%). After a median follow-up of 47 months (range, 3-153 mos), 72 patients (30%) developed pouchitis. Median time to diagnosis of pouchitis was 7 months (range, 1-116 mos). Pouchitis developed in 36% of pANCA+ patients vs. 16% of pANCA- patients (p=0.005), 46% of Cbir1+ patients vs. 26% of Cbir1- patients (p=0.02), and 54% of 35 pANCA +/Cbir1+ patients vs. 31% of 136 pANCA+/Cbir1- patients (p=0.02). AP was seen in 43 patients (18%) and CP seen in 29 patients (12%). AP developed in 37 pANCA+ patients (22%) vs. 6 pANCA- patients (9%) (p=0.02), and 12 Cbir1+ patients (26%) vs. 31 Cbir1- patients (16%) (p=0.1). Overall pANCA and Cbir1 were not associated with CP development. Twenty-one patients (12%) were high-level (HL) pANCA+ and 150 patients (88%) were lower-level (LL) pANCA+. Although AP was not influenced by pANCA level, AP was seen in 38% of LL pANCA +/Cbir1+ patients vs. 18% LL pANCA +/Cbir- patients (p=0.03). CP was seen in 29% of HL pANCA+ patients vs. 11% of LL pANCA+ patients (p=0.03). There was no significant difference in CP incidence between HL pANCA+/Cbir+ patients (50%) and LL pANCA +/Cbir- patients (20%) (p=0.3).

Both pANCA and Cbir1 expression are associated with pouchitis after IPAA. AP is influenced by both lower-level pANCA+ expression and Cbir1, whereas CP appears to be linked solely to high-level pANCA+ expression. These unique serologic patterns suggest that changes in reactivity to microbial antigens may manifest as different forms of pouchitis after IPAA.

Example 2

A Prospective Analysis of Predictive Factors for the Diagnosis of Crohn's Disease After Ileal Pouch-Anal Anastomosis for Ulcerative Colitis

About 5% to 10% of patients undergoing ileal-pouch-anal anastomosis (IPAA) with a diagnosis of ulcerative colitis (UC) at the time of surgery are subsequently diagnosed with Crohn's disease (CD). Predictors for CD post-IPAA have not been prospectively assessed. In this prospective study, the association of preoperative clinical and serologic factors with CD after IPAA in UC was evaluated.

238 consecutive patients with UC undergoing IPAA at a tertiary referral center were prospectively enrolled into a longitudinally updated database. Demographic and clinical factors were tabulated immediately after surgery. Serum drawn before surgery was assayed for the IBD-associated antibodies anti-Saccharomyces-cerevisiae (ASCA IgG and IgA), anti-outer membrane porin C (OmpC), anti-CBir1 flagellin, and perinuclear antineutrophil cytoplasmic antibody (pANCA) using ELISA. CD was defined by inflammation involving the small-bowel mucosa proximal to the ileal pouch or when a pouch fistula or other perianal complication developed more than 3 months after ileostomy closure. Clinical and serologic predictors were compared using univariate and time-dependent multivariate methods.

Sixteen of 238 patients (7%) were diagnosed with CD; 14 underwent IPAA for refractory disease and 2 had surgery for dysplasia. Median time to CD diagnosis was 5 months (range, 1-41 months); median follow-up was 41 months (1-153 months). CD was diagnosed on the basis of afferent ileal limb disease (n=12) and new perianal disease (n=4). Univariate predictors of CD with a p-value $\leq$0.15 used in the multivariate model included: family history of CD, pre-colectomy platelet count, sero-positivity for ASCA-IgA and pANCA. Multivariate Cox proportional hazards model identified family history of CD (hazard ratio 8.1, 95% confidence interval (CI) 2.6 – 24.9, p<0.001) and ASCA-IgA sero-positivity (hazard ratio 3.4, 95% CI 1.1 -10.5, p=0.03) as the 2 significant factors predictive of CD after IPAA. CD developed in only 8 of 198 (4%) patients without these predictors versus 8 of 40 (20%) in those with at least one of these factors (p=0.002).

Patients with UC who have a family history of CD or are ASCA-IgA sero-positive before surgery are more likely to be diagnosed with CD after IPAA.

While the description above refers to particular embodiments of the present invention, it should be readily apparent to people of ordinary skill in the art that a number of modifications may be made without departing from the spirit thereof. The presently disclosed embodiments are, therefore, to be considered in all respects as illustrative and not restrictive. One skilled in the art will recognize many methods and

materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described. Furthermore, one of skill in the art would recognize that the invention can be applied to various inflammatory conditions and disorders and autoimmune diseases besides that of inflammatory bowel disease. It will also be readily apparent to one of skill in the art that the invention can be used in conjunction with a variety of phenotypes, such as serological markers, additional genetic variants, biochemical markers, abnormally expressed biological pathways, and various clinical manifestations.

CLAIMS

1. A method of diagnosing susceptibility to acute pouchitis after ileal pouch anal anastomois for ulcerative colitis in an individual, comprising:

determining the presence or absence of positive antibody expression of pANCA and Cbir1 in the individual;

determining the presence or absence of a low immune reactivity of pANCA and Cbir1, wherein a low immune reactivity is less than 100 EU/ml in a serum sample taken from the individual; and

diagnosing susceptibility to acute pouchitis after ileal pouch anal anastomosis for ulcerative colitis in an individual based upon the presence of a positive antibody expression of pANCA and Cbir1 and the presence of a low immune reactivity of pANCA and Cbir1.

2. A method of diagnosing susceptibility to chronic pouchitis after ileal pouch anal anastomosis for ulcerative colitis in an individual, comprising:

determining the presence or absence of positive antibody expression of pANCA in the individual;

determining the presence or absence of a high immune reactivity of pANCA, wherein a high immune reactivity is more than 100 EU/ml in a serum sample taken from the individual; and

diagnosing susceptibility to chronic pouchitis after ileal pouch anal anastomosis for ulcerative colitis in an individual based upon the presence of a positive antibody expression of pANCA and the presence of a high immune reactivity of pANCA.

3. A method of diagnosing susceptibility to Crohn's Disease after ileal pouch anal anastomosis for ulcerative colitis in an individual, comprising:

determining the presence or absence of a high immune reactivity of ASCA relative to a healthy subject;

determining the presence or absence of a family history of Crohn's Disease; and

diagnosing susceptibility to Crohn's Disease after ileal pouch anal anastomosis for ulcerative colitis based upon the presence of a high immune reactivity of ASCA and the presence of a family history of Crohn's Disease.

4. A method of treating pouchitis in an individual, comprising:

determining the presence of positive antibody expression of pANCA and Cbir1 in the individual;

determining the presence of a low immune reactivity of pANCA and Cbir1, wherein a low immune reactivity is less than 100 EU/ml in a serum sample taken from the individual; and

treating the pouchitis in the individual.

5. A method of treating pouchitis in an individual, comprising:

determining the presence of positive antibody expression of pANCA in the individual;

determining the presence of a high immune reactivity of pANCA, wherein a high immune reactivity is more than 100 EU/ml in a serum sample taken from the individual; and

treating the pouchitis in the individual.

6. A method of treating Crohn's Disease after ileal pouch anal anastomosis for ulcerative colitis in an individual, comprising:

determining the presence of ASCA sero-positivity; and

determining the presence of a family history of Crohn's Disease; and

treating the Crohn's Disease after ileal pouch anal anastomosis for ulcerative colitis.

7. A method of determining the prognosis of ulcerative colitis after ileal pouch anal anastomosis ("IPAA") for ulcerative colitis in an individual, comprising, after IPAA:

determining the presence or absence of positive antibody expression of pANCA and Cbir1 in the individual;

determining the presence or absence of a low immune reactivity of pANCA and Cbir1, wherein a low immune reactivity is less than 100 EU/ml in a serum sample taken from the individual; and

prognosing a complicated case of ulcerative colitis if the individual demonstrates the presence of positive antibody expression of pANCA and Cbir1 and the presence of a low immune reactivity of pANCA and Cbir1.

8. The method of claim 7, wherein the complicated case of ulcerative colitis further comprises acute pouchitis.

9. A method of determining the prognosis of ulcerative colitis after ileal pouch anal anastomosis ("IPAA") for ulcerative colitis in an individual, comprising, after IPAA:

determining the presence or absence of positive antibody expression of pANCA in the individual;

determining the presence or absence of a high immune reactivity of pANCA in the individual, wherein a high immune reactivity is more than 100 EU/ml in a serum sample taken from the individual; and

prognosing a complicated case of ulcerative colitis if the individual demonstrates the presence of positive antibody expression of pANCA and the presence of a high immunity of pANCA.

10. The method of claim 9, wherein the complicated case of ulcerative colitis further comprises chronic pouchitis.