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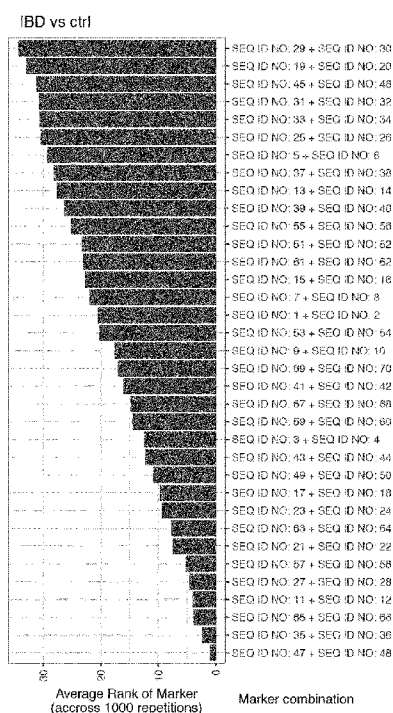
(71) Applicants: **UNIVERSITY OF COPENHAGEN** [DK/DK]; Nørregade 10, 1165 Copenhagen K (DK). **REGION HOVEDSTADEN V/HERLEV HOSPITAL** [DK/DK]; Herlev Ringvej 75, 2730 Herlev (DK).(72) Inventors: **SANDELIN, Albin Gustav**; Østerbrogade 64 3. tv., 2100 Copenhagen Ø (DK). **BOYD, Mette**; Flakholmen 8, 3., 2720 Vanløse (DK). **THODBERG, Malte**; Tagensvej 104, 1. th., 2200 Copenhagen N (DK). **VITEZIC, Morana**; Istedgade 95, 5. th., 1650 Copenhagen V (DK). **BORNHOLDT LANGE, Jette**; Kikhanebakken 28, 2840 Holte (DK). **VITTING-SEERUP, Kristoffer**; Gråspurvej 49, 3. th., 2400 Copenhagen NV (DK).**BJERRUM, Jacob**; Luftmarinegade 122, 1432 Copenhagen K (DK). **HAAGEN NIELSEN, Ole**; Søllerødvej 48, 2840 Holte (DK).(74) Agent: **HØIBERG P/S**; Adelgade 12, 1304 Copenhagen K (DK).

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(54) Title: MARKERS FOR DIAGNOSING INFLAMMATORY BOWEL DISEASES

FIG. 9



(57) Abstract: The present invention relates to genomic regions which are useful markers for determining whether a subject suffers from an inflammatory bowel disease, such as ulcerative colitis or Crohn's disease, or is healthy. Also disclosed are useful primers for measuring expression levels of said markers, as well as computer-implemented methods.

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Markers for diagnosing inflammatory bowel diseases

Technical field

The present invention relates to genomic regions which are useful markers for determining whether a subject suffers from an inflammatory bowel disease, such as ulcerative colitis or Crohn's disease, or is healthy. Also disclosed are useful primers for measuring expression levels of said markers, as well as computer-implemented methods.

Background

Inflammatory bowel disease (IBD) is an umbrella term for a range of chronic idiopathic disorders of which ulcerative colitis (UC) and Crohn's disease (CD) constitute the two major entities, both with an increasing incidence and prevalence worldwide affecting up to 0.5 % in the Western world. UC is characterized by mucosal inflammation of the colon, whereas CD may affect all layers of the intestine throughout the gastrointestinal tract (Fig.1A). The distinction between CD and UC is critical for correct medication and surgery, yet the diagnosis is challenging. Currently, at least 10-15% of patients are classified as 'IBD unclassified'.

Typically, diagnosis of IBDs such as ulcerative colitis or Crohn's disease is based on visual inspection of the gut through endoscopy, and histology assessment of pinch biopsies taken in the same colonoscopy, but can it also include radiology, x-ray and microbiology-based methods. These methods are time-consuming and assessment of the symptoms can be subjective. There is a need for easier methods which are quantitative and reliable, i.e. having high specificity, sensitivity and accuracy, and which can be performed routinely.

Summary

Here, a genome-wide RNA profiling method that sequences the 5' ends of RNAs (CAGE) was applied on biopsies from the descending colon from 94 IBD patients and controls, providing a genome-wide map of transcription start sites (TSSs) across individuals with and without IBD. From this set, we identified TSSs that diagnose inflammatory bowel diseases such Crohn's disease or ulcerative colitis with an accuracy of 85%, using qPCR to measure RNA expression, where the prediction method was trained on one cohort and evaluated in another independent cohort.

Provided herein are improved methods for diagnosing IBD and particularly for discriminating between UC and CD with a high level of accuracy. Correct diagnosis of IBD patients is important since the treatments for UC and CD are not the same.

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Provided herein is a method of diagnosing an inflammatory bowel disease, comprising the steps of

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a. providing a sample from a subject suffering from or suspected of suffering from an inflammatory bowel disease such as ulcerative colitis or Crohn's disease;

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b. analysing the expression profiles of at least 2 markers, such as at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at least 10 markers in said sample, wherein the markers are selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104 and SEQ ID NO: 105,

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thereby determining whether the subject is healthy or suffers from an inflammatory bowel disease such as ulcerative colitis or Crohn's disease.

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Also provided is a method of identifying a group of genomic regions having different expression profiles in a healthy subject and in a subject suffering from inflammatory bowel disease, the method comprising the steps of:

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- (i) providing a first sample from a healthy subject, having a first set of transcripts together representing a first transcriptome;
- (ii) providing a second sample from a subject suffering from inflammatory bowel disease, having a second set of transcripts together representing a second transcriptome;
- (iii) optionally extracting transcripts from the first and the second samples;

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- (iv) measuring and comparing the levels of at least part of the first set of transcripts and at least part of the second set of transcripts;
- (v) identifying the genomic regions for which the levels of at least part of the first set of transcripts and at least part of the second set of transcripts are different;

thereby identifying a group of genomic regions having different expression profiles in a healthy subject and in a subject suffering from inflammatory bowel disease.

A method of identifying a group of genomic regions having a first expression profile in a healthy subject, a second expression profile in a subject suffering from Crohn's disease, and a third expression profile in a subject suffering from ulcerative colitis, wherein at least two of the first, second and third expression profiles are different, the method comprising the steps of:

- (i) providing a first sample from a healthy subject, having a first set of transcripts together representing a first transcriptome;
- (ii) providing a second sample from a subject suffering from Crohn's disease, having a second set of transcripts together representing a second transcriptome;
- (iii) providing a third sample from a subject suffering from ulcerative colitis, having a third set of transcripts together representing a third transcriptome;
- (iv) optionally extracting transcripts from the first, the second and the third samples;
- (v) measuring and comparing the levels of at least part of the first set of transcripts, at least part of the second set of transcripts and at least part of the third set of transcripts;
- (vi) identifying the genomic regions for which the levels of at least two of said at least part of the first set of transcripts and at least part of the second set of transcripts and at least part of the third set of transcripts are different;

thereby identifying a group of genomic regions having different expression profiles in a healthy subject, in a subject suffering from Crohn's disease, and in a subject suffering from ulcerative colitis.

Also provided is a method of identifying a group of genomic regions having a first expression profile in a healthy subject, a second expression profile in a subject suffering from Crohn's disease, and a third expression profile in a subject suffering

from ulcerative colitis, wherein at least two of the first, second and third expression profiles are different, the method comprising the steps of:

- (i) providing a first sample from a healthy subject, having a first set of transcripts together representing a first transcriptome;
 - 5 (ii) providing a second sample from a subject suffering from Crohn's disease, having a second set of transcripts together representing a second transcriptome;
 - (iii) providing a third sample from a subject suffering from ulcerative colitis, having a third set of transcripts together representing a third transcriptome;
 - 10 (iv) optionally extracting transcripts from the first, the second and the third samples;
 - (v) measuring and comparing the levels of at least part of the first set of transcripts, at least part of the second set of transcripts and at least part of the third set of transcripts;
 - 15 (vi) identifying the genomic regions for which the levels of at least two of said at least part of the first set of transcripts and at least part of the second set of transcripts and at least part of the third set of transcripts are different;
- thereby identifying a group of genomic regions having different expression profiles in a healthy subject, in a subject suffering from Crohn's disease, and in a subject suffering
- 20 from ulcerative colitis.

Also provided is a kit of parts, comprising:

- primers for amplifying one of the markers as defined herein;
- instructions for use;
- 25 - optionally additional reagents for extracting RNA from biopsy samples;
- optionally a software for diagnosing an inflammatory bowel disease, Crohn's disease or ulcerative colitis.

Also provided is a computer implemented method for automatically determining

30 whether a subject is healthy or suffers from an inflammatory bowel disease, the method comprising the steps of:

- i) comparing the expression profiles of at least 2 markers in a sample obtained from said subject with a first expression signature representative of healthy subjects and with a second expression signature representative of
- 35 subjects suffering from an inflammatory bowel disease, wherein the markers are as defined in any one of the preceding claims, and wherein the

- 5 expression profile represents the expression levels of the at least 2 markers together in said subject, the first expression signature represents the average expression levels of the at least 2 markers together in a group of at least 20 healthy subjects, and the second expression signature represents the average expression levels of the at least 2 markers together in a group of subjects suffering from an inflammatory bowel disease;
- ii) determining whether the expression profile is closest to the first expression signature or to the second expression signature;

wherein:

- 10 - if the expression profile is closest to the first expression signature, the method determines that the subject is healthy;
- if the expression profile is closest to the second expression signature, determining that the subject suffers from an inflammatory bowel disease.

15 Also provided is a computer implemented method for automatically determining whether a subject suffers from ulcerative colitis or from Crohn's disease, the method comprising the steps of:

- i) comparing the expression profile of at least 2 markers in a sample obtained from said subject with a first reference profile representative of healthy subjects, with a second reference profile representative of subjects suffering from ulcerative colitis and with a third reference profile representative of subjects suffering from Crohn's disease, wherein the markers are as defined in any one of the preceding claims, and wherein the expression profile represents the expression levels of the at least 2 markers together in said subject, the first reference profile represents the average expression levels of the at least 2 markers together in a group of at least 20 healthy subjects, the second reference profile represents the average expression levels of the at least 2 markers together in a group of subjects suffering from ulcerative colitis and the third reference profile represents the average expression levels of the at least 2 markers together in a group of subjects suffering from Crohn's disease;
- 20
- 25
- 30 ii) determining whether the expression profile is closest to the first reference profile, to the second reference profile or to the third reference profile;

wherein:

- 35 - if the expression profile is closest to the first reference profile, determining that the subject is healthy;

- if the expression profile is closest to the second reference profile, determining that the subject suffers from ulcerative colitis;
- if the expression profile is closest to the third reference profile, determining that the subject suffers from Crohn's disease.

5 Description of the drawings

Figure 1: defining the TSS landscape of IBD: Overview of human subject datasets used for selection of biomarkers/features (cohort 1) and independent validation (cohort 2). For cohort 1, pinch biopsies from the descending colon were taken from 94 human subjects, classified into active ulcerative colitis (UCa), active Crohn's disease (CDa), UC and CD patients in remission (UCi, CDi) and controls (Ctrl: subjects screened for IBD where all subsequent investigations turned out normal. For each biopsy, a CAGE library was produced, resulting in the detection of transcription start sites (TSSs) and enhancer regions. Schematics show the typical inflammatory patterns in the intestinal system, the approximate location of biopsy sampling and number of subjects in each group. These samples were used to locate TSSs that were predictive for patient diagnosis, and qPCR primers were made to capture the expression of these TSSs. Finally, a computational prediction method was trained on qPCR data. Cohort 2 was sampled exactly as cohort1, but only CDa, UCa and Ctrl groups. As above, schematics show the typical inflammatory patterns in the intestinal system, the approximate location of biopsy sampling and number of subjects in each group. Following qPCR expression analysis using 35 primers as selected above, we predicted the diagnosis of subjects in cohort 2 using the computational model trained on cohort 1. For classification methodology, see Figure 2.

Figure 2: Differential expression of TSSs and genes in IBD: Number of differentially expressed TSSs. Left: Bar plot showing the number of differentially expressed TSSs in the four defined groups (comparison in parentheses).

Figure 3: Classification of IBD subtypes and controls. (A) Overview of analyses, iterative feature reduction and tests. Starting from all analyzed TSSs, which also includes TSS of unannotated transcript classes such as enhancer RNAs (referred to as features, $N=59263$) in cohort 1 we performed an initial feature selection using an ensemble approach to identify features with high potential to distinguish UCa, CDa and Ctrl groups, resulting in 263 features. We designed successful qPCR primer pairs for 161 of these features and applied microfluidics qPCR analysis to the same samples to

assess their expression with a CAGE-independent method. A secondary feature selection process was used to reduce the set of features to 35 primer pairs. We analyzed the RNA expression of these features in an independent validation cohort (cohort 2) using microfluidics qPCR. Classification analysis was performed at each step (see figures 4-6).

Figure 4: Prediction of UCa/CDa/Ctrl diagnosis labels based on CAGE expression data.

CAGE RNA expression data from cohort 1 from 263 selected features was used to train and evaluate a Random Forest prediction method based on 5-fold cross-validation. Left panel: average accuracy, sensitivity and specificity are shown for each subject group as bar plots along with the overall accuracy. Error-bars show 95% confidence intervals. Right panel: confusion matrix showing the average fractions of predictions that fall into each of the actual subject groups (columns add to 100% of predictions). Lower panel: Average prediction accuracy (Y-axis) as a function of the number of features used for training the Random Forests (X-axis) for predicting CD, UC and controls, as indicated on top of panels. Shaded areas indicate 95% confidence intervals across cross-validations.

Figure 5: Prediction of UCa/CDa/Ctrl diagnosis labels based on microfluidics qPCR expression data.

Plots are organized as in figure 4, but based on microfluidics qPCR RNA expression data from cohort 1 using 161 primers corresponding to the selected features.

Figure 6: Validation of the prediction method in an independent cohort. (A)

Feature reduction based on the data in panel C resulted in the selection of 35 features with corresponding primers. We trained a Random Forest model on microfluidics qPCR from these features from cohort 1 and evaluated it on corresponding data from an independent validation cohort (cohort 2). Classification results are shown. The upper right panel shows a comparison between the confusion matrix of the predictions and the confusion matrix obtained by repeating the analysis with randomly shuffled UCa, CDa and Ctrl training labels. Numbers indicate the average fold changes of actual vs. shuffled data. **(B)** An xgBoost model was trained on microfluidic qPCR data from the 35 biomarkers from cohort 1 and evaluated it on corresponding data from an independent cohort (cohort 2). Upper panel: average accuracy, sensitivity and specificity are shown for each subject group as bar plots along with overall accuracy. Error-bars show 95% confidence intervals across cross-validations. Dotted lines indicate 0.8 and 0.9. Lower

left panel: confusion matrix showing average fractions of predictions that fall into each of the actual subject groups (columns add to 100%). Lower right panel shows a comparison between the confusion matrix (as in panel b) of the predictions and the confusion matrix obtained by repeating the analysis with randomly shuffled training labels. Numbers indicate the average fold changes of fractions (actual vs. shuffled).

Figure 7: Ranking of selected makers for UCa vs. CDa . Using all 35 markers (x-axis) 1000 random forests were trained to distinguish UCa vs. CDa. For each random forest the importance of markers was ranked via the MeanDecreaseAccuracy measure and the average over the 1000 Random Forests was calculated (y-axis). Makers were sorted after increasing rank (decreasing importance for the classification performance).

Figure 8: Ranking of selected makers for UCa, CDa and Ctrl. Using all 35 markers (x-axis) 1000 random forests were trained to distinguish UCa, CDa and Ctrl. For each random forest the importance of markers was ranked via the MeanDecreaseAccuracy measure and the average over the 1000 Random Forests was calculated (y-axis). Makers were sorted after increasing rank (decreasing importance for the classification performance).

Figure 9: Ranking of selected makers for IBD vs Ctrl. Using all 35 markers (x-axis) 1000 random forests were trained to distinguish IBD vs Ctrl. For each random forest the importance of markers was ranked via the MeanDecreaseAccuracy measure and the average over the 1000 Random Forests was calculated (y-axis). Makers were sorted after increasing rank (decreasing importance for the classification performance).

Detailed description of the invention

The present disclosure is based on the identification of genomic regions useful as markers of inflammatory bowel diseases (IBD), such as Crohn's disease (CD) or ulcerative colitis (UC). As shown in the examples, the inventors have established that these markers can be used not only to diagnose whether a subject suffers from an IBD, but can also be used to discriminate between CD and UC, based on expression signatures characteristic of each disorder.

Definitions

Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBD) are defined by chronic, relapsing intestinal inflammation of obscure origin. IBD refers mainly to two distinct disorders, Crohn's disease and ulcerative colitis (UC). Both diseases appear to result from the unrestrained activation of an inflammatory response in the intestine. This inflammatory cascade is thought to be perpetuated through the actions of proinflammatory cytokines and selective activation of lymphocyte subsets. In patients with IBD, ulcers and inflammation of the inner lining of the intestines lead to symptoms of abdominal pain, diarrhea, and rectal bleeding. Ulcerative colitis occurs in the large intestine, while in Crohn's, the disease can involve the entire GI tract as well as the small and large intestines. For most patients, IBD is a chronic condition with symptoms lasting for months to years. It is most common in young adults, but can occur at any age. It is found worldwide, but is most common in industrialized countries such as the United States, England, and northern Europe. It is especially common in people of Jewish descent and has racial differences in incidence as well. Recent studies have identified genetic variations in specific genes, including ATG16L1, IL23R, IRGM, and NOD2, that influence the risk of developing Crohn's disease. As many as 30 human genes have been identified which contribute to ulcerative colitis susceptibility on the genetic level. However, genetic variation can only explain 15-20% of the disease phenotype, so DNA markers such as SNPs are not useful for diagnosis.

The clinical symptoms of IBD are intermittent rectal bleeding, cramping abdominal pain, weight loss and diarrhea. Diagnosis of IBD is based on the clinical symptoms, the use of a barium enema, but direct visualization (sigmoidoscopy or colonoscopy) is the most accurate test. Protracted IBD is a risk factor for colon cancer, and treatment of IBD can involve medications and surgery.

The main difference between Crohn's disease and UC is the *location* and *nature* of the inflammatory changes. Crohn's can affect any part of the gastrointestinal tract, from mouth to anus (*skip lesions*), although a majority of the cases start in the terminal ileum. Ulcerative colitis, in contrast, is restricted to the colon and the rectum. Some patients with UC only have disease in the rectum (proctitis). Others with UC have disease limited to the rectum and the adjacent left colon (proctosigmoiditis). Yet others have UC of the entire colon (universal IBD). Symptoms of UC are generally

more severe with more extensive disease (larger portion of the colon involved with disease).

5 The prognosis for patients with disease limited to the rectum (proctitis) or UC limited to the end of the left colon (proctosigmoiditis) is better than that of full colon UC. Brief periodic treatments using oral medications or enemas may be sufficient. In those with more extensive disease, blood loss from the inflamed intestines can lead to anemia, and may require treatment with iron supplements or even blood transfusions. Rarely, the colon can acutely dilate to a large size when the inflammation becomes very
10 severe. This condition is called toxic megacolon. Patients with toxic megacolon are extremely ill with fever, abdominal pain and distention, dehydration, and malnutrition. Unless the patient improves rapidly with medication, surgery is usually necessary to prevent colon rupture.

15 Crohn's disease can occur in all regions of the gastrointestinal tract. With this disease intestinal obstruction due to inflammation and fibrosis occurs in a large number of patients. Granulomas and fistula formation are frequent complications of Crohn's disease. Disease progression consequences include intravenous feeding, surgery and colostomy.

20 Accounting for far fewer cases are other forms of IBD, which are not always classified as typical IBD:

- Collagenous colitis
- Lymphocytic colitis
- Ischaemic colitis
- 25 • Diversion colitis
- Behçet's disease
- Indeterminate colitis

IBD may be treated medicinally. The most commonly used medications to treat IBD are anti-inflammatory drugs such as the salicylates. The salicylate preparations have been
30 effective in treating mild to moderate disease. They can also decrease the frequency of disease flares when the medications are taken on a prolonged basis. Examples of salicylates include sulfasalazine, azulfidine, olsalazine, and mesalamine. All of these medications are given orally in high doses for maximal therapeutic benefit. These

medicines are not without side effects. Azulfidine can cause upset stomach when taken in high doses, and rare cases of mild kidney inflammation have been reported with some salicylate preparations.

- 5 Corticosteroids are more potent and faster-acting than salicylates in the treatment of IBD, but potentially serious side effects limit the use of corticosteroids to patients with more severe disease. Side effects of corticosteroids usually occur with long-term use. They include thinning of the bone and skin, increased susceptibility to infections, diabetes, hypertension, glaucoma, muscle wasting/weakness, rounding of the face, 10 psychiatric disturbances, and, on rare occasions, destruction of hip joints.

- In IBD patients that do not respond to salicylates or corticosteroids, medications that suppress the immune system are used. Examples of immunosuppressants include azathioprine and 6-mercaptopurine. Immunosuppressants used in this situation help to 15 control IBD and allow gradual reduction or elimination of corticosteroids. However, immunosuppressants render the patient immuno-compromised and susceptible to many other diseases.

- Treatment of inflammatory bowel disease (IBD) has traditionally been accomplished 20 with administration of aminosalicylates, corticosteroids, thiopurines, methotrexate, and anti-tumor necrosis factor agents. Human beta defensins have long been thought to play a role in the occurrence and/or treatment of IBD.

- Typically, diagnosis of ulcerative colitis or Crohn's disease is based on visual 25 inspection of the gut through endoscopy, and histology assessment of pinch biopsies taken in the same colonoscopy, but can it also include radiology, x-ray and microbiology-based methods.

Remission

- 30 The term "Remission" denotes herein periods with disease control versus active disease which are often referred to as "attack". It generally refers to the state of absence of disease activity in patients known to have a chronic illness that cannot be cured. It is commonly used to refer to absence of active inflammatory bowel disease which is expected to manifest again in the future. A patient in remission thus exhibits 35 no disease activity of IBD, UC or CD.

Relapse

The term “relapse” denotes herein re-occurrence of the symptoms of IBD. The most common early symptoms of IBD are chronic diarrhea (which is sometimes bloody), cramping abdominal pain, fever, loss of appetite, and weight loss. Symptoms may continue for days or weeks and may resolve without treatment. IBD relapses at irregular intervals throughout the lifespan of a subject. Relapse can be mild or severe, brief or prolonged. Severe relapses can lead to intense pain, dehydration, and blood loss. Symptomatic periods may also be referred to as flares. A patient in relapse is a patient with active IBD, UC or CD.

Treatment

The terms “treatment” and “treating” as used herein refer to the management and care of a patient for the purpose of combating a condition, disease or disorder. The term is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound for the purpose of: alleviating or relieving symptoms or complications; delaying the progression of the condition, disease or disorder; curing or eliminating the condition, disease or disorder; and/or preventing the condition, disease or disorder, wherein “preventing” or “prevention” is to be understood to refer to the management and care of a patient for the purpose of hindering, reducing or delaying the development of the condition, disease or disorder, and includes the administration of the active compounds to prevent or reduce the risk of the onset of symptoms or complications. The patient to be treated is preferably a mammal, in particular a human being. The patients to be treated according to the present invention can be of various ages.

Expression

Expression refers to the expression of one or more RNAs. RNAs can, but does not have to correspond to annotated genes, and does not necessarily correspond to mRNAs.

Expression profile

An expression profile is a measurement of the expression levels of at least two markers. Markers may refer to known genes or un-annotated genes, including long non-coding RNAs and enhancer RNAs. In the present disclosure, the term preferably refers

to RNA expression levels of at least two markers in a sample. The sample is preferably derived from a subject for which no diagnosis of IBD, CD or UC is confirmed.

Expression signature

- 5 The term refers herein to the expression levels of at least two markers across a number of reference samples. By reference sample is understood a sample derived from a subject for which a diagnosis of IBD, CD or UC has been established in other ways than using the present methods.

10 Sensitivity

- Sensitivity refers to the test's true positive rate – the proportion of positives (e.g. IBD patients) that are predicted as such. Generally, a negative result in a method with high sensitivity is useful for ruling out the disease. A high sensitivity test is reliable when its result is negative, since it rarely misdiagnoses those who have the disease. A test with 15 100% sensitivity will recognize all patients with the disease. A negative test result would definitively rule out presence of the disease in a patient. A positive result in a test with high sensitivity is not useful for ascertaining that the subject has the disease.

Specificity

- Specificity relates to the true negative rate, i.e. it reflects the ability of a diagnostic method to correctly detect subjects without a condition. The specificity of a test is the proportion of negative (e.g. non-IBD) subjects who were also predicted to be negative. A positive result in a test with high specificity is useful for ascertaining that the subject has the disease. Such high specificity methods rarely yield positive results in healthy subjects. A test with 100% specificity will read negative and accurately exclude disease 25 for all healthy patients, while a positive result signifies a high probability of the presence of disease.

Accuracy

- The accuracy of a diagnostic method refers to the amount of agreement between the results of a method under evaluation and the results of a reference standard or test. It is the proportion of true results (both true positives and true negatives) vs. the total 30 number of cases examined.

Subject suffering from or suspected of suffering from an inflammatory bowel disease, ulcerative colitis or Crohn's disease

The present methods are particularly useful for diagnosing whether a subject suspected of suffering from an IBD such as UC or CD is healthy or does suffer from an IBD. The present methods can also be used to discriminate between subjects suffering from UC and subjects suffering from CD. This is important since treatments of UC and CD differ.

The subjects may have been diagnosed by methods otherwise known in the art, whereby the present methods are useful for confirming the diagnosis, or there may be no diagnosis yet, but a suspicion, e.g. based on known symptoms of IBD, that the subject suffers from IBD. Typically, diagnosis of IBDs, such as UC or CD, is based on visual inspection of the gut through endoscopy, and histology assessment of pinch biopsies taken in the same colonoscopy. Methods may also involve radiology analysis, X-ray analysis and microbiology-based methods. The pinch biopsy is usually from the descending colon.

The main goal of treatment of IBD, UC or CD is to induce remission. Once remission has been induced, the therapy is changed and the goal is to maintain remission. The treatments employed to induce remission are usually different from the treatments used to maintain remission.

Conventional treatments for UC patients include administration of mesalamine at the first stage, which is effective for both induction and maintenance of remission in mild to moderate patients. For the approximately 50% of patients who fail mesalamine therapy, the next line of treatment is either conventional corticosteroids or multimatrix budesonide (also known as Uceris, Pulmicort or Rhinocort), which delivers the drug to the colon. There are 3 anti-TNF drugs approved for induction and maintenance of remission of ulcerative colitis: infliximab, adalimumab, and golimumab. Finally, vedolizumab is effective for induction and maintenance of remission of ulcerative colitis and is corticosteroid-sparing. Approximately 25%-35% of ulcerative colitis patients will ultimately require surgery – typically colectomy.

Conventional treatments for CD patients include administration of corticosteroid formulations, anti-tumor necrosis factor (TNF) drugs, including infliximab, adalimumab

and certolizumab pegol. These agents are effective for both induction and maintenance of Crohn's disease, but they do not work in all patients. Resection is the most commonly surgical treatment of Crohns disease.

- 5 While there is some overlap between treatments for UC and CD, some of the above treatments are only effective for treating one of the two diseases. Times of administration and regimens may also differ. A review is provided in Wehkamp et al., Dtsch Arztebl Int 2016; 113: 72–82, particularly in eFigure1 and eFigure 2.

10 ***Markers useful for diagnosing an inflammatory bowel disease***

The present disclosure relates to the identification of markers useful for determining whether a subject suffers from an inflammatory bowel disease. The markers can also be used to discriminate whether the subject suffers from ulcerative colitis, from Crohn's disease or from another inflammatory bowel disease.

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CAGE was performed on biopsies from the descending colon from IBD patients and controls, providing a genome-wide map of TSS (transcription start sites for known and unknown RNAs and genes) across individuals with and without IBD. By analysis of CAGE data, the inventors identified sets of marker regions - genomic regions, whose RNA expression was useful in distinguishing controls, UC and CD samples.

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Importantly, such markers do not necessarily correspond to coding genomic regions or known genes – they often correspond to un-annotated non-coding RNAs.

- 25 The expression of such markers can be obtained from samples of subjects suffering from or suspected of suffering from an IBD such as UC or CD. Expression signatures derived from these markers can then be compared to reference expression signatures derived above, which in turn allows for determining whether the subject indeed suffers from an IBD such as CD or UC.

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Marker expression, and thereby expression profiles, can be determined by methods known in the art such as quantitative PCR (qPCR) or hybridization based measurement methods such as microarray analysis. Herein are also provided useful primer sets which can be used to establish expression profiles in a sample. The methods disclosed

herein may comprise a step of extracting RNA from a sample prior to analysing the expression profiles.

Sample

5 The present methods are based on measuring expression profiles in a sample from a subject suffering from or suspected of suffering from an IBD, for example UC or CD.

The sample from which the expression profiles are measured may be a sample from the colon, preferably the descending colon of a subject. In some embodiments, the sample is a pinch biopsy, for example from the colon, preferably the descending colon.
10 The sample may be a sample from an inflamed segment of the descending colon.

The skilled person knows how to obtain samples which are suitable for determining the expression profiles of markers as disclosed herein.

Diagnosing an inflammatory bowel disease

15 As mentioned herein above, available methods for diagnosing an IBD can rely on subjective assessment and can be time-consuming. Moreover, it can be difficult to discriminate between CD and UC, which is a problem because these two diseases are treated differently. The inventors have identified genetic markers which can be used to diagnose an IBD. The markers can also be used to discriminate between UC and CD.

Useful markers

Herein is provided a method of diagnosing an inflammatory bowel disease, comprising the steps of:

- a. providing a sample from a subject suffering from or suspected of suffering from an inflammatory bowel disease such as ulcerative colitis or Crohn's disease;
- 25 b. analysing the expression profiles of at least 2 markers, such as at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at least 10 markers in said sample, wherein the markers are selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95,

SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104 and SEQ ID NO: 105,
thereby determining whether the subject is healthy or suffers from an inflammatory
5 bowel disease such as ulcerative colitis or Crohn's disease.

The genomic regions as set forth in SEQ ID NO: 71 to SEQ ID NO: 105 are regions which display an expression profile in subjects suffering from IBD which is different from their expression profile in healthy subjects. They correspond to transcription start
10 sites (TSS) as identified by CAGE, as shown in the examples.

As will become apparent from the below, some markers may be more useful for diagnosing a given state than another. For example, some markers may be more specific for diagnosing UC than for diagnosing CD; while others may help discriminate
15 between IBD patients and healthy subjects.

In one embodiment, the expression profiles of 2 markers are analysed, wherein the markers are selected from the group consisting of SEQ ID NO: 71-105. In another embodiment, the expression profiles of 3 markers are analysed, wherein the markers
20 are selected from the group consisting of SEQ ID NO: 71-105. In another embodiment, the expression profiles of 4 markers are analysed, wherein the markers are selected from the group consisting of SEQ ID NO: 71-105. In another embodiment, the expression profiles of 5 markers are analysed, wherein the markers are selected from the group consisting of SEQ ID NO: 71-105. In another embodiment, the expression
25 profiles of 6 markers are analysed, wherein the markers are selected from the group consisting of SEQ ID NO: 71-105. In another embodiment, the expression profiles of 7 markers are analysed, wherein the markers are selected from the group consisting of SEQ ID NO: 71-105. In another embodiment, the expression profiles of 8 markers are analysed, wherein the markers are selected from the group consisting of SEQ ID NO: 71-105. In another embodiment, the expression profiles of 9 markers are analysed,
30 wherein the markers are selected from the group consisting of SEQ ID NO: 71-105. In another embodiment, the expression profiles of 10 markers are analysed, wherein the markers are selected from the group consisting of SEQ ID NO: 71-105. In another embodiment, the expression profiles of 11 markers are analysed, wherein the markers
35 are selected from the group consisting of SEQ ID NO: 71-105. In another embodiment, the expression profiles of 12 markers are analysed, wherein the markers are selected

[illegible]

SEQ ID NO: 71-105. In another embodiment, the expression profiles of 32 markers are analysed, wherein the markers are selected from the group consisting of SEQ ID NO: 71-105. In another embodiment, the expression profiles of 33 markers are analysed, wherein the markers are selected from the group consisting of SEQ ID NO: 71-105. In another embodiment, the expression profiles of 34 markers are analysed, wherein the markers are selected from the group consisting of SEQ ID NO: 71-105. In another embodiment, the expression profiles of 35 markers are analysed, wherein the markers are selected from the group consisting of SEQ ID NO: 71-105.

It will be clear to the person of skill in the art that the whole region as set forth in any of SEQ ID NO: 71-105 need not necessarily be amplified. In some embodiments, the at least 2 markers are thus selected from a group of genomic regions comprising at least part of a consecutive sequence comprised in each of SEQ ID: 71-105. The at least 2 markers may be at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at least 10 markers, such as at least 11 markers, such as at least 12 markers, such as at least 13 markers, such as at least 14 markers, such as at least 15 markers, such as at least 16 markers, such as at least 17 markers, such as at least 18 markers, such as at least 19 markers, such as at least 20 markers, such as at least 21 markers, such as at least 22 markers, such as at least 23 markers, such as at least 24 markers, such as at least 25 markers, such as at least 26 markers, such as at least 27 markers, such as at least 28 markers, such as at least 29 markers, such as at least 30 markers, such as at least 31 markers, such as at least 32 markers, such as at least 33 markers, such as at least 34 markers, such as 35 markers, selected from a group of genomic regions comprising at least part of a consecutive sequence comprised in each of SEQ ID NO: 71-105. The genomic regions comprising at least part of a consecutive sequence comprised in each of SEQ ID NO: 71-105 should be long enough that they can be specifically amplified by methods such as described herein.

It will be obvious to the skilled person that the boundaries of the genomic regions selected as markers can vary somewhat. Said genomic regions are used as markers for determining an expression profile by hybridisation-based methods, as described herein. The choice of the boundaries may vary and be dictated by the usual constraints of primer design, for example the sequence (to avoid formation of secondary structures potentially jeopardising the analysis, or the constraints linked to two primers in a pair

having preferably similar melting temperatures), so that the expression profiles from the selected genomic regions can be properly established by conventional methods.

In some embodiments, the markers for diagnosing if the subject suffers from an IBD such as UC or CD are selected from the group consisting of SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139 and SEQ ID NO: 140.

The above markers can thus be used to discriminate between healthy subjects and subjects suffering from an IBD, such as CD or UC, as detailed further below.

In some embodiments, the at least 2 markers are selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103 and SEQ ID NO: 105. The at least 2 markers may be at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at least 10 markers, such as at least 11 markers, such as at least 12 markers, such as at least 13 markers, such as at least 14 markers, such as at least 15 markers, such as at least 16 markers, such as at least 17 markers, such as at least 18 markers, such as at least 19 markers, such as at least 20 markers, such as at least 21 markers, such as at least 22 markers, such as at least 23 markers, such as at least 24 markers, such as at least 25 markers, such as at least 26 markers, such as 27 markers, selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID

NO: 92, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID
NO: 98, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103 and SEQ ID NO: 105. The
at least 2 markers may be at least 3 markers, such as at least 4 markers, such as at
least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at
least 8 markers, such as at least 9 markers, such as at least 10 markers, such as at
least 11 markers, such as at least 12 markers, such as at least 13 markers, such as at
least 14 markers, such as at least 15 markers, such as at least 16 markers, such as at
least 17 markers, such as at least 18 markers, such as at least 19 markers, such as at
least 20 markers, such as at least 21 markers, such as at least 22 markers, such as at
least 23 markers, such as at least 24 markers, such as 25 markers, selected from the
group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 75,
SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80,
SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87,
SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 96,
SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103
and SEQ ID NO: 105.

In other embodiments, the at least 2 markers are selected from the group consisting of
SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 76,
SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81,
SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 88,
SEQ ID NO: 89, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 96, SEQ ID NO: 97,
SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103 and SEQ ID NO:
105.

In some embodiments, the at least 2 markers may be at least 3 markers, such as at
least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at
least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at
least 10 markers, such as at least 11 markers, such as at least 12 markers, such as at
least 13 markers, such as at least 14 markers, such as at least 15 markers, such as at
least 16 markers, such as at least 17 markers, such as at least 18 markers, such as at
least 19 markers, such as at least 20 markers, such as at least 21 markers, such as at
least 22 markers, such as at least 23 markers, such as at least 24 markers, such as at
least 25 markers, such as at least 26 markers, such as 27 markers, selected from the
group consisting of SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO:
110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID

NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 138 and SEQ ID NO: 140.

5

In some embodiments, the at least 2 markers are at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at least 10 markers, such as at least 11 markers, such as at least 12 markers, such as at least 13 markers, such as at least 14 markers, such as at least 15 markers, such as at least 16 markers, such as at least 17 markers, such as at least 18 markers, such as at least 19 markers, such as at least 20 markers, such as at least 21 markers, such as at least 22 markers, such as at least 23 markers, such as at least 24 markers, such as 25 markers selected from the group consisting of SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 120, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 138 and SEQ ID NO: 140.

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Particularly useful markers for determining if a subject is healthy or suffers from an IBD are the markers as set forth in SEQ ID NO: 76, SEQ ID NO: 82, SEQ ID NO: 94, SEQ ID NO: 99 and SEQ ID NO: 102. Thus in some embodiments, the at least 2 markers are at least 3 markers, such as at least 4 markers, such as 5 markers selected from the group consisting of SEQ ID NO: 76, SEQ ID NO: 82, SEQ ID NO: 94, SEQ ID NO: 99 and SEQ ID NO: 102.

25

In some embodiments, the at least 2 markers are at least 3 markers, such as at least 4 markers, such as 5 markers selected from the group consisting of SEQ ID NO: 111, SEQ ID NO: 117, SEQ ID NO: 129, SEQ ID NO: 134 and SEQ ID NO: 137.

30

As can be seen in figures 7-9, and without being bound by theory, some markers provide more accurate results than others. In other embodiments, the at least 2 markers are selected from the group consisting of SEQ ID NO: 94, SEQ ID NO: 88, SEQ ID NO: 103, SEQ ID NO: 76, SEQ ID NO: 84, SEQ ID NO: 99, SEQ ID NO: 81, SEQ ID NO: 102, SEQ ID NO: 82, SEQ ID NO: 79, SEQ ID NO: 95, SEQ ID NO: 92,

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SEQ ID NO: 72, SEQ ID NO: 100, SEQ ID NO: 104, SEQ ID NO: 91, SEQ ID NO: 105,
SEQ ID NO: 75, SEQ ID NO: 97, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 78,
SEQ ID NO: 101, SEQ ID NO: 96, SEQ ID NO: 98, SEQ ID NO: 90, SEQ ID NO: 77,
SEQ ID NO: 89, SEQ ID NO: 73, SEQ ID NO: 83, SEQ ID NO: 87, SEQ ID NO: 86,
5 SEQ ID NO: 93, SEQ ID NO: 80 and SEQ ID NO: 85.

Preferably the at least 2 markers are at least 3 markers, such as at least 4 markers,
such as at least 5 markers, such as at least 6 markers, such as at least 7 markers,
such as at least 8 markers, such as at least 9 markers, such as at least 10 markers,
10 such as at least 11 markers, such as at least 12 markers, such as at least 13 markers,
such as at least 14 markers, such as at least 15 markers, such as at least 16 markers,
such as at least 17 markers, such as at least 18 markers, such as at least 19 markers,
such as at least 20 markers, such as at least 21 markers, such as at least 22 markers,
such as at least 23 markers, such as at least 24 markers, such as 25 markers selected
15 from the group consisting of SEQ ID NO: 94, SEQ ID NO: 88, SEQ ID NO: 103, SEQ
ID NO: 76, SEQ ID NO: 84, SEQ ID NO: 99, SEQ ID NO: 81, SEQ ID NO: 102, SEQ ID
NO: 82, SEQ ID NO: 79, SEQ ID NO: 95, SEQ ID NO: 92, SEQ ID NO: 72, SEQ ID
NO: 100, SEQ ID NO: 104, SEQ ID NO: 91, SEQ ID NO: 105, SEQ ID NO: 75, SEQ ID
NO: 97, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 78, SEQ ID NO: 101, SEQ ID
20 NO: 96 and SEQ ID NO: 98.

More preferably the at least 2 markers are at least 3 markers, such as at least 4
markers, such as at least 5 markers, such as at least 6 markers, such as at least 7
markers, such as at least 8 markers, such as at least 9 markers, such as 10 markers
25 selected from the group consisting of SEQ ID NO: 94, SEQ ID NO: 88, SEQ ID NO:
103, SEQ ID NO: 76, SEQ ID NO: 84, SEQ ID NO: 99, SEQ ID NO: 81, SEQ ID NO:
102, SEQ ID NO: 82 and SEQ ID NO: 79.

In some embodiments, the at least 2 markers are selected from the group consisting of
30 SEQ ID NO: 129, SEQ ID NO: 123, SEQ ID NO: 138, SEQ ID NO: 111, SEQ ID NO:
119, SEQ ID NO: 134, SEQ ID NO: 116, SEQ ID NO: 137, SEQ ID NO: 117, SEQ ID
NO: 114, SEQ ID NO: 130, SEQ ID NO: 127, SEQ ID NO: 107, SEQ ID NO: 135, SEQ
ID NO: 139, SEQ ID NO: 126, SEQ ID NO: 140, SEQ ID NO: 110, SEQ ID NO: 132,
SEQ ID NO: 106, SEQ ID NO: 109, SEQ ID NO: 113, SEQ ID NO: 136, SEQ ID NO:
35 131, SEQ ID NO: 133, SEQ ID NO: 125, SEQ ID NO: 112, SEQ ID NO: 124, SEQ ID

NO: 108, SEQ ID NO: 118, SEQ ID NO: 122, SEQ ID NO: 121, SEQ ID NO: 128, SEQ ID NO: 115 and SEQ ID NO: 120.

5 Preferably the at least 2 markers are at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at least 10 markers, such as at least 11 markers, such as at least 12 markers, such as at least 13 markers, such as at least 14 markers, such as at least 15 markers, such as at least 16 markers, such as at least 17 markers, such as at least 18 markers, such as at least 19 markers, 10 such as at least 20 markers, such as at least 21 markers, such as at least 22 markers, such as at least 23 markers, such as at least 24 markers, such as 25 markers selected from the group consisting of SEQ ID NO: 129, SEQ ID NO: 123, SEQ ID NO: 138, SEQ ID NO: 111, SEQ ID NO: 119, SEQ ID NO: 134, SEQ ID NO: 116, SEQ ID NO: 137, SEQ ID NO: 117, SEQ ID NO: 114, SEQ ID NO: 130, SEQ ID NO: 127, SEQ ID NO: 15 107, SEQ ID NO: 135, SEQ ID NO: 139, SEQ ID NO: 126, SEQ ID NO: 140, SEQ ID NO: 110, SEQ ID NO: 132, SEQ ID NO: 106, SEQ ID NO: 109, SEQ ID NO: 113, SEQ ID NO: 136, SEQ ID NO: 131 and SEQ ID NO: 133.

20 More preferably the at least 2 markers are at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as 10 markers selected from the group consisting of SEQ ID NO: 129, SEQ ID NO: 123, SEQ ID NO: 138, SEQ ID NO: 111, SEQ ID NO: 119, SEQ ID NO: 134, SEQ ID NO: 116, SEQ ID NO: 137, SEQ ID NO: 117 and SEQ ID NO: 114.

25 In some embodiments, the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 94, SEQ ID NO: 103, SEQ ID NO: 84, SEQ ID NO: 92, SEQ ID NO: 88, SEQ ID NO: 80, SEQ ID NO: 99, SEQ ID NO: 76, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 79, SEQ ID NO: 102, SEQ ID NO: 95, 30 SEQ ID NO: 72, SEQ ID NO: 104, SEQ ID NO: 75, SEQ ID NO: 86, SEQ ID NO: 77, SEQ ID NO: 83, SEQ ID NO: 105, SEQ ID NO: 96, SEQ ID NO: 90, SEQ ID NO: 97, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 89, SEQ ID NO: 101, SEQ ID NO: 73, SEQ ID NO: 98, SEQ ID NO: 87, SEQ ID NO: 93, SEQ ID NO: 85 and SEQ ID NO: 78.

35 Preferably the at least 2 markers are at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers,

such as at least 8 markers, such as at least 9 markers, such as at least 10 markers,
such as at least 11 markers, such as at least 12 markers, such as at least 13 markers,
such as at least 14 markers, such as at least 15 markers, such as at least 16 markers,
such as at least 17 markers, such as at least 18 markers, such as at least 19 markers,
5 such as at least 20 markers, such as at least 21 markers, such as at least 22 markers,
such as at least 23 markers, such as at least 24 markers, such as 25 markers selected
from the group consisting of SEQ ID NO: 100, SEQ ID NO: 94, SEQ ID NO: 103, SEQ
ID NO: 84, SEQ ID NO: 92, SEQ ID NO: 88, SEQ ID NO: 80, SEQ ID NO: 99, SEQ ID
NO: 76, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 79, SEQ ID
10 NO: 102, SEQ ID NO: 95, SEQ ID NO: 72, SEQ ID NO: 104, SEQ ID NO: 75, SEQ ID
NO: 86, SEQ ID NO: 77, SEQ ID NO: 83, SEQ ID NO: 105, SEQ ID NO: 96, SEQ ID
NO: 90, and SEQ ID NO: 97.

Even more preferably the at least 2 markers are at least 3 markers, such as at least 4
15 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7
markers, such as at least 8 markers, such as 9 markers selected from the group
consisting of SEQ ID NO: 100, SEQ ID NO: 94, SEQ ID NO: 103, SEQ ID NO: 84, SEQ
ID NO: 92, SEQ ID NO: 88, SEQ ID NO: 80, SEQ ID NO: 99 and SEQ ID NO: 76. Such
markers are useful for determining if a subject suffers from UC, from CD or is healthy.

20 In some embodiments, the at least 2 markers are selected from the group consisting of
SEQ ID NO: 135, SEQ ID NO: 129, SEQ ID NO: 138, SEQ ID NO: 119, SEQ ID NO:
127, SEQ ID NO: 123, SEQ ID NO: 115, SEQ ID NO: 134, SEQ ID NO: 111, SEQ ID
NO: 116, SEQ ID NO: 117, SEQ ID NO: 126, SEQ ID NO: 114, SEQ ID NO: 137, SEQ
25 ID NO: 130, SEQ ID NO: 107, SEQ ID NO: 139, SEQ ID NO: 110, SEQ ID NO: 121,
SEQ ID NO: 112, SEQ ID NO: 118, SEQ ID NO: 140, SEQ ID NO: 131, SEQ ID NO:
125, SEQ ID NO: 132, SEQ ID NO: 106, SEQ ID NO: 109, SEQ ID NO: 124, SEQ ID
NO: 136, SEQ ID NO: 108, SEQ ID NO: 133, SEQ ID NO: 122, SEQ ID NO: 128, SEQ
ID NO: 120 and SEQ ID NO: 113.

30 Preferably the at least 2 markers are at least 3 markers, such as at least 4 markers,
such as at least 5 markers, such as at least 6 markers, such as at least 7 markers,
such as at least 8 markers, such as at least 9 markers, such as at least 10 markers,
such as at least 11 markers, such as at least 12 markers, such as at least 13 markers,
35 such as at least 14 markers, such as at least 15 markers, such as at least 16 markers,
such as at least 17 markers, such as at least 18 markers, such as at least 19 markers,

- such as at least 20 markers, such as at least 21 markers, such as at least 22 markers, such as at least 23 markers, such as at least 24 markers, such as at least 25 markers, such as 26 markers selected from the group consisting of SEQ ID NO: 135, SEQ ID NO: 129, SEQ ID NO: 138, SEQ ID NO: 119, SEQ ID NO: 127, SEQ ID NO: 123, SEQ ID NO: 115, SEQ ID NO: 134, SEQ ID NO: 111, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 126, SEQ ID NO: 114, SEQ ID NO: 137, SEQ ID NO: 130, SEQ ID NO: 107, SEQ ID NO: 139, SEQ ID NO: 110, SEQ ID NO: 121, SEQ ID NO: 112, SEQ ID NO: 118, SEQ ID NO: 140, SEQ ID NO: 131, SEQ ID NO: 125 and SEQ ID NO: 132.
- More preferably, the at least 2 markers are at least 2 markers are at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such as 9 markers selected from the group consisting of SEQ ID NO: 135, SEQ ID NO: 129, SEQ ID NO: 138, SEQ ID NO: 119, SEQ ID NO: 127, SEQ ID NO: 123, SEQ ID NO: 115, SEQ ID NO: 134 and SEQ ID NO: 111. Such markers are useful for determining if a subject suffers from UC, from CD or is healthy.

The skilled person will know how to design appropriate hybridisation-based measurements of any of the above markers. Designing probes for microarray analysis can be done as is known in the field.

Useful primers

In some embodiments, the expression levels from the above at least 2 markers is determined by quantitative PCR, as is also known in the art.

- Useful primer pairs for determining the expression profiles from the present markers are provided herein, in particular primer pairs useful for diagnosing an IBD.

In some embodiments, the primer pair is selected from the group consisting of:

- (i) SEQ ID NO: 1 and SEQ ID NO: 2;
- (ii) SEQ ID NO: 3 and SEQ ID NO: 4;
- (iii) SEQ ID NO: 5 and SEQ ID NO: 6;
- (iv) SEQ ID NO: 7 and SEQ ID NO: 8;
- (v) SEQ ID NO: 9 and SEQ ID NO: 10;
- (vi) SEQ ID NO: 11 and SEQ ID NO: 12;
- (vii) SEQ ID NO: 13 and SEQ ID NO: 14;

- (viii) SEQ ID NO: 15 and SEQ ID NO: 16;
 (ix) SEQ ID NO: 17 and SEQ ID NO: 18;
 (x) SEQ ID NO: 19 and SEQ ID NO: 20;
 (xi) SEQ ID NO: 21 and SEQ ID NO: 22;
 5 (xii) SEQ ID NO: 23 and SEQ ID NO: 24;
 (xiii) SEQ ID NO: 25 and SEQ ID NO: 26;
 (xiv) SEQ ID NO: 27 and SEQ ID NO: 28;
 (xv) SEQ ID NO: 29 and SEQ ID NO: 30;
 (xvi) SEQ ID NO: 31 and SEQ ID NO: 32;
 10 (xvii) SEQ ID NO: 33 and SEQ ID NO: 34;
 (xviii) SEQ ID NO: 35 and SEQ ID NO: 36;
 (xix) SEQ ID NO: 37 and SEQ ID NO: 38;
 (xx) SEQ ID NO: 39 and SEQ ID NO: 40;
 (xxi) SEQ ID NO: 41 and SEQ ID NO: 42;
 15 (xxii) SEQ ID NO: 43 and SEQ ID NO: 44;
 (xxiii) SEQ ID NO: 45 and SEQ ID NO: 46;
 (xxiv) SEQ ID NO: 47 and SEQ ID NO: 48;
 (xxv) SEQ ID NO: 49 and SEQ ID NO: 50;
 (xxvi) SEQ ID NO: 51 and SEQ ID NO: 52;
 20 (xxvii) SEQ ID NO: 53 and SEQ ID NO: 54;
 (xxviii) SEQ ID NO: 55 and SEQ ID NO: 56;
 (xxix) SEQ ID NO: 57 and SEQ ID NO: 58;
 (xxx) SEQ ID NO: 59 and SEQ ID NO: 60;
 (xxxi) SEQ ID NO: 61 and SEQ ID NO: 62;
 25 (xxxii) SEQ ID NO: 63 and SEQ ID NO: 64;
 (xxxiii) SEQ ID NO: 65 and SEQ ID NO: 66;
 (xxxiv) SEQ ID NO: 67 and SEQ ID NO: 68; and
 (xxxv) SEQ ID NO: 69 and SEQ ID NO: 70.
- 30 The at least 2 primer pairs may be at least 3 primer pairs, such as at least 4 primer pairs, such as at least 5 primer pairs, such as at least 6 primer pairs, such as at least 7 primer pairs, such as at least 8 primer pairs, such as at least 9 primer pairs, such as at least 10 primer pairs, such as at least 11 primer pairs, such as at least 12 primer pairs, such as at least 13 primer pairs, such as at least 14 primer pairs, such as at least 15
 35 primer pairs, such as at least 16 primer pairs, such as at least 17 primer pairs, such as at least 18 primer pairs, such as at least 19 primer pairs, such as at least 20 primer

pairs, such as at least 21 primer pairs, such as at least 22 primer pairs, such as at least 23 primer pairs, such as at least 24 primer pairs, such as at least 25 primer pairs, such as at least 26 primer pairs, such as at least 27 primer pairs, such as at least 28 primer pairs, such as at least 29 primer pairs, such as at least 30 primer pairs, such as at least 31 primer pairs, such as at least 32 primer pairs, such as at least 33 primer pairs, such as at least 34 primer pairs, such as 35 primer pairs selected from the primer pairs (i) to (xxxv) above.

In some embodiments, the at least 2 primer pairs may be at least 3 primer pairs, such as at least 4 primer pairs, such as at least 5 primer pairs, such as at least 6 primer pairs, such as at least 7 primer pairs, such as at least 8 primer pairs, such as at least 9 primer pairs, such as at least 10 primer pairs, such as at least 11 primer pairs, such as at least 12 primer pairs, such as at least 13 primer pairs, such as at least 14 primer pairs, such as at least 15 primer pairs, such as at least 16 primer pairs, such as at least 17 primer pairs, such as at least 18 primer pairs, such as at least 19 primer pairs, such as at least 20 primer pairs, such as at least 21 primer pairs, such as at least 22 primer pairs, such as at least 23 primer pairs, such as at least 24 primer pairs, such as at least 25 primer pairs, such as at least 26 primer pairs, such as 27 primer pairs, selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 5 and SEQ ID NO: 6; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 43 and SEQ ID NO: 33; SEQ ID NO: 45 and SEQ ID NO: 46; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 53 and SEQ ID NO: 53; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 61 and SEQ ID NO: 62; SEQ ID NO: 65 and SEQ ID NO: 66; and SEQ ID NO: 69 and SEQ ID NO: 70.

In some embodiments, the at least 2 primer pairs are at least 3 primer pairs, such as at least 4 primer pairs, such as at least 5 primer pairs, such as at least 6 primer pairs, such as at least 7 primer pairs, such as at least 8 primer pairs, such as at least 9 primer pairs, such as at least 10 primer pairs, such as at least 11 primer pairs, such as at least 12 primer pairs, such as at least 13 primer pairs, such as at least 14 primer

pairs, such as at least 15 primer pairs, such as at least 16 primer pairs, such as at least 17 primer pairs, such as at least 18 primer pairs, such as at least 19 primer pairs, such as at least 20 primer pairs, such as at least 21 primer pairs, such as at least 22 primer pairs, such as at least 23 primer pairs, such as at least 24 primer pairs, such as 25
 5 primer pairs selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 5 and SEQ ID NO: 6; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 45 and SEQ ID NO: 46; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID NO: 57 and SEQ ID NO: 58; 15 SEQ ID NO: 61 and SEQ ID NO: 62; SEQ ID NO: 65 and SEQ ID NO: 66; and SEQ ID NO: 69 and SEQ ID NO: 70.

In order to discriminate between subjects suffering from IBD and healthy subjects, the at least 2 primer pairs may be selected from the group consisting of the following pairs:
 20 SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 57 and SEQ ID NO: 58; and SEQ ID NO: 63 and SEQ ID NO: 64. Thus the at least 2 primer pairs may be at least 3 primer pairs, such as at least 4 primer pairs, such as 5 primer pairs selected from the group consisting of
 25 SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 57 and SEQ ID NO: 58; and SEQ ID NO: 63 and SEQ ID NO: 64.

In other embodiments, the at least 2 primer pairs are selected from the group consisting of: SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 63 and SEQ ID NO: 64; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 59 and 35 SEQ ID NO: 60; SEQ ID NO: 67 and SEQ ID NO: 68; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 69 and SEQ ID NO: 70; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID

NO: 53 and SEQ ID NO: 54; SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 7 and
 SEQ ID NO: 8; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 61 and SEQ ID NO:
 62; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID
 NO: 39 and SEQ ID NO: 40; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 37 and
 5 SEQ ID NO: 38; SEQ ID NO: 5 and SEQ ID NO: 6; SEQ ID NO: 25 and SEQ ID NO:
 26; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID
 NO: 45 and SEQ ID NO: 46; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 29 and
 SEQ ID NO: 30.

10 Preferably the at least 2 primer pairs are at least 3 primer pairs, such as at least 4
 primer pairs, such as at least 5 primer pairs, such as at least 6 primer pairs, such as at
 least 7 primer pairs, such as at least 8 primer pairs, such as at least 9 primer pairs,
 such as at least 10 primer pairs, such as at least 11 primer pairs, such as at least 12
 primer pairs, such as at least 13 primer pairs, such as at least 14 primer pairs, such as
 15 at least 15 primer pairs, such as at least 16 primer pairs, such as at least 17 primer
 pairs, such as at least 18 primer pairs, such as at least 19 primer pairs, such as at least
 20 primer pairs, such as at least 21 primer pairs, such as at least 22 primer pairs, such
 as at least 23 primer pairs, such as at least 24 primer pairs, such as 25 primer pairs
 selected from the group consisting of the following pairs: SEQ ID NO: 47 and SEQ ID
 20 NO: 48; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 65 and SEQ ID NO: 66;
 SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO:
 57 and SEQ ID NO: 58; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 63 and SEQ
 ID NO: 64; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 17 and SEQ ID NO: 18;
 SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO:
 25 3 and SEQ ID NO: 4; SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 67 and SEQ ID
 NO: 68; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 69 and SEQ ID NO: 70;
 SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 1
 and SEQ ID NO: 2; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 15 and SEQ ID NO:
 16; SEQ ID NO: 61 and SEQ ID NO: 62; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID
 30 NO: 55 and SEQ ID NO: 56.

More preferably, the at least 2 primer pairs are at least 3 primer pairs, such as at least
 4 primer pairs, such as at least 5 primer pairs, such as at least 6 primer pairs, such as
 at least 7 primer pairs, such as at least 8 primer pairs, such as at least 9 primer pairs,
 35 such as 10 primer pairs selected from the group consisting of the following pairs: SEQ
 ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 65

and SEQ ID NO: 66; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 63 and SEQ ID NO: 64; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 17 and SEQ ID NO: 18.

5

In order to discriminate whether the tested subject suffers from UC or CD or is healthy, the primer pairs may be selected from the group consisting of the following pairs: SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 63 and SEQ ID NO: 64; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 67 and SEQ ID NO: 68; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 69 and SEQ ID NO: 70; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 61 and SEQ ID NO: 62; SEQ ID NO: 5 and SEQ ID NO: 6; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 45 and SEQ ID NO: 46; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 15 and SEQ ID NO: 16.

Preferably, the at least 2 primer pairs are at least 3 primer pairs, such as at least 4 primer pairs, such as at least 5 primer pairs, such as at least 6 primer pairs, such as at least 7 primer pairs, such as at least 8 primer pairs, such as at least 9 primer pairs, such as at least 10 primer pairs, such as at least 11 primer pairs, such as at least 12 primer pairs, such as at least 13 primer pairs, such as at least 14 primer pairs, such as at least 15 primer pairs, such as at least 16 primer pairs, such as at least 17 primer pairs, such as at least 18 primer pairs, such as at least 19 primer pairs, such as at least 20 primer pairs, such as at least 21 primer pairs, such as at least 22 primer pairs, such as at least 23 primer pairs, such as at least 24 primer pairs, such as 25 primer pairs selected from the group consisting of the following pairs: SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 57 and SEQ

ID NO: 58; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 63 and SEQ ID NO: 64; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 67 and SEQ ID NO: 68;
5 SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 69 and SEQ ID NO: 70; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 53 and SEQ ID NO: 54.

10 More preferably, the at least 2 primer pairs are at least 3 primer pairs, such as at least 4 primer pairs, such as at least 5 primer pairs, such as at least 6 primer pairs, such as at least 7 primer pairs, such as at least 8 primer pairs, such as 9 primer pairs selected from the group consisting of the following pairs: SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 11 and SEQ ID NO: 12.

20 The number of primer pairs employed should be at least equal to the double of the number of markers for which the expression profile is to be determined. Accordingly, in some embodiments, at least 2 primer pairs are used, such as at least 3 primer pairs, such as at least 4 primer pairs, such as at least 5 primer pairs, such as at least 6 primer pairs, such as at least 7 primer pairs, such as at least 8 primer pairs, such as at least 9 primer pairs, such as at least 10 primer pairs, such as at least 11 primer pairs, 25 such as at least 12 primer pairs, such as at least 13 primer pairs, such as at least 14 primer pairs, such as at least 15 primer pairs, such as at least 16 primer pairs, such as at least 17 primer pairs, such as at least 18 primer pairs, such as at least 19 primer pairs, such as at least 20 primer pairs, such as at least 21 primer pairs, such as at least 22 primer pairs, such as at least 23 primer pairs, such as at least 24 primer pairs, such as at least 25 primer pairs, such as at least 26 primer pairs, such as at least 27 primer pairs, such as at least 28 primer pairs, such as at least 29 primer pairs, such as at least 30 primer pairs, such as at least 31 primer pairs, such as at least 32 primer pairs, such as at least 33 primer pairs, such as at least 34 primer pairs, such as at least 35 primer pairs.

Diagnosing ulcerative colitis

The markers disclosed herein are useful for diagnosing if a subject suffers from ulcerative colitis.

Useful markers

- 5 Herein is thus provided a method of diagnosing an inflammatory bowel disease, wherein the disease is ulcerative colitis, comprising the steps of:
- a. providing a sample from a subject suffering from or suspected of suffering from an inflammatory bowel disease such as ulcerative colitis or Crohn's disease;
 - b. analysing the expression profiles of at least 2 markers, such as at least 3
- 10 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at least 10 markers in said sample, wherein the markers are selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID
- 15 NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO:
- 20 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104 and SEQ ID NO: 105,
- thereby determining whether the subject is healthy or suffers from ulcerative colitis.

25 In some embodiments, the at least 2 markers are selected from the group consisting of SEQ ID NO: 75, SEQ ID NO: 81, SEQ ID NO: 92, SEQ ID NO: 95, SEQ ID NO: 100 and SEQ ID NO: 104. The at least 2 markers may be at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as 6 markers selected from the group consisting of SEQ ID NO: 75, SEQ ID NO: 81, SEQ ID NO: 92, SEQ ID NO: 95, SEQ ID NO: 100 and SEQ ID NO: 104..

30 Useful primers

In order to determine whether the tested subject suffers from UC, the at least 2 primer pairs may be at least 3 primer pairs, such as at least 4 primer pairs, such as at least 5 primer pairs, such as 6 primer pairs selected from the group consisting of the following pairs: SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID

NO: 43 and SEQ ID NO: 44; SEQ ID NO: 45 and SEQ ID NO: 50; SEQ ID NO: 59 and SEQ ID NO: 60; and SEQ ID NO: 67 and SEQ ID NO: 68.

5 In some embodiments, the primer pairs are at least 2 primer pairs selected from the group consisting of the following pairs: SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 45 and SEQ ID NO: 50; SEQ ID NO: 59 and SEQ ID NO: 60; and SEQ ID NO: 67 and SEQ ID NO: 68. The at least 2 primer pairs may be at least 3 primer pairs, such as at least 4 primer pairs, such as at least 5 primer pairs, such as 6 primer pairs.

10 ***Diagnosing Crohn's disease***

The markers disclosed herein are also useful for diagnosing if a subject suffers from Crohn's disease.

Useful markers

15 In some embodiments, the at least 2 markers are selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 101 and SEQ ID NO: 105. In some
20 embodiments, the at least 2 markers are at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at least 10 markers, such as at least 11 markers, such as at least 12 markers, such as at least 13 markers, such as at least 14 markers, such as at least 15 markers, such as at least 16 markers, such as at least 17 markers, such as at least 18 markers, such as 19 markers.

25 In other embodiments, the at least 2 markers are at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at least 10 markers, such as at least 11 markers, such as at least 12 markers, such as at least 13
30 markers, such as at least 14 markers, such as at least 15 markers, such as at least 16 markers, such as at least 17 markers, such as at least 18 markers, such as 19 markers selected from the group consisting of SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ

ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 136 and SEQ ID NO: 140.

Useful primers

- In order to identify subjects suffering from CD, the at least 2 primer pairs may be selected from the group consisting of the following pairs: SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 4 and SEQ ID NO: 6; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID NO: 61 and SEQ ID NO: 62; and SEQ ID NO: 69 and SEQ ID NO: 70.
- In some embodiments, the at least 2 primer pairs are at least 3 primer pairs, such as at least 4 primer pairs, such as at least 5 primer pairs, such as at least 6 primer pairs, such as at least 7 primer pairs, such as at least 8 primer pairs, such as at least 9 primer pairs, such as at least 10 primer pairs, such as at least 11 primer pairs, such as at least 12 primer pairs, such as at least 13 primer pairs, such as at least 14 primer pairs, such as at least 15 primer pairs, such as at least 16 primer pairs, such as at least 17 primer pairs, such as at least 18 primer pairs, such as 19 primer pairs selected from SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 4 and SEQ ID NO: 6; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID NO: 61 and SEQ ID NO: 62; and SEQ ID NO: 69 and SEQ ID NO: 70.

Discriminating between UC and CD

Other markers are useful for discriminating whether a subject suffering from an IBD suffers from UC or from CD.

Useful markers

Accordingly, in some embodiments the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 80, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 86, SEQ ID NO: 79, SEQ ID NO: 83, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 89, SEQ ID NO: 84, SEQ ID NO: 97, SEQ ID NO: 81, SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 95, SEQ ID NO: 99, SEQ ID NO: 73, SEQ ID NO: 90, SEQ ID NO: 72, SEQ ID NO: 85, SEQ ID NO: 96, SEQ ID NO: 102, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 94, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 104, SEQ ID NO: 93, SEQ ID NO: 76, SEQ ID NO: 98, SEQ ID NO: 105, SEQ ID NO: 78 and SEQ ID NO: 101. The at least 2 markers may be at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at least 10 markers, such as at least 11 markers, such as at least 12 markers, such as at least 13 markers, such as at least 14 markers, such as at least 15 markers, such as at least 16 markers, such as at least 17 markers, such as at least 18 markers, such as at least 19 markers, such as at least 20 markers, such as at least 21 markers, such as at least 22 markers, such as at least 23 markers, such as at least 24 markers, such as at least 25 markers, such as at least 26 markers, such as at least 27 markers, such as at least 28 markers, such as at least 29 markers, such as at least 30 markers, such as at least 31 markers, such as at least 32 markers, such as at least 33 markers, such as at least 34 markers, such as 35 markers, selected from a group of genomic regions comprising at least part of a consecutive sequence comprised in each of SEQ ID NO: 71-105. The genomic regions comprising at least part of a consecutive sequence comprised in each of SEQ ID NO: 71-105 should be long enough that it can be specifically amplified by methods such as described herein.

Preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 80, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 86, SEQ ID NO: 79, SEQ ID NO: 83, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 89, SEQ ID NO: 84, SEQ ID NO: 97, SEQ ID NO: 81, SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 95, SEQ ID NO: 99, SEQ ID NO: 73, SEQ ID NO: 90, SEQ ID NO: 72, SEQ ID NO: 85, SEQ ID NO: 96, SEQ ID NO: 102, SEQ ID NO: 71 and SEQ ID NO: 74. The at least 2 markers may be at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at least 10 markers, such as at least 11 markers, such as at least 12 markers, such as at least 13 markers, such as at least 14

markers, such as at least 15 markers, such as at least 16 markers, such as at least 17 markers, such as at least 18 markers, such as at least 19 markers, such as at least 20 markers, such as at least 21 markers, such as at least 22 markers, such as at least 23 markers, such as at least 24 markers, such as 25 markers selected from the group
5 consisting of SEQ ID NO: 100, SEQ ID NO: 80, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 86, SEQ ID NO: 79, SEQ ID NO: 83, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 89, SEQ ID NO: 84, SEQ ID NO: 97, SEQ ID NO: 81, SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 95, SEQ ID NO: 99, SEQ ID NO: 73, SEQ ID NO: 90, SEQ ID NO: 72, SEQ ID NO: 85, SEQ ID NO: 96, SEQ ID NO: 102, SEQ ID NO: 71 and SEQ
10 ID NO: 74.

More preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 80, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 86, SEQ ID NO: 79 and SEQ ID NO: 83. The at least 2 markers may be at least 3 markers, such as
15 at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as 7 markers selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 80, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 86, SEQ ID NO: 79 and SEQ ID NO: 83.

Also useful for discriminating whether a subject suffering from an IBD suffers from UC or from CD, are methods wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 135, SEQ ID NO: 115, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 121, SEQ ID NO: 114, SEQ ID NO: 118, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 124, SEQ ID NO: 119, SEQ ID NO: 132, SEQ ID NO: 116, SEQ ID NO: 138, SEQ ID NO: 117, SEQ ID NO: 130, SEQ ID NO: 134, SEQ ID NO: 108, SEQ
25 ID NO: 125, SEQ ID NO: 107, SEQ ID NO: 120, SEQ ID NO: 131, SEQ ID NO: 137, SEQ ID NO: 106, SEQ ID NO: 109, SEQ ID NO: 129, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 139, SEQ ID NO: 128, SEQ ID NO: 111, SEQ ID NO: 133, SEQ ID NO: 140, SEQ ID NO: 113 and SEQ ID NO: 136. The at least 2 markers may be at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at
30 least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at least 10 markers, such as at least 11 markers, such as at least 12 markers, such as at least 13 markers, such as at least 14 markers, such as at least 15 markers, such as at least 16 markers, such as at least 17 markers, such as at least 18 markers, such as at least 19 markers, such as at least 20 markers, such as at
35 least 21 markers, such as at least 22 markers, such as at least 23 markers, such as at least 24 markers, such as 25 markers selected from the group consisting of SEQ ID

NO: 135, SEQ ID NO: 115, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 121, SEQ ID NO: 114, SEQ ID NO: 118, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 124, SEQ ID NO: 119, SEQ ID NO: 132, SEQ ID NO: 116, SEQ ID NO: 138, SEQ ID NO: 117, SEQ ID NO: 130, SEQ ID NO: 134, SEQ ID NO: 108, SEQ ID NO: 125, SEQ ID NO: 107, SEQ ID NO: 120, SEQ ID NO: 131, SEQ ID NO: 137, SEQ ID NO: 106, SEQ ID NO: 109, SEQ ID NO: 129, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 139, SEQ ID NO: 128, SEQ ID NO: 111, SEQ ID NO: 133, SEQ ID NO: 140, SEQ ID NO: 113 and SEQ ID NO: 136.

10 Preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 135, SEQ ID NO: 115, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 121, SEQ ID NO: 114, SEQ ID NO: 118, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 124, SEQ ID NO: 119, SEQ ID NO: 132, SEQ ID NO: 116, SEQ ID NO: 138, SEQ ID NO: 117, SEQ ID NO: 130, SEQ ID NO: 134, SEQ ID NO: 108, SEQ ID NO: 125, SEQ ID NO: 107, SEQ ID NO: 120, SEQ ID NO: 131, SEQ ID NO: 137, SEQ ID NO: 106 and SEQ ID NO: 109. The at least 2 markers may be at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at least 10 markers, such as at least 11 markers, such as at least 12 markers, such as at least 13 markers, such as at least 14 markers, such as at least 15 markers, such as at least 16 markers, such as at least 17 markers, such as at least 18 markers, such as at least 19 markers, such as at least 20 markers, such as at least 21 markers, such as at least 22 markers, such as at least 23 markers, such as at least 24 markers, such as 25 markers selected from the group consisting of SEQ ID NO: 135, SEQ ID NO: 115, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 121, SEQ ID NO: 114, SEQ ID NO: 118, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 124, SEQ ID NO: 119, SEQ ID NO: 132, SEQ ID NO: 116, SEQ ID NO: 138, SEQ ID NO: 117, SEQ ID NO: 130, SEQ ID NO: 134, SEQ ID NO: 108, SEQ ID NO: 125, SEQ ID NO: 107, SEQ ID NO: 120, SEQ ID NO: 131, SEQ ID NO: 137, SEQ ID NO: 106 and SEQ ID NO: 109.

30 More preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 135, SEQ ID NO: 115, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 121, SEQ ID NO: 114 and SEQ ID NO: 118. The at least 2 markers may be at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as 7 markers selected from the group consisting of SEQ ID NO: 135,

SEQ ID NO: 115, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 121, SEQ ID NO: 114 and SEQ ID NO: 118.

Useful primers

5 Useful primer pairs to discriminate whether a subject suffering from an IBD suffers from UC or CD are also provided herein.

Thus in some embodiments, the at least 2 primer pairs are selected from the group consisting of the following pairs: SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 5 and SEQ ID NO: 6; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 63 and SEQ ID NO: 64; SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 67 and SEQ ID NO: 68; SEQ ID NO: 45 and SEQ ID NO: 46; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID NO: 69 and SEQ ID NO: 70; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 61 and SEQ ID NO: 62. The at least 2 primer pairs may be at least 3 primer pairs, such as at least 4 primer pairs, such as at least 5 primer pairs, such as at least 6 primer pairs, such as at least 7 primer pairs, such as at least 8 primer pairs, such as at least 9 primer pairs, such as at least 10 primer pairs, such as at least 11 primer pairs, such as at least 12 primer pairs, such as at least 13 primer pairs, such as at least 14 primer pairs, such as at least 15 primer pairs, such as at least 16 primer pairs, such as at least 17 primer pairs, such as at least 18 primer pairs, such as at least 19 primer pairs, such as at least 20 primer pairs, such as at least 21 primer pairs, such as at least 22 primer pairs, such as at least 23 primer pairs, such as at least 24 primer pairs, such as at least 25 primer pairs, such as at least 26 primer pairs, such as at least 27 primer pairs, such as at least 28 primer pairs, such as at least 29 primer pairs, such as at least 30 primer pairs, such as at least 31 primer pairs, such as at least 32 primer pairs, such as at least 33 primer pairs, such as at least 34 primer pairs, such as 35 primer pairs,

selected from the group consisting of SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 5 and SEQ ID NO: 6; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 63 and SEQ ID NO: 64; SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 67 and SEQ ID NO: 68; SEQ ID NO: 45 and SEQ ID NO: 46; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID NO: 69 and SEQ ID NO: 70; SEQ ID NO: 15 and SEQ ID NO: 16; and SEQ ID NO: 61 and SEQ ID NO: 62.

Preferably the at least 2 primer pairs are selected from the group consisting of the following pairs: SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 5 and SEQ ID NO: 6; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 63 and SEQ ID NO: 64; SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 7 and SEQ ID NO: 8. The at least 2 primer pairs may be at least 3 primer pairs, such as at least 4 primer pairs, such as at least 5 primer pairs, such as at least 6 primer pairs, such as at least 7 primer pairs, such as at least 8 primer pairs, such as at least 9 primer pairs, such as at least 10 primer pairs, such as at least 11 primer pairs, such as at least 12 primer pairs, such as at least 13 primer pairs, such as at least 14 primer pairs, such as at least 15 primer pairs, such as at least 16 primer pairs, such as at least 17 primer pairs, such as at least 18 primer pairs, such as at least 19 primer pairs, such as at least 20 primer pairs, such

as at least 21 primer pairs, such as at least 22 primer pairs, such as at least 23 primer pairs, such as at least 24 primer pairs, such as 25 primer pairs selected from the group consisting of SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 5 and SEQ ID NO: 6; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 63 and SEQ ID NO: 64; SEQ ID NO: 1 and SEQ ID NO: 2; and SEQ ID NO: 7 and SEQ ID NO: 8.

More preferably, the at least 2 primer pairs are selected from the group consisting of the following pairs: SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 25 and SEQ ID NO: 26. The at least 2 primer pairs may be at least 3 primer pairs, such as at least 4 primer pairs, such as at least 5 primer pairs, such as at least 6 primer pairs, such as 7 primer pairs selected from the group consisting of SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 25 and SEQ ID NO: 26.

Marker combinations

Specific marker combinations may be particularly useful in the above methods and are also disclosed herein. The following section discloses such specific combinations, which may apply to all of the methods disclosed herein.

In some embodiments, if one of the at least two markers is SEQ ID NO: 102, then at least one of the other markers is selected from SEQ ID NO: 96, SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 87, SEQ ID NO: 81, SEQ ID NO: 95, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77. Preferably at least one of the other

markers is selected from SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77.

- 5 In some embodiments, if one of the at least two markers is SEQ ID NO: 94, then at least one of the other markers is selected from SEQ ID NO: 86, SEQ ID NO: 71, SEQ ID NO: 96, SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 87, SEQ ID NO: 81, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77. Preferably at least one of the other markers is selected from SEQ ID NO: 86, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 85, SEQ ID NO: 75 and SEQ ID NO: 76.
- 10
- 15 In some embodiments, if one of the at least two markers is SEQ ID NO: 91, then at least one of the other markers is selected from SEQ ID NO: 97, SEQ ID NO: 71, SEQ ID NO: 98, SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 87, SEQ ID NO: 81, SEQ ID NO: 95, SEQ ID NO: 83, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73 and SEQ ID NO: 76. Preferably at least one of the other markers is selected from SEQ ID NO: 105, SEQ ID NO: 87, SEQ ID NO: 92, SEQ ID NO: 85, SEQ ID NO: 75, SEQ ID NO: 99, SEQ ID NO: 88 and SEQ ID NO: 79.
- 20
- 25 In some embodiments, if one of the at least two markers is SEQ ID NO: 100, then at least one of the other markers is selected from SEQ ID NO: 97, SEQ ID NO: 81, , SEQ ID NO: 95, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77. Preferably at least one of the other markers is selected from SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78 and SEQ ID NO: 76.
- 30
- 35 In some embodiments, if one of the at least two markers is SEQ ID NO: 84, then at least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 93, SEQ

ID NO: 105, SEQ ID NO: 95, SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 76 and SEQ ID NO: 77. Preferably at least one of the other markers is selected from SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88 and SEQ ID NO: 73.

In some embodiments, if one of the at least two markers is SEQ ID NO: 90, then at least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 81, SEQ ID NO: 85 and SEQ ID NO: 89. Preferably at least one of the other markers is selected from SEQ ID NO: 72 and SEQ ID NO: 89.

In some embodiments, if one of the at least two markers is SEQ ID NO: 104, then at least one of the other markers is selected from SEQ ID NO: 81, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77. Preferably at least one of the other markers is selected from SEQ ID NO: 81, SEQ ID NO: 99 and SEQ ID NO: 77.

In some embodiments, if one of the at least two markers is SEQ ID NO: 74, then at least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 105, SEQ ID NO: 81, SEQ ID NO: 95, SEQ ID NO: 101, SEQ ID NO: 83, SEQ ID NO: 103, SEQ ID NO: 85, SEQ ID NO: 99, SEQ ID NO: 88 and SEQ ID NO: 73. Preferably at least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 95, SEQ ID NO: 83 and SEQ ID NO: 73.

Accordingly, in some embodiments, if one of the at least two markers is SEQ ID NO: 137, then at least one of the other markers is selected from SEQ ID NO: 131, SEQ ID NO: 107, SEQ ID NO: 128, SEQ ID NO: 140, SEQ ID NO: 122, SEQ ID NO: 116, SEQ ID NO: 130, SEQ ID NO: 138, SEQ ID NO: 127, SEQ ID NO: 117, SEQ ID NO: 115, SEQ ID NO: 110, SEQ ID NO: 124, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID NO: 108, SEQ ID NO: 113, SEQ ID NO: 111 and SEQ ID NO: 112; preferably at least one of the other markers is selected from SEQ ID NO: 107, SEQ ID NO: 128, SEQ ID NO: 140, SEQ ID NO: 115, SEQ ID NO: 110, SEQ ID NO: 124, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID NO: 108, SEQ ID NO: 113, SEQ ID NO: 111 and SEQ ID NO: 112.

In some embodiments, if one of the at least two markers is SEQ ID NO: 129, then at least one of the other markers is selected from SEQ ID NO: 121, SEQ ID NO: 106, SEQ ID NO: 131, SEQ ID NO: 107, SEQ ID NO: 128, SEQ ID NO: 140, SEQ ID NO: 122, SEQ ID NO: 116, SEQ ID NO: 136, SEQ ID NO: 138, SEQ ID NO: 127, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 115, SEQ ID NO: 110, SEQ ID NO: 124, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID NO: 108, SEQ ID NO: 113, SEQ ID NO: 111 and SEQ ID NO: 112; preferably at least one of the other markers is selected from SEQ ID NO: 121, SEQ ID NO: 138, SEQ ID NO: 127, SEQ ID NO: 120, SEQ ID NO: 110 and SEQ ID NO: 111.

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In some embodiments, if one of the at least two markers is SEQ ID NO: 126, then at least one of the other markers is selected from SEQ ID NO: 132, SEQ ID NO: 106, SEQ ID NO: 133, SEQ ID NO: 107, SEQ ID NO: 128, SEQ ID NO: 140, SEQ ID NO: 122, SEQ ID NO: 116, SEQ ID NO: 130, SEQ ID NO: 118, SEQ ID NO: 138, SEQ ID NO: 127, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 110, SEQ ID NO: 124, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID NO: 108 and SEQ ID NO: 111; preferably at least one of the other markers is selected from SEQ ID NO: 140, SEQ ID NO: 122, SEQ ID NO: 127, SEQ ID NO: 120, SEQ ID NO: 110, SEQ ID NO: 134, SEQ ID NO: 123 and SEQ ID NO: 114.

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In some embodiments, if one of the at least two markers is SEQ ID NO: 135, then at least one of the other markers is selected from SEQ ID NO: 132, SEQ ID NO: 116, SEQ ID NO: 130, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 127, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 115, SEQ ID NO: 110, SEQ ID NO: 124, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID NO: 108, SEQ ID NO: 113, SEQ ID NO: 111 and SEQ ID NO: 112; preferably at least one of the other markers is selected from SEQ ID NO: 127, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 115, SEQ ID NO: 110, SEQ ID NO: 124, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID NO: 108, SEQ ID NO: 113 and SEQ ID NO: 111.

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In some embodiments, if one of the at least two markers is SEQ ID NO: 119, then at least one of the other markers is selected from SEQ ID NO: 107, SEQ ID NO: 128, SEQ ID NO: 140, SEQ ID NO: 130, SEQ ID NO: 138, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 115, SEQ ID NO: 110, SEQ ID NO: 124, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID NO: 108, SEQ ID NO: 111 and SEQ ID NO: 112; preferably at least one of the other markers is selected from SEQ ID NO: SEQ ID NO:

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138, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 115, SEQ ID NO: 110, SEQ ID NO: 124, SEQ ID NO: 134, SEQ ID NO: 123 and SEQ ID NO: 108.

5 In some embodiments, if one of the at least two markers is SEQ ID NO: 125, then at least one of the other markers is selected from SEQ ID NO: 107, SEQ ID NO: 116, SEQ ID NO: 120 and SEQ ID NO: 124; preferably at least one of the other markers is selected from SEQ ID NO: 107 and SEQ ID NO: 124.

10 In some embodiments, if one of the at least two markers is SEQ ID NO: 139, then at least one of the other markers is selected from SEQ ID NO: 116, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID NO: 111 and SEQ ID NO: 112; preferably at least one of the other markers is selected from SEQ ID NO: 116, SEQ ID NO: 134 and SEQ ID NO: 112.

15 In some embodiments, if one of the at least two markers is SEQ ID NO: 109, then at least one of the other markers is selected from SEQ ID NO: 107, SEQ ID NO: 140, SEQ ID NO: 117, SEQ ID NO: 130, SEQ ID NO: 136, SEQ ID NO: 118, SEQ ID NO: 138, SEQ ID NO: 120, SEQ ID NO: 134, SEQ ID NO: 123 and SEQ ID NO: 108; preferably at least one of the other markers is selected from SEQ ID NO: 107, SEQ ID NO: 130, SEQ ID NO: 118 and SEQ ID NO: 108.

Accuracy, specificity and sensitivity

The methods disclosed herein display surprisingly good sensitivity, specificity and accuracy thereby allowing for correct diagnosis and treatment of patients.

Subjects suffering from UC

25 In preferred embodiments, the specificity of a method for diagnosing a subject with UC is at least 0.75, such as at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.

30 In some embodiments, the sensitivity of such a method is at least 0.3. In preferred embodiments, the sensitivity is at least 0.75, such as at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.

In some embodiments, the accuracy is at least 0.5. In preferred embodiments, the accuracy is at least 0.75, such as at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more

Subjects suffering from CD

5 In preferred embodiments, the sensitivity of a method using at least 2 markers as disclosed herein for determining whether a subject suffers from CD is at least 0.5, such as at least 0.55, such as at least 0.6, such as at least 0.65, such as at least 0.7, such as at least 0.75, such as at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.

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In preferred embodiments, the specificity of a method using at least 2 markers as disclosed herein for determining whether a subject suffers from CD is at least 0.8 or more, such as 0.85 or more, such as 0.9 or more, such as 0.95 or more.

15

In preferred embodiments, the accuracy of a method using at least 2 markers as disclosed herein for determining whether a subject suffers from CD is at least 0.7 or more, such as 0.75 or more, such as 0.8 or more, such as 0.85 or more, such as 0.9 or more, such as 0.95 or more.

Healthy subjects

20 In preferred embodiments, the specificity of a method for determining whether a subject is healthy is at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.

25 In preferred embodiments, the sensitivity of a method for determining whether a subject is healthy is at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.

30 In some embodiments, the accuracy of a method for determining whether a subject is healthy is at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.

Computer implemented methods

The present markers are useful in computer implemented methods for automatically determining whether a subject is healthy or suffers from an IBD. Such methods comprise the steps of:

- 5 i) comparing the expression profiles of at least 2 markers in a sample obtained from said subject with a first expression signature representative of healthy subjects and with a second expression signature representative of subjects suffering from an inflammatory bowel disease, wherein the markers are as defined herein, and wherein the expression profile represents the expression levels of the at least 2 markers together in said subject, the first expression signature represents the average expression levels of the at least 2 markers together in a group of at least 20 healthy subjects, and the second expression signature represents the average expression levels of the at least 2 markers together in a group of subjects suffering from an inflammatory bowel disease;
- 10 ii) determining whether the expression profile is closest to the first expression signature or to the second expression signature;
- wherein:
- 15 - if the expression profile is closest to the first expression signature, the method determines that the subject is healthy;
- if the expression profile is closest to the second expression signature, determining that the subject suffers from an inflammatory bowel disease.
- 20 The skilled person will know how to compare an expression profile with an expression signature. The comparison may be done by a trained person, which can visually assess whether the overall shape of the expression profile from a given sample most resembles a first expression signature or a second expression signature, i.e. the trained person determines to which expression signature the expression profile is
- 25 closest. Upon assessment, the trained person then determines whether the subject is healthy or suffers from an IBD. The comparison may also be done by a software. Methods to train software to perform such classification of samples are known in the art, and may involve a machine learning algorithm such as Random Forests, Support Vector Machines, or neural networks. By supplying marker expression measurements and corresponding diagnosis of reference samples (healthy subject versus IBD subjects, or UC subjects versus CD subjects, or any combination thereof), the algorithm can be trained to compare expression profiles from samples derived from subjects where no diagnosis has been precisely established with expression signatures characteristic of a disorder, and thereby predict whether the subject suffers from a
- 30 given condition or is healthy.
- 35

Treatment of subjects having an IBD, UC or CD

Also disclosed herein is a method of diagnosing and treating an inflammatory bowel disease in a subject in need thereof, said method comprising the steps of:

- a. diagnosing an inflammatory bowel disease with a method as disclosed herein;
5 thereby determining whether the subject is healthy or suffers from an inflammatory bowel disease such as ulcerative colitis or Crohn's disease;
- b. if the subject is found to suffer from an inflammatory bowel disease, treating said subject.

10 The person skilled in the art knows how to treat patients suffering from IBD, as also described in the section "subjects suffering from or suspected of suffering from an inflammatory bowel disease, ulcerative colitis or Crohn's disease".

15 Accordingly is disclosed herein a method of treating an inflammatory bowel disease, wherein the disease is diagnosed as described herein above, before the subject suffering from the disease is treated. The inflammatory bowel disease may be UC or CD.

20 If the subject is found to suffer from UC, the treatment may comprise or consist of mesalamine administration, corticosteroid administration, multimatrix administration, budesonide administration, infliximab administration, adalimumab administration, golimumab administration, vedolizumab administration, surgery, or of a combination thereof. The choice of the therapeutic agent to be administered depends for example on the stage of the disease. Mesalamine can be used in a first stage to induce
25 remission and/or maintain remission in cases with mild or moderate exacerbation, while infliximab will be administered typically if remission cannot be established or maintained.

30 If the subject is found to suffer from CD, the treatment may comprise or consist of budesonide or sulfasalazine administration, corticosteroid administration, anti-tumor necrosis factor drug administration, such as infliximab, adalimumab and certolizumab pegol, surgery, or a combination thereof. Sulfasalazine and budesonide are typically administered to subjects having mild to moderate exacerbation, while methotrexate
35 may be appropriate for cases of recurrence or intolerance.

Although some of the agents administered for treating UC and CD overlap to some extent, there may be differences in the regimen and time of administration.

Kit of parts

5 Also disclosed herein is a kit of parts comprising primers, instructions for use, optionally additional reagents for extracting RNA from biopsy samples, and optionally a software for diagnosing an inflammatory bowel disease, Crohn's disease or ulcerative colitis.

10 The primers are designed to allow measurement of an expression profile as disclosed herein from a sample derived from a subject suspected of suffering from an IBD, UC or CD. The primers thus preferably allow the detection of at least two of the markers disclosed herein. The kit thus preferably comprises at least two primer pairs, as described in the subsections "useful primers" above.

Method for identifying genomic regions useful as markers of an IBD, UC or CD

15 The present methods are based on the identification of a number of genomic regions which can be used as markers for an inflammatory bowel disease, ulcerative colitis and/or Crohn's disease. Starting from samples derived from subjects which are known to be healthy, or to suffer from an inflammatory bowel disease, such as ulcerative colitis or Crohn's disease, it is possible to identify genomic regions which display an
20 expression profile which is characteristic for a given state (healthy, suffering from an IBD, suffering from UC or suffering from CD). Expression profiles which are characteristic for samples derived from subjects suffering from one of the above diseases define expression signatures, which can then be used as reference in the methods of diagnosis disclosed herein. The expression profiles of the same markers in
25 samples derived from subjects suspected of suffering from a disease can be directly compared with the reference expression signatures, and a diagnosis can be made.

Accordingly is provided herein is a method of identifying a group of genomic regions having a first expression profile in a healthy subject, a second expression profile in a
30 subject suffering from Crohn's disease, and a third expression profile in a subject suffering from ulcerative colitis, wherein at least two of the first, second and third expression profiles are different, the method comprising the steps of:

- (i) providing a first sample from a healthy subject, having a first set of transcripts together representing a first transcriptome;

- 5 (ii) providing a second sample from a subject suffering from Crohn's disease, having a second set of transcripts together representing a second transcriptome;
- (iii) providing a third sample from a subject suffering from ulcerative colitis, having a third set of transcripts together representing a third transcriptome;
- 10 (iv) optionally extracting transcripts from the first, the second and the third samples;
- (v) measuring and comparing the levels of at least part of the first set of transcripts, at least part of the second set of transcripts and at least part of the third set of transcripts;
- 15 (vi) identifying the genomic regions for which the levels of at least two of said at least part of the first set of transcripts and at least part of the second set of transcripts and at least part of the third set of transcripts are different; thereby identifying a group of genomic regions having different expression profiles in a healthy subject, in a subject suffering from Crohn's disease, and in a subject suffering from ulcerative colitis.

As shown in the examples, measuring and comparing the transcript levels can be performed at the genome-wide level by using transcriptome measurement methods such as RNA sequencing or 5'-RNA sequencing of capped RNAs (CAGE).

Suitable samples for this purpose are as described in the section "sample".

25 In order for such a method to identify markers which can be used for determining a state such as CD, UC or an IBD, the number of samples should be large enough. Preferably, the markers are identified using samples from at least 20 subjects in each of the groups to be compared (healthy, suffering from an IBD, suffering from UC, suffering from CD). While using larger numbers of samples may refine the accuracy, sensitivity and/or specificity of the method, this should be balanced with considerations on whether it is practically feasible to obtain and/or to analyse very large numbers of samples.

30

Examples

Example 1 - Summary

Genome-wide 5'-RNA sequencing of capped RNAs (CAGE) can detect transcription start sites (TSSs) for known genes and un-annotated RNAs, such as non-coding
5 RNAs. We first applied CAGE on biopsies from the descending colon from 94 IBD patients and controls, providing a genome-wide map of TSS activity across individuals with and without IBD (Fig.1).

We first defined differentially expressed TSS regions using the CAGE data. Because of
10 the high similarity between CDa and UCa, we first defined sets of up-/down-regulated TSSs in both CDa and UCa vs. Ctrl (IBD_{up} and IBD_{down}, respectively). Second, we identified TSSs up-regulated in CDa vs. UCa, defined as CD_{spec}, and TSSs up-regulated in UCa vs. CDa, defined as UC_{spec}. The number of TSSs within IBD_{up} (4376) and IBD_{down} (2536) was much larger than in CD_{spec} (337) and UC_{spec} (71) (Fig.2). The
15 inclusion of additional patient data in the analysis, i.e. gender and previous medication, did not affect the number of differentially expressed TSSs substantially, strongly suggesting these effects are minor compared to the CD/UC/Ctrl diagnosis.

Molecular biomarkers distinguishing IBD subgroups and controls would be highly
20 beneficial for improved diagnostics. We sought to reduce the number of biomarkers or "features" (CAGE TSSs or enhancers), enabling robust and clinically feasible qPCR-based measurements. To achieve this, we used successive steps of feature selection and testing (Fig. 3A). First, we analysed the CAGE data from cohort 1 with an ensemble of statistical and manual curation methods to extract 263 TSSs or enhancers
25 distinguishing UCa, CDa and Ctrl groups (See methods below). We then used a Random Forrest (RF) classification framework on the CAGE data for these 263 features, which could predict UC, CD and Ctrl diagnosis with an overall accuracy of 95% assessed by 5-fold cross-validation (Fig. 4, top panels). This high accuracy could be retained when reducing the number of features (Fig.4, lower panels). Based on this,
30 we designed qPCR primers corresponding to 161 of these features, and analyzed their expression using microfluidics qPCR on the same biopsies (cohort 1) as above (161 primer pairs analyzed in biopsies from 74 subjects). RF classification using the microfluidics qPCR expression data gave an overall accuracy of 84% assessed by 5-fold cross-validation (Fig.5, top panels), showing that accurate classification is
35 achievable across experimental methods.. As with CAGE, similar accuracy levels could

be retained down to 30-40 features (Fig. 5, lower panels). Encouraged by this, we used feature reduction to define a final set of 35 features. We trained a RF on microfluidics qPCR data from 35 features from cohort 1 and evaluated it on corresponding measurements from an independent validation cohort (cohort 2: 18 CDa, 46 Ctrl, 37 UCa; Fig 1 and Fig 6A). We achieved an overall accuracy of 85% in this independent cohort, comparable to the training cohort (Fig. 6A, top panels). Our results were substantially better than expected by chance, estimated by using randomly shuffled cohort 1 labels to predict the labels of cohort 2, indicating little or no overfitting (Fig. 6A, lower panel). To explore whether CD sensitivity could be improved further, we employed the gradient boosting decision tree method implemented in XGBoost41, training on the same 35 biomarkers cohort 1 and predicted the diagnosis of the patients in cohort 2. This resulted in an increase in CDa classification sensitivity by 13% points with no overall classification performance decrease (Fig. 6B).

While the accuracies shown in figure 4-6 are using the full set of primers/features as indicated, much smaller set of primers are also informative (see Figures 7-9). Thus, accurate molecular classification of IBD is feasible with few well-chosen biomarkers, and with technology platforms available at many hospitals.

Example 2 – materials and methods

Human samples and cohorts. Two independent cohorts, including IBD patients and controls, were analyzed (figure 1). Cohort 1 (N=94) was used for Cap Analysis of Gene Expression (CAGE) assay and subsequent microfluidics real-time quantitative reverse transcription polymerase chain reaction (real-time qRT-PCR) validation. This cohort included 25 patients with active UC (UCa), 17 patients with UC in remission (UCi), 20 patients with active CD (CDa), 3 patients with CD in remission (CDi) and 29 healthy controls (Ctrl). Cohort 2 (N=101) was used for an independent qPCR validation of selected target genes. The cohort included 37 UCa, 18 CDa, and 46 Ctrl subjects. All included subjects underwent a routine sigmoidoscopy or colonoscopy as part of their clinical evaluation at the Department of Gastroenterology, Medical Section, Herlev Hospital, Denmark or Department of Gastroenterology, Medical Section, Hvidovre Hospital, Denmark due to their clinical symptoms. They were included into the study as UC or CD patients with active disease, or as controls (i.e., an endoscopy was

performed due to gastrointestinal symptoms but all clinical and paraclinical investigations subsequently turned out to be normal). All individuals with IBD had their diagnosis established on well-defined criteria¹ and disease activity of all UC patients were graded in accordance with the Mayo score: a score ≤ 2 with endoscopic sub-score of 0 (i.e., no macroscopic inflammation) as quiescent UC and > 2 as active UC, and CD patients were graded in accordance with the Harvey-Bradshaw score: a score ≤ 5 as quiescent CD and > 5 as active CD. Exclusion criteria were: age above 80 or below 18 years, clinical evidence of infection, recent (within 14 days) use of antibiotics or probiotics, pregnancy, and severe mental illness.

Ethics. The IBD sample collection and CAGE study was approved by the Scientific Ethics Committee of the Capital Region of Denmark, filed under the ethical permission numbers 36538/H-C-2009-057, 22484/H-C-2009-057, 43691/H-6-2014-051 and 53619/H-6-2014-051, covering both biopsy collection and the application of data to next-generation sequencing approaches. All individuals provided written informed consent to participate in this study. In this context, participation meant that 5 extra biopsies were obtained in addition to the number of biopsies required on medical grounds, extending the examination time by 2-3 minutes. Ctrl subjects were a subset of the above set, but were assigned 'Ctrl' when all clinical and paraclinical investigations subsequently indicated no inflammation. Participants were informed both orally and in writing in compliance with the Declaration of Helsinki and the guidelines of the Danish National Scientific Ethics Committee. The gut epithelia organoid and monocyte study was approved by the local bioethical committee (ethical approval numbers 1302159 and 51899, respectively). All samples were obtained from patients who provided informed consent before surgery (for gut organoids) or blood sampling (monocytes).

RNA Extraction

We extracted RNA from pinch biopsies from the descending colon cohort 1 (Fig.1). For UC_a and CD_a, biopsies were taken from inflamed segments, as confirmed by subsequent histology. All mucosal pinch biopsies, each approximately 15 mg, were obtained from the areas of the descending colon using routine endoscopic forceps. The descending colon was chosen to avoid any intersegmental variation. The endoscopic diagnosis of active or inactive disease was confirmed by histopathology conducted on parallel biopsies taken within an inch of the 1st biopsy. The biopsies were immediately placed in RNeasy[®] Stabilization Solution (Ambion[™], Life Technologies) and kept at 4 °C for 24 hours before long term storage at -80 °C. The RNA was extracted using PureLink[®] RNA Mini Kit (Ambion[™], Life Technologies) with freshly made lysis buffer

containing 1% 2-mercaptoethanol (Sigma). The biopsies were homogenized directly in the lysis buffer using an ULTRA-TURRAX® (IKA Works, Inc). The purification was performed following the manufacturer's instructions including an on-column DNase treatment with the PureLink® DNase Set (Ambion™, Life Technologies). For 16
5 samples RNA extraction was performed. Quantity and quality of the RNA was determined for all the samples on a Nanodrop ND-1000 spectrophotometer (Thermo Scientific). The purity was measured as the A260/280 ratio and was between 1.9 and 2.1. RNA integrity was determined using the 2100 Bioanalyzer Instrument (Agilent Technologies) with the Agilent RNA 6000 Pico Kit (Agilent Technologies) as
10 recommended by manufacturer. In cohort 1 the average RNA integrity number (RIN) was 7.6 and no samples were below 5.3. For cohort 2 the average RIN value was 8.0 and no samples were below 6.2.

Identifying biomarkers

CAGE library preparation, sequencing, mapping and processing. CAGE libraries
15 were prepared with an input of 1500 ng of total RNA as starting material. CAGE libraries were prepared individually, but prior to sequencing four CAGE libraries with different barcodes were pooled and applied to the same sequencing lane. The following four barcodes were used: no.2 (CTT), no.3 (GAT), no.6 (ACG) and no.8 (ATC). All used primers and adaptors were purchased from Integrated DNA
20 technologies (IDT). Sequencing of the libraries was performed on a HiSeq2000 instrument from Illumina at the National High-throughput DNA sequencing Centre, University of Copenhagen. To compensate for the low complexity in the 5'ends of the CAGE libraries, 30% Phi-X spike-ins were added to each sequencing lane, as recommended by Illumina. CAGE reads were assigned to their respective originating
25 samples according to identically matching barcodes. Assigned reads were trimmed to remove linker sequences and subsequently filtered for a minimum sequencing quality of 30 in 50% of the bases with the FASTX-Toolkit
(http://hannonlab.cshl.edu/fastx_toolkit/) with the length of 25bp.

30 CAGE tags were mapped using Bowtie4 (version 0.12.7) to the hg19 assembly using v=2 and otherwise standard settings but allowing for multiple alignments. Subsequently, only uniquely mapping reads were retained. Reads that mapped to chrM were discarded. To generate a genome wide map of transcription start sites, 5' ends of the CAGE tags that mapped close to each other on the same strand were grouped into
35 tag clusters (TCs) which were used for all the post analysis. To remove cluster tails

before subsequent expression analysis a queue-based trimming algorithm was applied to all clusters, removing tags from the ends until a maximum of 10 % of the total number of tags had been trimmed away. Expression was calculated as Tags Per Million (TPM), by counting the number of tags per TSS and normalizing to library size (tags/total tags in library*1e6). Unless otherwise mentioned, only TCs having ≥ 1 TPM in at least 3 libraries were retained for further analysis. For simplicity, we refer to TCs as “CAGE-defined TSSs”. A summit, or ‘TC peak’, was identified in each TC, defined as the single base pair position within the TC with highest total TPM coverage across all samples.

Annotation of CAGE-defined TSSs and gene-level expression.

CAGE-defined TSSs were annotated using Gencode v19 annotation (Harrow et al., 2012). The canonical start site was defined as the most upstream annotated start site in the gene model. CAGE-defined TSSs within ± 100 bp of the most upstream annotated TSS for a Gencode-annotated gene were thus labelled as canonical TSSs. CAGE-defined TSSs within ± 100 bp from all other annotated TSS were annotated as known alternative TSS. CAGE-defined TSSs within gene bodies but > 100 bp from an annotated TSS were defined as novel alternative TSSs, CAGE-defined TSSs > 100 bp distant from gene annotation were annotated as novel intergenic TSSs and finally all TSSs located on the antisense strand to annotated genes were defined as novel antisense TSSs. Some analyses were performed at the level of annotated genes, rather than on CAGE-defined TSS level. For these analyses, based on the annotation described above, we summed up all CAGE-defined TSSs overlapping the gene on the same strand.

Statistical tests for differential expression of TSSs and genes.

The edgeR package (Robinson et al., 2009; McCarthy et al., 2012) was used to test for differential expression at both TSS- and gene-level using the GLM quasi-likelihood framework (default settings were used, with the exception that robust estimation at the empirical Bayes stage was used). Only CDa, UCa and Ctrl samples were included in this analysis. The four major batches were included as blocking factors. The following contrasts were used: i) IBD: average of CDa and UCa different from Ctrl and ii) CDvsUC: CD different from UC. Resulting P-values were corrected for multiple testing Benjamini-Hochberg method (producing FDR values). To obtain the final sets of differentially expressed TSSs (or genes) used, we filtered TSSs (or genes) with a log2 fold change of at least -1 or 1 and a FDR of less than 0.05. The IBD_{up}/IBD_{down} sets corresponds to TSSs (or genes) with a positive/negative log2 fold change in contrast i)

and the CDspec/UCspec sets corresponds to TSSs (or genes) with a positive/negative log2 fold change in contrast ii), where a positive log2 fold change corresponds to higher expression in CDa compared to UCa.

Selection of features for classification and microfluidics qPCR validation

5 In order to create an initial candidate list for machine learning-based selection and classification, we reasoned that any single prioritization method has its own disadvantages. Therefore, we performed an ensemble approach where we integrated the results of multiple different analysis methods each aimed to extract TSSs with high power to distinguish our patient groups.

10

As our main goal was classification by machine learning, we will refer to these TSS regions as “features” in this section. Because the shared inflammatory response in UCa and CDa vs. Ctrl was strong, we divided our analysis into an IBD set of features (shared CDa and UCa up- or down-regulation vs. Ctrl), and a set of features
15 corresponding to features differentially expressed between UCa and CDa.

The ensemble analysis consisted of the following components:

- 1) **edgeR14**. In a similar fashion to the quasi-likelihood implementation explained above, standard edgeR (fitGLM and glmLRT) was used to test for effects of CDa vs. Ctrl, UCa vs. Ctrl, CDa vs. UCa and CDa&UCa vs. Ctrl (shared inflammatory response), while controlling for batch effects. Extracted TSSs had a Benjamini-Hochberg FDR < 0.05 and a $|\log_2 \text{fold change}| > 1$, for a total of 4 sets.
- 2) **Partial Least Squares Discriminant Analysis (PLSDA)**: The plsDA function from the R-package DiscrMiner (<https://cran.r-project.org/package=DiscrMiner>) was used to
25 perform PLSDA with 2 components on the variance stabilized expression values from above, using all samples, including quiescent patients, in 3 groups: CDa+CDi, UCa+UCi and Ctrl. The 500 TSSs with the highest and lowest loadings for the component separating Ctrl from the remaining samples were extracted for a total of 1000 TSSs.
- 3) **ComBat13 followed by PCA**: ComBat corrected values were used for PCA
30 analysis. We identified the component that contributed the most to the difference between the two states and sampled 1000 TSS from each side with the highest rotation values. We focused on the PCAs that gave the most explanations for each of the comparisons (PCA1 for shared IBD specific signal and PCA2 for CDspec and UCspec),

producing two lists for IBD (from each side one list) and one list for CDspec and UCspec (from each side one list).

4) **ComBat followed by limma23:** Combat normalized data (as described above) was used for differential expression analysis using the limma package and the lmFit function. TSSs that passed the threshold of log fold change $> |1|$ and FDR < 0.05 were taken into account making two lists for IBD (overrepresented in UC_a vs. Ctrl and overrepresented in CD_a vs. Ctrl) and one list for CD_a vs. UC_a.

5) **Random Forest analysis:** We utilized the inherent ability for Random Forests (RFs) to rank features by their importance for classification accuracy. To do this we used the randomForest function from the randomForest R package (<https://CRAN.R-project.org/package=randomForest>) on Combat-normalized TC expression data (as described above in the "Exploratory data analysis" section). To circumvent the "low N high P" problem with our data (74 samples, 48593 TCs), which makes it very hard to find the most predictive features, we used an iterative feature selection approach where we in each step remove a subset of the least important features. More specifically: in each iteration first we evenly divided all the data into subsets each containing max 500 features. For each of these data subsets a RF was trained to classify the patient labels based only on the data in that particular subset. Next, for each of the data subsets, we removed the 5% of features that had the lowest classification power (lowest MeanDecreaseAccuracy values) resulting in a list of features that is analyzed in the next iteration of the procedure. To make sure an important feature was not lost due to a challenging subset of data, in each iteration we randomly divided all our data into subsets 10 times. In other words, features had several chances of showing its importance. This iterative procedure was terminated when less than 200 features were left. Each RF was made with default parameters except specifying that 501 trees per forest should be generated and specifying the number of variables randomly sampled as candidates at each split by setting the 'mtry' parameter to $(\sqrt{x} - 1) * 2$, where x was the number of features supplied to the individual RF. Using this approach we generated 4 candidate lists: two which enabled classification of IBD patients (CD_a and UC_a) from healthy patients (Ctrl) and two lists which aimed at differentiating between CD_a and UC_a. For the two lists in each category one was based on the full dataset (n=48593 TCs) and the other was based on a high confidence dataset (n=9699 TCs). The high confidence dataset was obtained by requiring i) the tag cluster was annotated as "5_prime_UTR", "intergenic", "known_alternative_cds", "known_alternative_tss", "proximal" or "tss". ii) the width of

the TC was in the range of 2-100 nucleotides (both included). iii) the TC was expressed more than 10 TPM in at least 3 patients.

As a summary, the ensemble produced 10 candidate sets for separating CDa & UCa from Ctrl (3 edgeR, 4 ComBat, 2 RandomForest, 1 PLSDA) and 5 candidate sets for separating CDa and UCa (edgeR, limma, 2 RandomForests, and PCA).

Next, we overlapped the lists from each comparison to find a consensus set of classification candidates. For the IBD vs. Ctrl comparison, we selected features that appeared in at least 9 out of 10 lists, resulting in 63 features. From the UC/CD set we selected the 169 features that appeared in at least 2 out of 5 lists. The reasoning behind this unbalanced selection was to have a higher number of features for the more difficult task of distinguishing CD from UC, compared to the easier task of distinguishing Ctrl from UC or CD.

The two lists were merged and a short list of expert-curated known and novel biomarkers (21 TSSs and 10 enhancers) were added. The combined list was then further pruned by manual curation, taking into account overall expression strength and genomic loci complexity. In total, the initial list comprised of 263 features, which was used for initial classification using CAGE data (see below).

Primer Design

For qPCR analysis, the 263 features identified above were assessed for qPCR primer targeting suitability. 181 candidates were taken into the primer design stage, where genomic complexity and primer design feasibility was evaluated manually.

Primers were designed using Primer3 (v.0.4.0)²⁴ aiming for an amplicon length of 70 - 110 bp and a primer melting temperature of 60 °C calculated by the Breslauer thermodynamics (Breslauer et al., 1986). Primers were designed to be intron-spanning when possible, and each designed primer-set was analyzed with UCSC browser in-silico PCR tool in order to ensure a unique region would be amplified. Primers were synthesized by Integrated DNA Technologies (IDT). Primer amplification efficiencies and dynamic ranges were acquired from standard curves constructed from several separate dilution series of pooled cDNA: with the dilutions 1:5, 1:25, 1:100, 1:500 and 1:2500. For further validation melting curves of amplicons were measured to certify

primer specificity. 161 primer pairs (features) successfully passed our quality control and were used for analysis of cohort 1 on the Fluidigm® platform.

Analysis of RNA using Primers

cDNA synthesis, pre-amplification and real-time quantitative PCR (cohort 1). The cDNA
5 synthesis and preamplification was performed. Extracted total RNA was converted into
cDNA by reverse transcription of 500 ng RNA (biopsies) using the QuantiTECT
Reverse Transcription kit (Qiagen), containing a mix of random primers and oligo-dT,
according to the manufacturer's instructions. Two separate cDNA reactions were
performed for each RNA sample. Preamplification was performed using TaqMan
10 PreAmp Master Mix (Applied Biosystems). A 500 µl primer mix (200 nM) combining all
primers to be used on the Fluidigm® plate was prepared by pooling 5 µl of all
primerpairs (20 µM) and filling up the remaining volume with low EDTA TE-buffer (VWR
International). TaqMan PreAmp Master Mix (5 µl) was mixed with 2.5 µl of the 200 nM
primer mix, 2.5 µl diluted cDNA, and incubated at 95 °C for 10 min, followed by 15 to
15 21 cycles of 95 °C for 15 s and 60 °C for 4 min (the number of cycles depended on the
expression measured by CAGE). 16 U of Exonuclease I (New England BioLabs) was
added to the preamplified cDNA, and incubated 30 min at 37 °C, 80 °C for 15 min. The
preamplified cDNA was diluted with low EDTA TE-buffer (VWR International) either 1:5
if the cDNA was preamplified for 21 cycles or 1:10 if the cDNA was preamplified for 19
20 or 15 cycles.

RNA expression was analyzed by real-time qRT-PCR in the microfluidics system
BioMark™ 96.96 Dynamic Array (Fluidigm®). The following cycle parameter was used:
Thermal Mix with 2 min at 50 °C, 30 min at 70 °C, 10 min at 25 °C, UNG and Hot start
25 with 2 min at 50 °C, 10 min at 95 °C, followed by 35 cycles with denaturing for 15 s at 95
°C and annealing/elongation for 1 min at 60 °C. Melting curves were generated after
each run to confirm a single PCR product (from 60 °C to 95 °C, increasing 1 °C/3 s).
Reactions were performed in duplicates (cDNA replicates). Non-template controls
(NTC) were included to indicate potential problems with non-specific amplification or
30 sample contaminations. Non-reverse transcriptase controls were included to assess
potential DNA contamination.

Expression data (Cq values) were acquired using the Fluidigm Real-Time PCR
Analysis software 3.0.2 (Fluidigm®) and exported to GenEx (MultiD) for data pre-
35 processing including interplate calibration, individual PCR efficiency correction for each

primer assay, normalization to reference genes, and averaging of cDNA technical replicates. Using GeNorm (Dillies et al., 2013) and NormFinder (Leng et al., 2013), we identified the most stable reference genes of the 10 reference genes included on the plates. This was done separately for all plates run with the same number of preamplification cycles. By normalizing to these reference genes, ΔCq values were calculated and used in the down-stream analysis.

cDNA synthesis, pre-amplification and real-time quantitative PCR (cohort 2). For cohort 2, the 161 features were reduced to 36 features by ranking the features for classification power. Briefly, a RF was trained to predict subject groups, both using all groups and one-vs-rest specification (i.e. UCa vs. non-UCa) using the randomForest R package (Skovgaard et al., 2013). The optimal value for the mtry parameter was found using 100 five-fold cross-validations using the caret package (<https://github.com/topepo/caret/>) train-function and ntree=1000. Feature importance for both classification tasks were extracted using the importance function with type=2 (mean decrease in node impurity or gini index). Primer pairs with a high importance in both complete and one-vs-rest classification were selected as the most predictive. In addition to these random forest predictive features, 6 gene based features were selected to evaluate potentially interesting stories identified in the first cohort.

cDNA synthesis and preamplification was performed as described above for cohort 1 with an adjustment of the number of pre-amplification cycles. In this cohort cDNA was either preamplified 15 or 20 cycles, depending on expression level of the primer targets. The preamplified cDNA was diluted with low EDTA TE-buffer (VWR International) either 1:5 if the cDNA was preamplified for 20 cycles, or 1:10 if the cDNA was preamplified for 15 cycles. RNA expression was analyzed by real-time qRT-PCR in the microfluidics system BioMark™ 192.24 Dynamic Array (Fluidigm®) following the same protocol as used for the cohort 1 runs, with volumes adjusted to the 192.24 format, as described by manufacturer. Expression data (ΔCq values) were acquired and treated similar to cohort 1 (see above).

Analysis of microfluidics qPCR data

Batch correction and expression normalization. For each primer all ΔCq value from cohort 1 and cohort 2 were batch corrected using the removeBatchEffect function from limma (Untergasser et al., 2013), giving the subject/group labels (CDa, UCa, Ctrl) as covariates and cohort and hospital of origin as batch effects and specifying the 'robust'

method should be used for the linear models. Afterwards the batch corrected $\Delta\Delta Cq$ values were calculated in a two-step process: 1) $x = 2^{(-1 * \Delta Cq)}$. 2), $\Delta\Delta Cq = \log_2(x/\min(x))$.

5 **Preprocessing of microfluidics qPCR data for classification analysis for cohort 1 and 2.** For classification analysis (see below), only Ctrl, UCa and CDa subjects were considered. We removed one subject and one primer pair from the analysis which both had >10% 'NA' values from the $\Delta\Delta Cq$ Fluidigm® data, making the final feature count 35. The remaining missing values (N=16, 0.26% of total) were imputed via bagged
10 regression trees using the preprocess function from the "caret" R package (<https://CRAN.R-project.org/package=caret>) specifying methods to the bagImpute function. Experimental practice and reporting were performed according to MIQE guidelines (Liaw et al., 2002).

15 **Prediction of IBD subject diagnosis (classification analysis)**

For all three classification analyses performed we used a two-step RF classification approach with the randomForest function from the randomForest R package (<https://CRAN.R-project.org/package=randomForest>). In this approach the first step was a RF trained to distinguish IBD (CDa and UCa) from healthy subjects (Ctrl) and the
20 second step was a RF trained to distinguish CDa from UCa. The two-step approach was chosen over an all-in-one approach because it was based on 5-fold cross-validation in the CAGE data resulting in better CDa sensitivities (data not shown).

To optimize the parameters most important for a RF model, m indicating the number of
25 variables randomly sampled as candidates at each split and n indicating the minimum size of terminal nodes (corresponding to the mtry and nodesize options in the R RandomForest package), we used a grid search approach testing each pairwise combination where $n=\{2,3,4,5\}$ and $m=(\sqrt{(x-1)})^y$, where x is the number of features supplied to the RF and $y=\{1/2, 3/4, 1, 6/4, 2\}$. For each of the three classifications
30 analyses performed the final m and n parameters were chosen as the combination giving the highest overall accuracy in the two-step RF approach based on the average result of 5-fold cross-validation in cohort 1. Apart from this all RFs were created with default parameters except specifying that each RF should have 1001 trees.

35 To assess the accuracy of the classification model we performed 101 RF iterations of 5-fold cross validation. The only exception to this was the classification of subject

labels on cohort 2, where 101 RFs were created based on data from cohort 1 and used for prediction in cohort 2. For each of the 101 iterations, the overall accuracy and CDa, UCa and Ctrl-group-specific accuracy, sensitivity and specificity were calculated. For each of these, we reported the average and 95% confidence interval across the 101 iterations. The CDa, UCa and Ctrl-group specific performance measures were calculated by for each labels recasting the problem in a binary setting (e.g. for the 'Ctrl label converting both CDa and UCa to 'non-Ctrl) and then assessing accuracy, sensitivity and specificity. The overall accuracy was assessed on all three categories.

To assess the observed vs. expected performance in classification, we trained 1001 RF models on randomly shuffled labels (again only based on cohort 1 data). These models were then used to predict the patient labels of cohort 2 and these predictions were compared to the true labels. Performance measures were calculated as described above.

To analyze the relation between number of features in the model and classification accuracy, for a selected number of features referred to as i , we randomly selected i features from the total set of features and performed 5-fold cross-validation with the same parameters as identified by the grid search above. This procedure was repeated 11 times for each selected i . The average accuracy and 95% confidence interval of these repeated analyses were reported for each i .

Example 3 – sensitivity, specificity and accuracy

We show three examples of marker combinations and their predictive performance for diagnosing UC, CD, or absence of IBD.

Combination 1

Forward primers: SEQ ID NO: 59, SEQ ID NO: 47, SEQ ID NO: 65.

Reverse primers: SEQ ID NO: 60, SEQ ID NO: 48, SEQ ID NO: 66.

Combination 2

Forward primers: SEQ ID NO: 59, SEQ ID NO: 19, SEQ ID NO: 41, SEQ ID NO: 47, SEQ ID NO: 65, SEQ ID NO: 35.

Reverse primers: SEQ ID NO: 60, SEQ ID NO: 20, SEQ ID NO: 42, SEQ ID NO: 48, SEQ ID NO: 66, SEQ ID NO: 36.

Combination 3

Forward primers: SEQ ID NO: 59, SEQ ID NO: 19, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 31, SEQ ID NO: 47, SEQ ID NO: 65, SEQ ID NO: 27, SEQ ID NO: 35, SEQ ID NO: 11.

- 5 Reverse primers: SEQ ID NO: 60, SEQ ID NO: 20, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 32, SEQ ID NO: 48, SEQ ID NO: 66, SEQ ID NO: 28, SEQ ID NO: 36, SEQ ID NO: 12.

Diagnosing UC

Marker combination	UC accuracy	UC sensitivity	UC specificity
1	0.854	0.868	0.847
2	0.864	0.868	0.862
3	0.875	0.895	0.863

10

- 15 Diagnosing CD

Marker combination	CD accuracy	CD sensitivity	CD specificity
1	0.853	0.505	0.947
2	0.856	0.525	0.945
3	0.868	0.534	0.958

Determining absence of IBD

Marker combination	Healthy accuracy	Healthy sensitivity	Healthy specificity
1	0.935	0.938	0.933
2	0.949	0.960	0.941
3	0.951	0.960	0.943

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Sequence overview

Sequence name	Gene Name [laboratory name]	Sequence
SEQ ID NO: 1	.	TGATATCCCAGCCTGTTCAA
SEQ ID NO: 2	.	GCAGAGTAGCCAGGTTGGAG
SEQ ID NO: 3	.	TCATTCCTCGGGTTGCAG
SEQ ID NO: 4	.	GAGCATGGACCCCTGGAT
SEQ ID NO: 5	RP11-293M10.1	CCAGCCAACCTGAACAAAAT
SEQ ID NO: 6	RP11-293M10.1	AATTCAGCCAGGATGGAAGA
SEQ ID NO: 7	E6_NOD2	GAGGCTTTTCAGGCACAGAG
SEQ ID NO: 8	E6_NOD2	GTCCAGGACACTCTCGAAGC
SEQ ID NO: 9	LRP8	CTGCAGCTCCAGCATCTTG
SEQ ID NO: 10	LRP8	GCACTGGAATTGGTCCTTTT
SEQ ID NO: 11	C2CD4B	TGCAACCAGATCCAGAGACA
SEQ ID NO: 12	C2CD4B	GGCCGAGGAACAGAGTTTC
SEQ ID NO: 13	APOB	CGAAGAGGAAATGCTGGAAA
SEQ ID NO: 14	APOB	GTACTTCCGGAGGTGCTTGA
SEQ ID NO: 15	DDX5	CGTCAAAGGATTATCAGACACG
SEQ ID NO: 16	DDX5	CAAATCGAGGTGCACCAAA
SEQ ID NO: 17	CCL25	TGCAGCATGAACCTGTGG

SEQ ID NO: 18	CCL25	CAGGCAGCAGTCCTCAAAG
SEQ ID NO: 19	SLC9A3R2	GGAATGTGGGCCACTGAC
SEQ ID NO: 20	SLC9A3R2	CTCCACAGCCTTGATCCTTT
SEQ ID NO: 21	PFKFB3	AAGATGCCGTTGGAAGTAC
SEQ ID NO: 22	PFKFB3	GGGAGTTGGTCAGCTTTGG
SEQ ID NO: 23	CLDN2	GGTGTTCAAGGAGCAAGAGC
SEQ ID NO: 24	CLDN2	CAAGTTGGAGGCCAAGAGAG
SEQ ID NO: 25	ALKBH4	CATCCGGACCTGTCTGATCT
SEQ ID NO: 26	ALKBH4	GGTGTCTGGAGCAGTAAATGAA
SEQ ID NO: 27	CHI3L1	AAGGGAAGAGGCCACACC
SEQ ID NO: 28	CHI3L1	CAGCACCAGGACCACAAAG
SEQ ID NO: 29	LARP1B_antisense	GCCTACCTCAGACCAAAATACTTC
SEQ ID NO: 30	LARP1B_antisense	GATTACAGGCATGAGCCACTG
SEQ ID NO: 31	HSD3B2	TGGACTCCTCTGTCCAGCTT
SEQ ID NO: 32	HSD3B2	GGAAACACTTGCCAGGAAAC
SEQ ID NO: 33	IGLV7-43	ATGGCCTGGACTCCTCTCTT
SEQ ID NO: 34	IGLV7-43	CTCCTGGGGACACAGTCAGT
SEQ ID NO: 35	CD55	GCTGCTGGTGTCTGTTGTG
SEQ ID NO: 36	CD55	TCCTCGGGAAAACCTTGACG
SEQ ID NO: 37	IGLV10-54	TCCTGACCCTCCTCACTCAC
SEQ ID NO: 38	IGLV10-54	AGTGTGGCGGTCTGTCTCA
SEQ ID NO: 39	SRSF5	TACGGACCTGTCTGGGTCTC
SEQ ID NO: 40	SRSF5	ATGAATACCCGACAGCCACT
SEQ ID NO: 41	CDX2	GAACCTGTGCGAGTGGATG
SEQ ID NO: 42	CDX2	TTGTCTTTTCGTCTGGTTTTTC
SEQ ID NO: 43	PDK2	CGCTGTCCATGAAGCAGTT
SEQ ID NO: 44	PDK2	TGAGGAAGGTGAAGGAGGTTT
SEQ ID NO: 45	GABARAPL2	GCCATGAAGTGGATGTTCAA
SEQ ID NO: 46	GABARAPL2	GGAACCCTGTCTGGGATATTT
SEQ ID NO: 47	CXCL1	ATTCACCCCAAGAACATCCA
SEQ ID NO: 48	CXCL1	TTTCCGCCATTCTTGAGT
SEQ ID NO: 49	SLC6A14	CTTCAAGTGCAGGGAGAAGG
SEQ ID NO: 50	SLC6A14	CCAGTTACCACGGTCCTGAT
SEQ ID NO: 51	WFDC2	ATAGCACCATGCCTGCTTGT
SEQ ID NO: 52	WFDC2	GCCAGTCTTCTCTGCTCCTG
SEQ ID NO: 53	IGLV2-8_MIR650	TCCTCACCTCCTCACTCAG
SEQ ID NO: 54	IGLV2-8_MIR650	TGCAGGAGATGGTGACTGAC
SEQ ID NO: 55	IGHV3-49	GACCACCAACCATGGAGTTT
SEQ ID NO: 56	IGHV3-49	GCTGCACCTCACATTGGAC
SEQ ID NO: 57	BHLHE40	GACTGGAGCACGGAGACCTA
SEQ ID NO: 58	BHLHE40	GCTTTATTCCCCGTCTTGACT
SEQ ID NO: 59	HNF4G	TGGACATGGCAAATTACAGTG
SEQ ID NO: 60	HNF4G	CTTGTCTCTGGGGCAGAACT
SEQ ID NO: 61	FABP6	GGCAAGTTCGAGATGGAGAG
SEQ ID NO: 62	FABP6	TTCGATTACATCGCTGGAGA
SEQ ID NO: 63	DUOXA2	TCTGTTCATAGGCGCAGAAA
SEQ ID NO: 64	DUOXA2	CGCTGAAGGCTTTGTAGGAT
SEQ ID NO: 65	HMGCS2	AGGAAACCTCCCTCACACCT
SEQ ID NO: 66	HMGCS2	CGTCCTTTGGCCAAGTATCT
SEQ ID NO: 67	CFLAR	CTGTCTACCAAGGATCCCTTTC
SEQ ID NO: 68	CFLAR	TGGGTGGTCTCCCTGACTTA

SEQ ID NO: 69	NA	AAGGAAACAGCTGGATCTGC
SEQ ID NO: 70	NA	CCATTTGTCTCCGGGTAAGA
Target		
[X95]	SEQ ID NO: 71	SEQ ID NO: 106
[X112]	SEQ ID NO: 72	SEQ ID NO: 107
RP11-293M10.1	SEQ ID NO: 73	SEQ ID NO: 108
E6_NOD2	SEQ ID NO: 74	SEQ ID NO: 109
LRP8	SEQ ID NO: 75	SEQ ID NO: 110
C2CD4B	SEQ ID NO: 76	SEQ ID NO: 111
APOB	SEQ ID NO: 77	SEQ ID NO: 112
DDX5	SEQ ID NO: 78	SEQ ID NO: 113
CCL25	SEQ ID NO: 79	SEQ ID NO: 114
SLC9A3R2	SEQ ID NO: 80	SEQ ID NO: 115
PFKFB3	SEQ ID NO: 81	SEQ ID NO: 116
CLDN2	SEQ ID NO: 82	SEQ ID NO: 117
ALKBH4	SEQ ID NO: 83	SEQ ID NO: 118
CHI3L1	SEQ ID NO: 84	SEQ ID NO: 119
LARP1B_antisense	SEQ ID NO: 85	SEQ ID NO: 120
HSD3B2	SEQ ID NO: 86	SEQ ID NO: 121
IGLV7-43	SEQ ID NO: 87	SEQ ID NO: 122
CD55	SEQ ID NO: 88	SEQ ID NO: 123
IGLV10-54	SEQ ID NO: 89	SEQ ID NO: 124
SRSF5	SEQ ID NO: 90	SEQ ID NO: 125
CDX2	SEQ ID NO: 91	SEQ ID NO: 126
PDK2	SEQ ID NO: 92	SEQ ID NO: 127
GABARAPL2	SEQ ID NO: 93	SEQ ID NO: 128
CXCL1	SEQ ID NO: 94	SEQ ID NO: 129
SLC6A14	SEQ ID NO: 95	SEQ ID NO: 130
WFDC2	SEQ ID NO: 96	SEQ ID NO: 131
IGLV2-8_MIR650	SEQ ID NO: 97	SEQ ID NO: 132
IGHV3-49	SEQ ID NO: 98	SEQ ID NO: 133
BHLHE40	SEQ ID NO: 99	SEQ ID NO: 134
HNF4G	SEQ ID NO: 100	SEQ ID NO: 135
FABP6	SEQ ID NO: 101	SEQ ID NO: 136
DUOXA2	SEQ ID NO: 102	SEQ ID NO: 137
HMGCS2	SEQ ID NO: 103	SEQ ID NO: 138
CFLAR	SEQ ID NO: 104	SEQ ID NO: 139
NA	SEQ ID NO: 105	SEQ ID NO: 140

Items

1. A method of diagnosing an inflammatory bowel disease, comprising the steps of
 - a. providing a sample from a subject suffering from or suspected of suffering from an inflammatory bowel disease such as ulcerative colitis or Crohn's disease;
 - b. analysing the expression profiles of at least 2 markers, such as at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at

least 6 markers, such as at least 7 markers, such as at least 8 markers, such as at least 9 markers, such as at least 10 markers in said sample, wherein the markers are selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104 and SEQ ID NO: 105,

thereby determining whether the subject is healthy or suffers from an inflammatory bowel disease such as ulcerative colitis or Crohn's disease.

2. The method according to item 1, wherein the markers are selected from the group consisting of SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139 and SEQ ID NO: 140.

3. The method according to any one of the preceding items, wherein the method of diagnosis determines whether the subject suffers from ulcerative colitis.

4. The method according to any one of the preceding items, wherein the method of diagnosis determines whether the subject suffers from Crohn's disease.

5. The method according to any one of the preceding items, wherein the method of diagnosis can discriminate between healthy subjects and subjects suffering from an inflammatory bowel disease.

6. The method according to any one of the preceding items, wherein the method of diagnosis can discriminate between subjects suffering from Crohn's disease and subjects suffering from ulcerative colitis.
- 5 7. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103 and SEQ ID NO: 105.
- 10 8. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 138 and SEQ ID NO: 140.
- 15 20 9. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103 and SEQ ID NO: 105.
- 25 30 10. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 120, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 138 and SEQ ID NO: 140.
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NO: 123, SEQ ID NO: 124, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 138 and SEQ ID NO: 140.

- 5 11. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 76, SEQ ID NO: 82, SEQ ID NO: 94, SEQ ID NO: 99 and SEQ ID NO: 102.
- 10 12. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 111, SEQ ID NO: 117, SEQ ID NO: 129, SEQ ID NO: 134 and SEQ ID NO: 137.
- 15 13. The method according to any one of items 11 or 12, wherein the method determines whether the subject is healthy or suffers from an inflammatory bowel disease.
- 20 14. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 101 and SEQ ID NO: 105.
- 25 15. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 136 and SEQ ID NO: 140.
- 30 16. The method according to any one of items 14 or 15, wherein the method determines whether the subject suffers from Crohn's disease.

17. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 75, SEQ ID NO: 81, SEQ ID NO: 92, SEQ ID NO: 95, SEQ ID NO: 100 and SEQ ID NO: 104.
- 5 18. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 110, SEQ ID NO: 116, SEQ ID NO: 127, SEQ ID NO: 130, SEQ ID NO: 135 and SEQ ID NO: 139.
- 10 19. The method according to item 17 or 18, wherein the method determines whether the subject suffers from ulcerative colitis.
- 15 20. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 94, SEQ ID NO: 103, SEQ ID NO: 84, SEQ ID NO: 92, SEQ ID NO: 88, SEQ ID NO: 80, SEQ ID NO: 99, SEQ ID NO: 76, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 79, SEQ ID NO: 102, SEQ ID NO: 95, SEQ ID NO: 72, SEQ ID NO: 104, SEQ ID NO: 75, SEQ ID NO: 86, SEQ ID NO: 77, SEQ ID NO: 83, SEQ ID NO: 105, SEQ ID NO: 96, SEQ ID NO: 90, SEQ ID NO: 97, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 89, SEQ ID NO: 101, SEQ ID NO: 73, SEQ ID NO: 98, SEQ ID NO: 87, SEQ ID NO: 93, SEQ ID NO: 85 and SEQ ID NO: 78, preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 94, SEQ ID NO: 103, SEQ ID NO: 84, SEQ ID NO: 92, SEQ ID NO: 88, SEQ ID NO: 80, SEQ ID NO: 99, SEQ ID NO: 76, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 79, SEQ ID NO: 102, SEQ ID NO: 95, SEQ ID NO: 72, SEQ ID NO: 104, SEQ ID NO: 75, SEQ ID NO: 86, SEQ ID NO: 77, SEQ ID NO: 83, SEQ ID NO: 105, SEQ ID NO: 96, SEQ ID NO: 90, and SEQ ID NO: 97, more preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 94, SEQ ID NO: 103, SEQ ID NO: 84, SEQ ID NO: 92, SEQ ID NO: 88, SEQ ID NO: 80, SEQ ID NO: 99 and SEQ ID NO: 76.
- 25 21. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 135, SEQ ID NO: 129, SEQ ID NO: 138, SEQ ID NO: 119, SEQ ID NO: 127, SEQ ID NO: 123, SEQ ID NO: 115, SEQ ID NO: 134, SEQ ID NO: 111, SEQ ID NO: 116,
- 30 35

SEQ ID NO: 117, SEQ ID NO: 126, SEQ ID NO: 114, SEQ ID NO: 137, SEQ ID NO: 130, SEQ ID NO: 107, SEQ ID NO: 139, SEQ ID NO: 110, SEQ ID NO: 121, SEQ ID NO: 112, SEQ ID NO: 118, SEQ ID NO: 140, SEQ ID NO: 131, SEQ ID NO: 125, SEQ ID NO: 132, SEQ ID NO: 106, SEQ ID NO: 109, SEQ ID NO: 124, SEQ ID NO: 136, SEQ ID NO: 108, SEQ ID NO: 133, SEQ ID NO: 122, SEQ ID NO: 128, SEQ ID NO: 120 and SEQ ID NO: 113, preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 135, SEQ ID NO: 129, SEQ ID NO: 138, SEQ ID NO: 119, SEQ ID NO: 127, SEQ ID NO: 123, SEQ ID NO: 115, SEQ ID NO: 134, SEQ ID NO: 111, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 126, SEQ ID NO: 114, SEQ ID NO: 137, SEQ ID NO: 130, SEQ ID NO: 107, SEQ ID NO: 139, SEQ ID NO: 110, SEQ ID NO: 121, SEQ ID NO: 112, SEQ ID NO: 118, SEQ ID NO: 140, SEQ ID NO: 131, SEQ ID NO: 125 and SEQ ID NO: 132, more preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 135, SEQ ID NO: 129, SEQ ID NO: 138, SEQ ID NO: 119, SEQ ID NO: 127, SEQ ID NO: 123, SEQ ID NO: 115, SEQ ID NO: 134 and SEQ ID NO: 111.

22. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 94, SEQ ID NO: 88, SEQ ID NO: 103, SEQ ID NO: 76, SEQ ID NO: 84, SEQ ID NO: 99, SEQ ID NO: 81, SEQ ID NO: 102, SEQ ID NO: 82, SEQ ID NO: 79, SEQ ID NO: 95, SEQ ID NO: 92, SEQ ID NO: 72, SEQ ID NO: 100, SEQ ID NO: 104, SEQ ID NO: 91, SEQ ID NO: 105, SEQ ID NO: 75, SEQ ID NO: 97, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 78, SEQ ID NO: 101, SEQ ID NO: 96, SEQ ID NO: 98, SEQ ID NO: 90, SEQ ID NO: 77, SEQ ID NO: 89, SEQ ID NO: 73, SEQ ID NO: 83, SEQ ID NO: 87, SEQ ID NO: 86, SEQ ID NO: 93, SEQ ID NO: 80 and SEQ ID NO: 85, preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 94, SEQ ID NO: 88, SEQ ID NO: 103, SEQ ID NO: 76, SEQ ID NO: 84, SEQ ID NO: 99, SEQ ID NO: 81, SEQ ID NO: 102, SEQ ID NO: 82, SEQ ID NO: 79, SEQ ID NO: 95, SEQ ID NO: 92, SEQ ID NO: 72, SEQ ID NO: 100, SEQ ID NO: 104, SEQ ID NO: 91, SEQ ID NO: 105, SEQ ID NO: 75, SEQ ID NO: 97, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 78, SEQ ID NO: 101, SEQ ID NO: 96 and SEQ ID NO: 98, more preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 94, SEQ ID NO: 88, SEQ ID NO: 103, SEQ ID NO: 76, SEQ ID NO: 84, SEQ ID NO: 99, SEQ ID NO: 81, SEQ ID NO: 102, SEQ ID NO: 82 and SEQ ID NO: 79.

23. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 129, SEQ ID NO: 123, SEQ ID NO: 138, SEQ ID NO: 111, SEQ ID NO: 119, SEQ ID NO: 134, SEQ ID NO: 116, SEQ ID NO: 137, SEQ ID NO: 117, SEQ ID NO: 114, SEQ ID NO: 130, SEQ ID NO: 127, SEQ ID NO: 107, SEQ ID NO: 135, SEQ ID NO: 139, SEQ ID NO: 126, SEQ ID NO: 140, SEQ ID NO: 110, SEQ ID NO: 132, SEQ ID NO: 106, SEQ ID NO: 109, SEQ ID NO: 113, SEQ ID NO: 136, SEQ ID NO: 131, SEQ ID NO: 133, SEQ ID NO: 125, SEQ ID NO: 112, SEQ ID NO: 124, SEQ ID NO: 108, SEQ ID NO: 118, SEQ ID NO: 122, SEQ ID NO: 121, SEQ ID NO: 128, SEQ ID NO: 115 and SEQ ID NO: 120, preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 129, SEQ ID NO: 123, SEQ ID NO: 138, SEQ ID NO: 111, SEQ ID NO: 119, SEQ ID NO: 134, SEQ ID NO: 116, SEQ ID NO: 137, SEQ ID NO: 117, SEQ ID NO: 114, SEQ ID NO: 130, SEQ ID NO: 127, SEQ ID NO: 107, SEQ ID NO: 135, SEQ ID NO: 139, SEQ ID NO: 126, SEQ ID NO: 140, SEQ ID NO: 110, SEQ ID NO: 132, SEQ ID NO: 106, SEQ ID NO: 109, SEQ ID NO: 113, SEQ ID NO: 136, SEQ ID NO: 131 and SEQ ID NO: 133, more preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 129, SEQ ID NO: 123, SEQ ID NO: 138, SEQ ID NO: 111, SEQ ID NO: 119, SEQ ID NO: 134, SEQ ID NO: 116, SEQ ID NO: 137, SEQ ID NO: 117 and SEQ ID NO: 114.
24. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 80, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 86, SEQ ID NO: 79, SEQ ID NO: 83, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 89, SEQ ID NO: 84, SEQ ID NO: 97, SEQ ID NO: 81, SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 95, SEQ ID NO: 99, SEQ ID NO: 73, SEQ ID NO: 90, SEQ ID NO: 72, SEQ ID NO: 85, SEQ ID NO: 96, SEQ ID NO: 102, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 94, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 104, SEQ ID NO: 93, SEQ ID NO: 76, SEQ ID NO: 98, SEQ ID NO: 105, SEQ ID NO: 78 and SEQ ID NO: 101, preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 80, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 86, SEQ ID NO: 79, SEQ ID NO: 83, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 89, SEQ ID NO: 84, SEQ ID NO: 97, SEQ ID

5 NO: 81, SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 95, SEQ ID NO: 99, SEQ ID NO: 73, SEQ ID NO: 90, SEQ ID NO: 72, SEQ ID NO: 85, SEQ ID NO: 96, SEQ ID NO: 102, SEQ ID NO: 71 and SEQ ID NO: 74, more preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 80, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 86, SEQ ID NO: 79 and SEQ ID NO: 83.

10 25. The method according to any one of the preceding items, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 135, SEQ ID NO: 115, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 121, SEQ ID NO: 114, SEQ ID NO: 118, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 124, SEQ ID NO: 119, SEQ ID NO: 132, SEQ ID NO: 116, SEQ ID NO: 138, SEQ ID NO: 117, SEQ ID NO: 130, SEQ ID NO: 134, SEQ ID NO: 108, SEQ ID NO: 125, SEQ ID NO: 107, SEQ ID NO: 120, SEQ ID NO: 131, SEQ ID NO: 137, SEQ ID NO: 106, SEQ ID NO: 109, SEQ ID NO: 129, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 139, SEQ ID NO: 128, SEQ ID NO: 111, SEQ ID NO: 133, SEQ ID NO: 140, SEQ ID NO: 113 and SEQ ID NO: 136, preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 135, SEQ ID NO: 115, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 121, SEQ ID NO: 114, SEQ ID NO: 118, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 124, SEQ ID NO: 119, SEQ ID NO: 132, SEQ ID NO: 116, SEQ ID NO: 138, SEQ ID NO: 117, SEQ ID NO: 130, SEQ ID NO: 134, SEQ ID NO: 108, SEQ ID NO: 125, SEQ ID NO: 107, SEQ ID NO: 120, SEQ ID NO: 131, SEQ ID NO: 137, SEQ ID NO: 106 and SEQ ID NO: 109, more preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 135, SEQ ID NO: 115, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 121, SEQ ID NO: 114 and SEQ ID NO: 118.

30 26. The method according to any one of the preceding items, wherein analysing the expression profile of the at least two markers is performed by quantitative PCR (qPCR) or hybridization based measurement methods such as microarray analysis.

35 27. The method according to any one of the preceding items, wherein the expression profile is analysed by qPCR performed with a primer pair selected from the group consisting of the following pairs:

- (i) SEQ ID NO: 1 and SEQ ID NO: 2;
- (ii) SEQ ID NO: 3 and SEQ ID NO: 4;
- (iii) SEQ ID NO: 5 and SEQ ID NO: 6;
- (iv) SEQ ID NO: 7 and SEQ ID NO: 8;
- 5 (v) SEQ ID NO: 9 and SEQ ID NO: 10;
- (vi) SEQ ID NO: 11 and SEQ ID NO: 12;
- (vii) SEQ ID NO: 13 and SEQ ID NO: 14;
- (viii) SEQ ID NO: 15 and SEQ ID NO: 16;
- (ix) SEQ ID NO: 17 and SEQ ID NO: 18;
- 10 (x) SEQ ID NO: 19 and SEQ ID NO: 20;
- (xi) SEQ ID NO: 21 and SEQ ID NO: 22;
- (xii) SEQ ID NO: 23 and SEQ ID NO: 24;
- (xiii) SEQ ID NO: 25 and SEQ ID NO: 26;
- (xiv) SEQ ID NO: 27 and SEQ ID NO: 28;
- 15 (xv) SEQ ID NO: 29 and SEQ ID NO: 30;
- (xvi) SEQ ID NO: 31 and SEQ ID NO: 32;
- (xvii) SEQ ID NO: 33 and SEQ ID NO: 34;
- (xviii) SEQ ID NO: 35 and SEQ ID NO: 36;
- (xix) SEQ ID NO: 37 and SEQ ID NO: 38;
- 20 (xx) SEQ ID NO: 39 and SEQ ID NO: 40;
- (xxi) SEQ ID NO: 41 and SEQ ID NO: 42;
- (xxii) SEQ ID NO: 43 and SEQ ID NO: 44;
- (xxiii) SEQ ID NO: 45 and SEQ ID NO: 46;
- (xxiv) SEQ ID NO: 47 and SEQ ID NO: 48;
- 25 (xxv) SEQ ID NO: 49 and SEQ ID NO: 50;
- (xxvi) SEQ ID NO: 51 and SEQ ID NO: 52;
- (xxvii) SEQ ID NO: 53 and SEQ ID NO: 54;
- (xxviii) SEQ ID NO: 55 and SEQ ID NO: 56;
- (xxix) SEQ ID NO: 57 and SEQ ID NO: 58;
- 30 (xxx) SEQ ID NO: 59 and SEQ ID NO: 60;
- (xxxi) SEQ ID NO: 61 and SEQ ID NO: 62;
- (xxxii) SEQ ID NO: 63 and SEQ ID NO: 64;
- (xxxiii) SEQ ID NO: 65 and SEQ ID NO: 66;
- (xxxiv) SEQ ID NO: 67 and SEQ ID NO: 68; and
- 35 (xxxv) SEQ ID NO: 69 and SEQ ID NO: 70.

28. The method according to any one of the preceding items, wherein the expression profile is analysed by qPCR performed with a primer pair selected from the group consisting of the following pairs: SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 57 and SEQ ID NO: 58; and SEQ ID NO: 63 and SEQ ID NO: 64.
29. The method according to any one of the preceding items, wherein the expression profile is analysed by qPCR performed with a primer pair selected from the group consisting of the following pairs: SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 4 and SEQ ID NO: 6; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID NO: 61 and SEQ ID NO: 62; and SEQ ID NO: 69 and SEQ ID NO: 70.
30. The method according to any one of the preceding items, wherein the expression profile is analysed by qPCR performed with a primer pair selected from the group consisting of the following pairs: SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 45 and SEQ ID NO: 50; SEQ ID NO: 59 and SEQ ID NO: 60; and SEQ ID NO: 67 and SEQ ID NO: 68.
31. The method according to any one of the preceding items, wherein the expression profile is analysed by qPCR performed with a primer pair selected from the group consisting of the following pairs: SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 63

and SEQ ID NO: 64; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 67 and SEQ ID NO: 68; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 69 and SEQ ID NO: 70; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 61 and SEQ ID NO: 62; SEQ ID NO: 5 and SEQ ID NO: 6; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 45 and SEQ ID NO: 46; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 15 and SEQ ID NO: 16; preferably, the primer pair is selected from the group consisting of the following pairs: SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 63 and SEQ ID NO: 64; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 67 and SEQ ID NO: 68; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 69 and SEQ ID NO: 70; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 53 and SEQ ID NO: 54; more preferably, the primer pair is selected from the group consisting of the following pairs: SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 11 and SEQ ID NO: 12.

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32. The method according to any one of the preceding items, wherein the expression profile is analysed by qPCR performed with a primer pair selected from the group consisting of the following pairs: SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ

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ID NO: 63 and SEQ ID NO: 64; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID
 NO: 17 and SEQ ID NO: 18; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO:
 43 and SEQ ID NO: 44; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 59 and
 SEQ ID NO: 60; SEQ ID NO: 67 and SEQ ID NO: 68; SEQ ID NO: 41 and SEQ
 ID NO: 42; SEQ ID NO: 69 and SEQ ID NO: 70; SEQ ID NO: 9 and SEQ ID NO:
 10; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 1 and SEQ ID NO: 2;
 SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID
 NO: 61 and SEQ ID NO: 62; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO:
 55 and SEQ ID NO: 56; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 13
 and SEQ ID NO: 14; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 5 and
 SEQ ID NO: 6; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 33 and SEQ
 ID NO: 34; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 45 and SEQ ID
 NO: 46; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 29 and SEQ ID NO:
 30; preferably the primer pair is selected from the group consisting of the
 following pairs: SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 35 and SEQ
 ID NO: 36; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 11 and SEQ ID
 NO: 12; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 57 and SEQ ID NO:
 58; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 63 and SEQ ID NO: 64;
 SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ
 ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID
 NO: 3 and SEQ ID NO: 4; SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 67
 and SEQ ID NO: 68; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 69 and
 SEQ ID NO: 70; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 53 and SEQ
 ID NO: 54; SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 7 and SEQ ID NO: 8;
 SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 61 and SEQ ID NO: 62; SEQ
 ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 55 and SEQ ID NO: 56; more
 preferably, the primer pair is selected from the group consisting of the following
 pairs: SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 35 and SEQ ID NO: 36;
 SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ
 ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID
 NO: 21 and SEQ ID NO: 22; SEQ ID NO: 63 and SEQ ID NO: 64; SEQ ID NO:
 23 and SEQ ID NO: 24; SEQ ID NO: 17 and SEQ ID NO: 18.

33. The method according to any one of the preceding items, wherein the
 expression profile is analysed by qPCR performed with a primer pair selected
 from the group consisting of the following pairs: SEQ ID NO: 59 and SEQ ID

NO: 60; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 5 and SEQ ID NO: 6; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 63 and SEQ ID NO: 64; SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 67 and SEQ ID NO: 68; SEQ ID NO: 45 and SEQ ID NO: 46; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 55 and SEQ ID NO: 56; SEQ ID NO: 69 and SEQ ID NO: 70; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 61 and SEQ ID NO: 62; preferably the primer pair is selected from the group consisting of the following pairs: SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 65 and SEQ ID NO: 66; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 57 and SEQ ID NO: 58; SEQ ID NO: 5 and SEQ ID NO: 6; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 63 and SEQ ID NO: 64; SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 7 and SEQ ID NO: 8; more preferably, the primer pair is selected from the group consisting of the following pairs: SEQ ID NO: 59 and SEQ ID NO: 60; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 25 and SEQ ID NO: 26.

34. The method according to any one of the preceding items, wherein the expression profile is analysed using hybridization based measurement methods such as a microarray configured to detect at least two of the transcription products of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104 and SEQ ID NO: 105.
35. The method according to any one of the preceding items, wherein the sample is a sample from the colon, preferably the descending colon of said subject.
36. The method according to any one of the preceding items, wherein the sample is a pinch biopsy, for example a sample from the colon, preferably the descending colon.
37. The method according to any one of the preceding items, wherein the sample is a sample from an inflamed segment of the descending colon.
38. The method according to any one of the preceding items, wherein the subject has previously been diagnosed with an inflammatory bowel disease such as ulcerative colitis or Crohn's disease.
39. The method according to any one of the preceding items, wherein the method comprises a step of extracting RNA from said sample prior to analysing the expression profiles.
40. The method according to any one of the preceding items, wherein:
- (a) if one of the at least two markers is SEQ ID NO: 102, then at least one of the other markers is selected from SEQ ID NO: 96, SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 87, SEQ ID NO: 81, SEQ ID NO: 95, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO:

- 73, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77, preferably at least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77; or
- 5 (b) if one of the at least two markers is SEQ ID NO: 94, then at least one of the other markers is selected from SEQ ID NO: 86, SEQ ID NO: 71, SEQ ID NO: 96, SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 87, SEQ ID NO: 81, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77, preferably at least one of the other markers is selected from SEQ ID NO: 86, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 85, SEQ ID NO: 75 and SEQ ID NO: 76; or
- 10 (c) if one of the at least two markers is SEQ ID NO: 91, then at least one of the other markers is selected from SEQ ID NO: 97, SEQ ID NO: 71, SEQ ID NO: 98, SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 87, SEQ ID NO: 81, SEQ ID NO: 95, SEQ ID NO: 83, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73 and SEQ ID NO: 76, preferably at least one of the other markers is selected from SEQ ID NO: 105, SEQ ID NO: 87, SEQ ID NO: 92, SEQ ID NO: 85, SEQ ID NO: 75, SEQ ID NO: 99, SEQ ID NO: 88 and SEQ ID NO: 79; or
- 15 (d) if one of the at least two markers is SEQ ID NO: 100, then at least one of the other markers is selected from SEQ ID NO: 97, SEQ ID NO: 81, , SEQ ID NO: 95, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77, preferably at least one of the other markers is selected from SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78 and SEQ ID NO: 76; or
- 20 (e) if one of the at least two markers is SEQ ID NO: 84, then at least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 95, SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78 and SEQ ID NO: 76; or
- 25 (f) if one of the at least two markers is SEQ ID NO: 84, then at least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 95, SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78 and SEQ ID NO: 76; or
- 30 (g) if one of the at least two markers is SEQ ID NO: 84, then at least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 95, SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78 and SEQ ID NO: 76; or
- 35 (h) if one of the at least two markers is SEQ ID NO: 84, then at least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 95, SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78 and SEQ ID NO: 76; or

- SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 76 and SEQ ID NO: 77,
preferably at least one of the other markers is selected from SEQ ID NO: SEQ
ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75,
SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88 and SEQ ID NO: 73; or
- 5 (f) if one of the at least two markers is SEQ ID NO: 90, then at least one of the
other markers is selected from SEQ ID NO: 72, SEQ ID NO: 81, SEQ ID NO: 85
and SEQ ID NO: 89, preferably at least one of the other markers is selected
from SEQ ID NO: 72 and SEQ ID NO: 89; or
- 10 (g) if one of the at least two markers is SEQ ID NO: 104, then at least one of the
other markers is selected from SEQ ID NO: 81, SEQ ID NO: 99, SEQ ID NO:
88, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77, preferably at least
one of the other markers is selected from SEQ ID NO: 81, SEQ ID NO: 99 and
SEQ ID NO: 77; or
- 15 (h) if one of the at least two markers is SEQ ID NO: 74, then at least one of the
other markers is selected from SEQ ID NO: 72, SEQ ID NO: 105, SEQ ID NO:
81, SEQ ID NO: 95, SEQ ID NO: 101, SEQ ID NO: 83, SEQ ID NO: 103, SEQ
ID NO: 85, SEQ ID NO: 99, SEQ ID NO: 88 and SEQ ID NO: 73, preferably at
least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 95,
SEQ ID NO: 83 and SEQ ID NO: 73.
- 20
41. The method of any one of the preceding items, wherein:
- (a) if one of the at least two markers is SEQ ID NO: 137, then at least one of the
other markers is selected from SEQ ID NO: 131, SEQ ID NO: 107, SEQ ID NO:
128, SEQ ID NO: 140, SEQ ID NO: 122, SEQ ID NO: 116, SEQ ID NO: 130,
25 SEQ ID NO: 138, SEQ ID NO: 127, SEQ ID NO: 117, SEQ ID NO: 115, SEQ ID
NO: 110, SEQ ID NO: 124, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO:
114, SEQ ID NO: 108, SEQ ID NO: 113, SEQ ID NO: 111 and SEQ ID NO:
112, preferably at least one of the other markers is selected from SEQ ID NO:
107, SEQ ID NO: 128, SEQ ID NO: 140, SEQ ID NO: 115, SEQ ID NO: 110,
30 SEQ ID NO: 124, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID
NO: 108, SEQ ID NO: 113, SEQ ID NO: 111 and SEQ ID NO: 112; or
- (b) if one of the at least two markers is SEQ ID NO: 129, then at least one of the
other markers is selected from SEQ ID NO: 121, SEQ ID NO: 106, SEQ ID NO:
131, SEQ ID NO: 107, SEQ ID NO: 128, SEQ ID NO: 140, SEQ ID NO: 122,
35 SEQ ID NO: 116, SEQ ID NO: 136, SEQ ID NO: 138, SEQ ID NO: 127, SEQ ID
NO: 117, SEQ ID NO: 120, SEQ ID NO: 115, SEQ ID NO: 110, SEQ ID NO:

- 124, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID NO: 108, SEQ ID NO: 113, SEQ ID NO: 111 and SEQ ID NO: 112, preferably at least one of the other markers is selected from SEQ ID NO: 121, SEQ ID NO: 138, SEQ ID NO: 127, SEQ ID NO: 120, SEQ ID NO: 110 and SEQ ID NO: 111; or
- 5 (c) if one of the at least two markers is SEQ ID NO: 126, then at least one of the other markers is selected from SEQ ID NO: 132, SEQ ID NO: 106, SEQ ID NO: 133, SEQ ID NO: 107, SEQ ID NO: 128, SEQ ID NO: 140, SEQ ID NO: 122, SEQ ID NO: 116, SEQ ID NO: 130, SEQ ID NO: 118, SEQ ID NO: 138, SEQ ID NO: 127, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 110, SEQ ID NO:
- 10 124, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID NO: 108 and SEQ ID NO: 111, preferably at least one of the other markers is selected from SEQ ID NO: 140, SEQ ID NO: 122, SEQ ID NO: 127, SEQ ID NO: 120, SEQ ID NO: 110, SEQ ID NO: 134, SEQ ID NO: 123 and SEQ ID NO: 114; or
- (d) if one of the at least two markers is SEQ ID NO: 135, then at least one of the
- 15 other markers is selected from SEQ ID NO: 132, SEQ ID NO: 116, SEQ ID NO: 130, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 127, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 115, SEQ ID NO: 110, SEQ ID NO: 124, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID NO: 108, SEQ ID NO: 113, SEQ ID NO: 111 and SEQ ID NO: 112, preferably at least one of the other
- 20 markers is selected from SEQ ID NO: 127, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 115, SEQ ID NO: 110, SEQ ID NO: 124, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID NO: 108, SEQ ID NO: 113 and SEQ ID NO: 111; or
- (e) if one of the at least two markers is SEQ ID NO: 119, then at least one of the
- 25 other markers is selected from SEQ ID NO: 107, SEQ ID NO: 128, SEQ ID NO: 140, SEQ ID NO: 130, SEQ ID NO: 138, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 115, SEQ ID NO: 110, SEQ ID NO: 124, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID NO: 108, SEQ ID NO: 111 and SEQ ID NO: 112, preferably at least one of the other markers is selected from SEQ ID NO:
- 30 SEQ ID NO: 138, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 115, SEQ ID NO: 110, SEQ ID NO: 124, SEQ ID NO: 134, SEQ ID NO: 123 and SEQ ID NO: 108; or
- (f) if one of the at least two markers is SEQ ID NO: 125, then at least one of the
- 35 other markers is selected from SEQ ID NO: 107, SEQ ID NO: 116, SEQ ID NO: 120 and SEQ ID NO: 124, preferably at least one of the other markers is selected from SEQ ID NO: 107 and SEQ ID NO: 124; or

- (g) if one of the at least two markers is SEQ ID NO: 139, then at least one of the other markers is selected from SEQ ID NO: 116, SEQ ID NO: 134, SEQ ID NO: 123, SEQ ID NO: 114, SEQ ID NO: 111 and SEQ ID NO: 112, preferably at least one of the other markers is selected from SEQ ID NO: 116, SEQ ID NO: 134 and SEQ ID NO: 112; or
- (h) if one of the at least two markers is SEQ ID NO: 109, then at least one of the other markers is selected from SEQ ID NO: 107, SEQ ID NO: 140, SEQ ID NO: 117, SEQ ID NO: 130, SEQ ID NO: 136, SEQ ID NO: 118, SEQ ID NO: 138, SEQ ID NO: 120, SEQ ID NO: 134, SEQ ID NO: 123 and SEQ ID NO: 108, preferably at least one of the other markers is selected from SEQ ID NO: 107, SEQ ID NO: 130, SEQ ID NO: 118 and SEQ ID NO: 108.
42. The method according to any one of the preceding items, wherein the sensitivity of the method for determining whether the subject suffers from UC is at least 0.3, such as at least 0.35, such as at least 0.4, such as at least 0.45, such as at least 0.5, such as at least 0.55, such as at least 0.6, such as at least 0.65, such as at least 0.7, such as at least 0.75, such as at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.
43. The method according to any one of the preceding items, wherein the specificity of the method for determining whether the subject suffers from UC is at least 0.3, such as at least 0.35, such as at least 0.4, such as at least 0.45, such as at least 0.5, such as at least 0.55, such as at least 0.6, such as at least 0.65, such as at least 0.7, such as at least 0.75, such as at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.
44. The method according to any one of the preceding items, wherein the accuracy of the method for determining whether the subject suffers from UC is at least 0.25, such as at least 0.3, such as at least 0.35, such as at least 0.4, such as at least 0.45, such as at least 0.5, such as at least 0.55, such as at least 0.6, such as at least 0.65, such as at least 0.7, such as at least 0.75, such as at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.
45. The method according to any one of the preceding items, wherein the sensitivity of the method for determining whether the subject suffers from CD is at least 0.05, such as at least 0.1, such as at least 0.15, such as at least 0.2, such as at

- least 0.25, such as at least 0.3, such as at least 0.35, such as at least 0.4, such as at least 0.45, such as at least 0.5, such as at least 0.55, such as at least 0.6, such as at least 0.65, such as at least 0.7, such as at least 0.75, such as at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.
- 5
46. The method according to any one of the preceding items, wherein the specificity of the method for determining whether the subject suffers from CD is at least 0.3, such as at least 0.35, such as at least 0.4, such as at least 0.45, such as at least 0.5, such as at least 0.55, such as at least 0.6, such as at least 0.65, such as at least 0.7, such as at least 0.75, such as at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.
- 10
47. The method according to any one of the preceding items, wherein the accuracy of the method for determining whether the subject suffers from CD is at least 0.25, such as at least 0.3, such as at least 0.35, such as at least 0.4, such as at least 0.45, such as at least 0.5, such as at least 0.55, such as at least 0.6, such as at least 0.65, such as at least 0.7, such as at least 0.75, such as at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.
- 15
- 20
48. The method according to any one of the preceding items, wherein the sensitivity of the method for determining whether the subject is healthy is at least 0.3, such as at least 0.35, such as at least 0.4, such as at least 0.45, such as at least 0.5, such as at least 0.55, such as at least 0.6, such as at least 0.65, such as at least 0.7, such as at least 0.75, such as at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.
- 25
49. The method according to any one of the preceding items, wherein the specificity of the method for determining whether the subject is healthy is at least 0.3, such as at least 0.35, such as at least 0.4, such as at least 0.45, such as at least 0.5, such as at least 0.55, such as at least 0.6, such as at least 0.65, such as at least 0.7, such as at least 0.75, such as at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.
- 30
50. The method according to any one of the preceding items, wherein the accuracy of the method for determining whether the subject is healthy is at least 0.25,
- 35

such as at least 0.3, such as at least 0.35, such as at least 0.4, such as at least 0.45, such as at least 0.5, such as at least 0.55, such as at least 0.6, such as at least 0.65, such as at least 0.7, such as at least 0.75, such as at least 0.8, such as at least 0.85, such as at least 0.9, such as at least 0.95 or more.

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51. A method of diagnosing and treating a disorder selected from ulcerative colitis or Crohn's disease in a subject suffering or suspected of suffering therefrom, said method comprising the steps of:

- 10
- a. diagnosing the disorder with a method according to any one of items 1 to 50; thereby determining whether the subject is healthy or suffers from ulcerative colitis or Crohn's disease;
 - b. if the subject is found to suffer from ulcerative colitis or Crohn's disease, treating said subject.

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52. A method of diagnosing and treating an inflammatory bowel disease in a subject in need thereof, said method comprising the steps of:

- 20
- a. diagnosing an inflammatory bowel disease with a method according to any one of items 1 to 50; thereby determining whether the subject is healthy or suffers from an inflammatory bowel disease such as ulcerative colitis or Crohn's disease;
 - b. if the subject is found to suffer from an inflammatory bowel disease, treating said subject.

25

53. The method according to item 52, wherein the inflammatory bowel disease is Crohn's diseases or ulcerative colitis.

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54. The method according to any one of items 52 to 53, wherein the inflammatory bowel disease is ulcerative colitis and the treatment comprises or consists of mesalamine administration, corticosteroid administration, multimatrix administration, budesonide administration, infliximab administration, adalimumab administration, golimumab administration, vedolizumab administration, surgery, or of a combination thereof.

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55. The method according to any one of items 52 to 53, wherein the inflammatory bowel disease is Crohn's disease and the treatment comprises or consists of corticosteroid administration, anti-tumor necrosis factor drug administration,

such as infliximab, adalimumab and certolizumab pegol, surgery, or a combination thereof.

- 5 56. A method of identifying a group of genomic regions having different expression profiles in a healthy subject and in a subject suffering from inflammatory bowel disease, the method comprising the steps of:
- (i) providing a first sample from a healthy subject, having a first set of transcripts together representing a first transcriptome;
 - 10 (ii) providing a second sample from a subject suffering from inflammatory bowel disease, having a second set of transcripts together representing a second transcriptome;
 - (iii) optionally extracting transcripts from the first and the second samples;
 - (iv) measuring and comparing the levels of at least part of the first set of transcripts and at least part of the second set of transcripts;
 - 15 (v) identifying the genomic regions for which the levels of at least part of the first set of transcripts and at least part of the second set of transcripts are different;

thereby identifying a group of genomic regions having different expression profiles in a healthy subject and in a subject suffering from inflammatory bowel disease.

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57. A method of identifying a group of genomic regions having a first expression profile in a healthy subject, a second expression profile in a subject suffering from Crohn's disease, and a third expression profile in a subject suffering from ulcerative colitis, wherein at least two of the first, second and third expression profiles are different, the method comprising the steps of:
- 25 (i) providing a first sample from a healthy subject, having a first set of transcripts together representing a first transcriptome;
 - (ii) providing a second sample from a subject suffering from Crohn's disease, having a second set of transcripts together representing a second transcriptome;
 - 30 (iii) providing a third sample from a subject suffering from ulcerative colitis, having a third set of transcripts together representing a third transcriptome;
 - (iv) optionally extracting transcripts from the first, the second and the third samples;

- (v) measuring and comparing the levels of at least part of the first set of transcripts, at least part of the second set of transcripts and at least part of the third set of transcripts;
- (vi) identifying the genomic regions for which the levels of at least two of said at least part of the first set of transcripts and at least part of the second set of transcripts and at least part of the third set of transcripts are different; thereby identifying a group of genomic regions having different expression profiles in a healthy subject, in a subject suffering from Crohn's disease, and in a subject suffering from ulcerative colitis.

58. The method according to any one of items 56 to 57, wherein the step of measuring and comparing the transcript levels is performed using genome-wide transcriptome measurement methods such as RNA sequencing or 5'-RNA sequencing of capped RNAs (CAGE).

59. The method according to any one of items 56 to 58, wherein the sample is a sample from the colon, preferably the descending colon of said subject.

60. The method according to any one of items 56 to 59, wherein the sample is a pinch biopsy, for example a sample from the colon, preferably from the descending colon.

61. The method according to any one of items 56 to 60, wherein the sample is a sample from an inflamed segment of the descending colon.

62. The method according to any one of items 56 to 61, wherein the subject has previously been diagnosed with an inflammatory bowel disease such as ulcerative colitis or Crohn's disease.

63. A kit of parts, comprising:

- primers for amplifying one of the markers as defined in any one of items 1 to 56;
- instructions for use;
- optionally additional reagents for extracting RNA from biopsy samples;
- optionally a software for diagnosing an inflammatory bowel disease, Crohn's disease or ulcerative colitis.

64. A computer implemented method for automatically determining whether a subject is healthy or suffers from an inflammatory bowel disease, the method comprising the steps of:

- 5 i) comparing the expression profiles of at least 2 markers in a sample
obtained from said subject with a first expression signature representative of
healthy subjects and with a second expression signature representative of
subjects suffering from an inflammatory bowel disease, wherein the markers
are as defined in any one of the preceding items, and wherein the
expression profile represents the expression levels of the at least 2 markers
10 together in said subject, the first expression signature represents the
average expression levels of the at least 2 markers together in a group of at
least 20 healthy subjects, and the second expression signature represents
the average expression levels of the at least 2 markers together in a group
of subjects suffering from an inflammatory bowel disease;
- 15 ii) determining whether the expression profile is closest to the first expression
signature or to the second expression signature;

wherein:

- if the expression profile is closest to the first expression signature, the method determines that the subject is healthy;
- if the expression profile is closest to the second expression signature, determining that the subject suffers from an inflammatory bowel disease.

65. A computer implemented method for determining whether a subject suffers from ulcerative colitis or from Crohn's disease, the method comprising the steps of:

- 25 i) comparing the expression profile of at least 2 markers in a sample obtained from said subject with a first reference profile representative of healthy subjects, with a second reference profile representative of subjects suffering from ulcerative colitis and with a third reference profile representative of subjects suffering from Crohn's disease, wherein the markers are as defined
30 in any one of the preceding items, and wherein the expression profile represents the expression levels of the at least 2 markers together in said subject, the first reference profile represents the average expression levels of the at least 2 markers together in a group of at least 20 healthy subjects, the second reference profile represents the average expression levels of the at least 2 markers together in a group of subjects suffering from ulcerative
35 colitis and the third reference profile represents the average expression

levels of the at least 2 markers together in a group of subjects suffering from Crohn's disease;

- ii) determining whether the expression profile is closest to the first reference profile, to the second reference profile or to the third reference profile;

5 wherein:

- if the expression profile is closest to the first reference profile, determining that the subject is healthy;
- if the expression profile is closest to the second reference profile, determining that the subject suffers from ulcerative colitis;
- 10 - if the expression profile is closest to the third reference profile, determining that the subject suffers from Crohn's disease.

66. A system comprising a computer and a computer implemented method according to item 65.

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Claims

1. A method of diagnosing an inflammatory bowel disease, comprising the steps of
 - a. providing a sample from a subject suffering from or suspected of suffering
5 from an inflammatory bowel disease such as ulcerative colitis or Crohn's disease;
 - b. analysing the expression profiles of at least 2 markers, such as at least 3 markers, such as at least 4 markers, such as at least 5 markers, such as at least 6 markers, such as at least 7 markers, such as at least 8 markers, such
10 as at least 9 markers, such as at least 10 markers in said sample, wherein the markers are selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO:
15 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104 and SEQ ID NO: 105,
20 thereby determining whether the subject is healthy or suffers from an inflammatory bowel disease such as ulcerative colitis or Crohn's disease.
2. The method according to claim 1, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73,
25 SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103 and
30 SEQ ID NO: 105.
3. The method according to any one of the preceding claims, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77,
35 SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO:

82, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103 and SEQ ID NO: 105.

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4. The method according to any one of the preceding claims, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 101 and SEQ ID NO: 105.

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5. The method according to any one of the preceding claims, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 75, SEQ ID NO: 81, SEQ ID NO: 92, SEQ ID NO: 95, SEQ ID NO: 100 and SEQ ID NO: 104.

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6. The method according to any one of the preceding claims, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 94, SEQ ID NO: 103, SEQ ID NO: 84, SEQ ID NO: 92, SEQ ID NO: 88, SEQ ID NO: 80, SEQ ID NO: 99, SEQ ID NO: 76, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 79, SEQ ID NO: 102, SEQ ID NO: 95, SEQ ID NO: 72, SEQ ID NO: 104, SEQ ID NO: 75, SEQ ID NO: 86, SEQ ID NO: 77, SEQ ID NO: 83, SEQ ID NO: 105, SEQ ID NO: 96, SEQ ID NO: 90, SEQ ID NO: 97, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 89, SEQ ID NO: 101, SEQ ID NO: 73, SEQ ID NO: 98, SEQ ID NO: 87, SEQ ID NO: 93, SEQ ID NO: 85 and SEQ ID NO: 78, preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 94, SEQ ID NO: 103, SEQ ID NO: 84, SEQ ID NO: 92, SEQ ID NO: 88, SEQ ID NO: 80, SEQ ID NO: 99, SEQ ID NO: 76, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 79, SEQ ID NO: 102, SEQ ID NO: 95, SEQ ID NO: 72, SEQ ID NO: 104, SEQ ID NO: 75, SEQ ID NO: 86, SEQ ID NO: 77, SEQ ID NO: 83, SEQ ID NO: 105, SEQ ID NO: 96, SEQ ID NO: 90, and SEQ ID NO: 97, more preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 94, SEQ ID NO: 103, SEQ ID NO: 84, SEQ ID NO: 92, SEQ ID NO: 88, SEQ ID NO: 80, SEQ ID NO: 99 and SEQ ID NO: 76.

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7. The method according to any one of the preceding claims, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 94, SEQ ID NO: 88, SEQ ID NO: 103, SEQ ID NO: 76, SEQ ID NO: 84, SEQ ID NO: 99, SEQ ID NO: 81, SEQ ID NO: 102, SEQ ID NO: 82, SEQ ID NO: 79, SEQ ID NO: 95, SEQ ID NO: 92, SEQ ID NO: 72, SEQ ID NO: 100, SEQ ID NO: 104, SEQ ID NO: 91, SEQ ID NO: 105, SEQ ID NO: 75, SEQ ID NO: 97, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 78, SEQ ID NO: 101, SEQ ID NO: 96, SEQ ID NO: 98, SEQ ID NO: 90, SEQ ID NO: 77, SEQ ID NO: 89, SEQ ID NO: 73, SEQ ID NO: 83, SEQ ID NO: 87, SEQ ID NO: 86, SEQ ID NO: 93, SEQ ID NO: 80 and SEQ ID NO: 85, preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 94, SEQ ID NO: 88, SEQ ID NO: 103, SEQ ID NO: 76, SEQ ID NO: 84, SEQ ID NO: 99, SEQ ID NO: 81, SEQ ID NO: 102, SEQ ID NO: 82, SEQ ID NO: 79, SEQ ID NO: 95, SEQ ID NO: 92, SEQ ID NO: 72, SEQ ID NO: 100, SEQ ID NO: 104, SEQ ID NO: 91, SEQ ID NO: 105, SEQ ID NO: 75, SEQ ID NO: 97, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 78, SEQ ID NO: 101, SEQ ID NO: 96 and SEQ ID NO: 98, more preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 94, SEQ ID NO: 88, SEQ ID NO: 103, SEQ ID NO: 76, SEQ ID NO: 84, SEQ ID NO: 99, SEQ ID NO: 81, SEQ ID NO: 102, SEQ ID NO: 82 and SEQ ID NO: 79.
8. The method according to any one of the preceding claims, wherein the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 80, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 86, SEQ ID NO: 79, SEQ ID NO: 83, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 89, SEQ ID NO: 84, SEQ ID NO: 97, SEQ ID NO: 81, SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 95, SEQ ID NO: 99, SEQ ID NO: 73, SEQ ID NO: 90, SEQ ID NO: 72, SEQ ID NO: 85, SEQ ID NO: 96, SEQ ID NO: 102, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 94, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 104, SEQ ID NO: 93, SEQ ID NO: 76, SEQ ID NO: 98, SEQ ID NO: 105, SEQ ID NO: 78 and SEQ ID NO: 101, preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 80, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 86, SEQ ID NO: 79, SEQ ID NO: 83, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 89, SEQ ID NO: 84, SEQ ID NO: 97, SEQ ID NO: 81, SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 95, SEQ ID NO: 99, SEQ ID NO: 73, SEQ ID NO: 90, SEQ ID NO: 72, SEQ ID NO: 85, SEQ ID NO: 96, SEQ ID NO: 102, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 94, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 104, SEQ ID NO: 93, SEQ ID NO: 76, SEQ ID NO: 98, SEQ ID NO: 105, SEQ ID NO: 78 and SEQ ID NO: 101.

96, SEQ ID NO: 102, SEQ ID NO: 71 and SEQ ID NO: 74, more preferably the at least 2 markers are selected from the group consisting of SEQ ID NO: 100, SEQ ID NO: 80, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 86, SEQ ID NO: 79 and SEQ ID NO: 83.

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9. The method according to any one of the preceding claims, wherein the expression profile is analysed using hybridization based measurement methods such as a microarray configured to detect at least two of the transcription products of SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104 and SEQ ID NO: 105.

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10. The method according to any one of the preceding claims, wherein:

(a) if one of the at least two markers is SEQ ID NO: 102, then at least one of the other markers is selected from SEQ ID NO: 96, SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 87, SEQ ID NO: 81, SEQ ID NO: 95, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77, preferably at least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77; or

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(b) if one of the at least two markers is SEQ ID NO: 94, then at least one of the other markers is selected from SEQ ID NO: 86, SEQ ID NO: 71, SEQ ID NO: 96, SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 87, SEQ ID NO: 81, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77, preferably at least one of the other markers is

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selected from SEQ ID NO: 86, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 85, SEQ ID NO: 75 and SEQ ID NO: 76; or

- 5 (c) if one of the at least two markers is SEQ ID NO: 91, then at least one of the other markers is selected from SEQ ID NO: 97, SEQ ID NO: 71, SEQ ID NO: 98, SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 87, SEQ ID NO: 81, SEQ ID NO: 95, SEQ ID NO: 83, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73 and SEQ ID NO: 76, preferably at least one of the other markers is selected from SEQ ID NO: 105, SEQ ID NO: 87, SEQ ID NO: 92, SEQ ID NO: 85, SEQ ID NO: 75, SEQ ID NO: 99, SEQ ID NO: 88 and SEQ ID NO: 79; or
- 10 (d) if one of the at least two markers is SEQ ID NO: 100, then at least one of the other markers is selected from SEQ ID NO: 97, SEQ ID NO: 81, , SEQ ID NO: 95, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77, preferably at least one of the other markers is selected from SEQ ID NO: 92, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 78 and SEQ ID NO: 76; or
- 15 (e) if one of the at least two markers is SEQ ID NO: 84, then at least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 93, SEQ ID NO: 105, SEQ ID NO: 95, SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 79, SEQ ID NO: 73, SEQ ID NO: 76 and SEQ ID NO: 77, preferably at least one of the other markers is selected from SEQ ID NO: SEQ ID NO: 103, SEQ ID NO: 82, SEQ ID NO: 85, SEQ ID NO: 80, SEQ ID NO: 75, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 88 and SEQ ID NO: 73; or
- 20 (f) if one of the at least two markers is SEQ ID NO: 90, then at least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 81, SEQ ID NO: 85 and SEQ ID NO: 89, preferably at least one of the other markers is selected from SEQ ID NO: 72 and SEQ ID NO: 89; or
- 25 (g) if one of the at least two markers is SEQ ID NO: 104, then at least one of the other markers is selected from SEQ ID NO: 81, SEQ ID NO: 99, SEQ ID NO: 88, SEQ ID NO: 78, SEQ ID NO: 76 and SEQ ID NO: 77, preferably at least
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one of the other markers is selected from SEQ ID NO: 81, SEQ ID NO: 99 and SEQ ID NO: 77; or

- 5 (h) if one of the at least two markers is SEQ ID NO: 74, then at least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 105, SEQ ID NO: 81, SEQ ID NO: 95, SEQ ID NO: 101, SEQ ID NO: 83, SEQ ID NO: 103, SEQ ID NO: 85, SEQ ID NO: 99, SEQ ID NO: 88 and SEQ ID NO: 73, preferably at least one of the other markers is selected from SEQ ID NO: 72, SEQ ID NO: 95, SEQ ID NO: 83 and SEQ ID NO: 73.

- 10 11. A method of identifying a group of genomic regions having different expression profiles in a healthy subject and in a subject suffering from inflammatory bowel disease, the method comprising the steps of:
- (i) providing a first sample from a healthy subject, having a first set of transcripts together representing a first transcriptome;
 - 15 (ii) providing a second sample from a subject suffering from inflammatory bowel disease, having a second set of transcripts together representing a second transcriptome;
 - (iii) optionally extracting transcripts from the first and the second samples;
 - (iv) measuring and comparing the levels of at least part of the first set of transcripts and at least part of the second set of transcripts;
 - 20 (v) identifying the genomic regions for which the levels of at least part of the first set of transcripts and at least part of the second set of transcripts are different;

25 thereby identifying a group of genomic regions having different expression profiles in a healthy subject and in a subject suffering from inflammatory bowel disease.

- 30 12. A method of identifying a group of genomic regions having a first expression profile in a healthy subject, a second expression profile in a subject suffering from Crohn's disease, and a third expression profile in a subject suffering from ulcerative colitis, wherein at least two of the first, second and third expression profiles are different, the method comprising the steps of:
- (i) providing a first sample from a healthy subject, having a first set of transcripts together representing a first transcriptome;
 - (ii) providing a second sample from a subject suffering from Crohn's disease, 35 having a second set of transcripts together representing a second transcriptome;

- (iii) providing a third sample from a subject suffering from ulcerative colitis, having a third set of transcripts together representing a third transcriptome;
- (iv) optionally extracting transcripts from the first, the second and the third samples;
- 5 (v) measuring and comparing the levels of at least part of the first set of transcripts, at least part of the second set of transcripts and at least part of the third set of transcripts;
- (vi) identifying the genomic regions for which the levels of at least two of said at least part of the first set of transcripts and at least part of the second set of transcripts and at least part of the third set of transcripts are different;
- 10 thereby identifying a group of genomic regions having different expression profiles in a healthy subject, in a subject suffering from Crohn's disease, and in a subject suffering from ulcerative colitis.
- 15 13. A kit of parts, comprising:
- primers for amplifying one of the markers as defined in any one of claims 1 to 12;
 - instructions for use;
 - optionally additional reagents for extracting RNA from biopsy samples;

20 - optionally a software for diagnosing an inflammatory bowel disease, Crohn's disease or ulcerative colitis.
- 25 14. A computer implemented method for automatically determining whether a subject is healthy or suffers from an inflammatory bowel disease, the method comprising the steps of:
- i) comparing the expression profiles of at least 2 markers in a sample obtained from said subject with a first expression signature representative of healthy subjects and with a second expression signature representative of subjects suffering from an inflammatory bowel disease, wherein the markers are as defined in any one of the preceding claims, and wherein the expression profile represents the expression levels of the at least 2 markers together in said subject, the first expression signature represents the average expression levels of the at least 2 markers together in a group of at least 20 healthy subjects, and the second expression signature represents the average expression levels of the at least 2 markers together in a group of subjects suffering from an inflammatory bowel disease;
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- ii) determining whether the expression profile is closest to the first expression signature or to the second expression signature;

wherein:

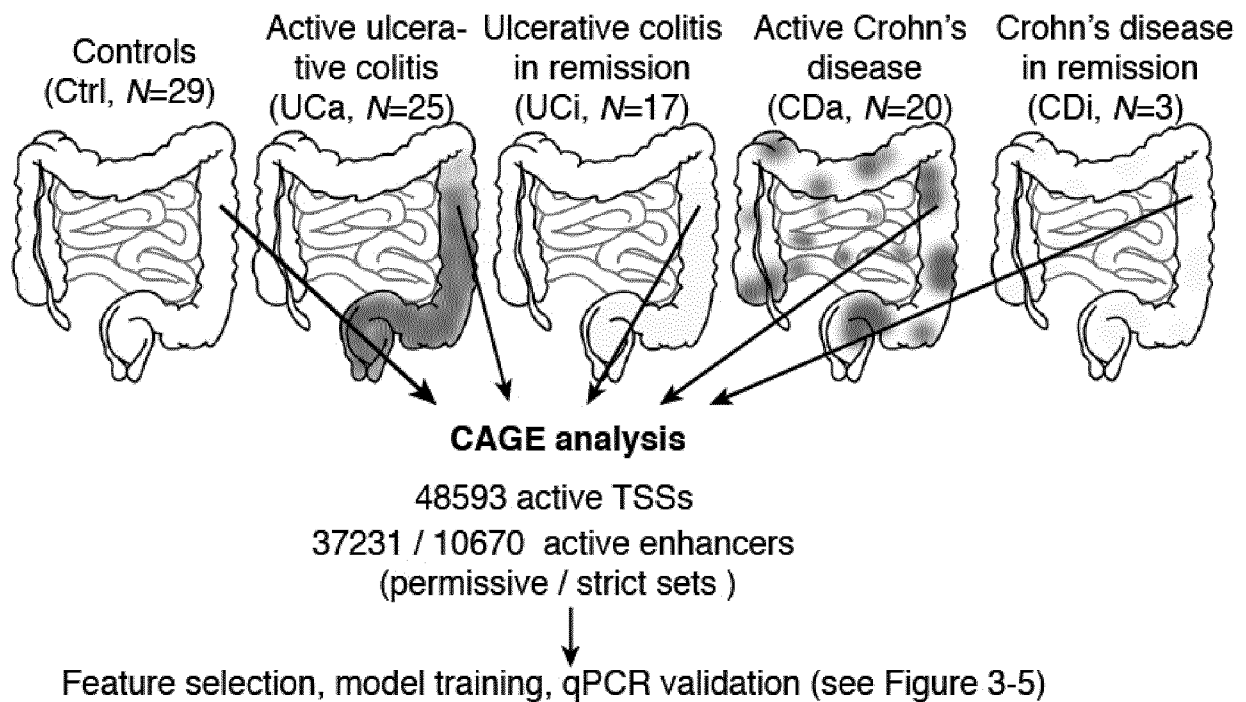
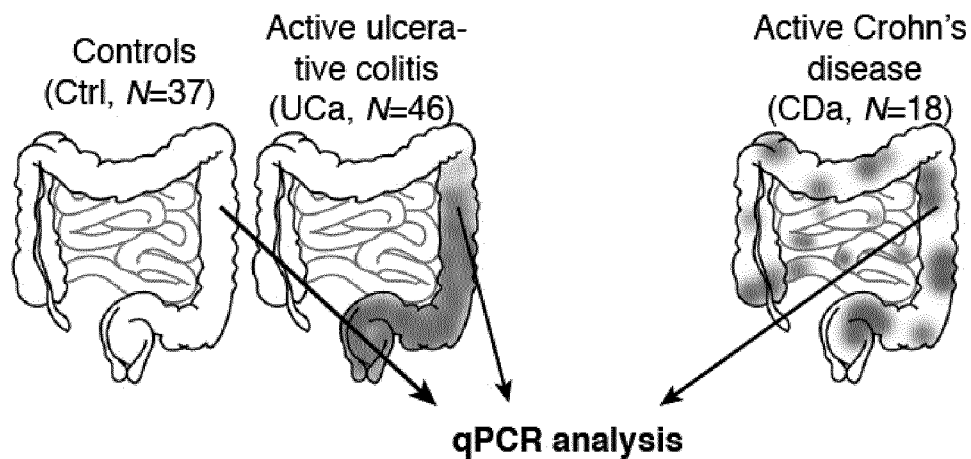
- if the expression profile is closest to the first expression signature, the method determines that the subject is healthy;
- if the expression profile is closest to the second expression signature, determining that the subject suffers from an inflammatory bowel disease.

15. A computer implemented method for automatically determining whether a subject suffers from ulcerative colitis or from Crohn's disease, the method comprising the steps of:

- i) comparing the expression profile of at least 2 markers in a sample obtained from said subject with a first reference profile representative of healthy subjects, with a second reference profile representative of subjects suffering from ulcerative colitis and with a third reference profile representative of subjects suffering from Crohn's disease, wherein the markers are as defined in any one of the preceding claims, and wherein the expression profile represents the expression levels of the at least 2 markers together in said subject, the first reference profile represents the average expression levels of the at least 2 markers together in a group of at least 20 healthy subjects, the second reference profile represents the average expression levels of the at least 2 markers together in a group of subjects suffering from ulcerative colitis and the third reference profile represents the average expression levels of the at least 2 markers together in a group of subjects suffering from Crohn's disease;
- ii) determining whether the expression profile is closest to the first reference profile, to the second reference profile or to the third reference profile;

wherein:

- if the expression profile is closest to the first reference profile, determining that the subject is healthy;
- if the expression profile is closest to the second reference profile, determining that the subject suffers from ulcerative colitis;
- if the expression profile is closest to the third reference profile, determining that the subject suffers from Crohn's disease.

FIG. 1**Cohort 1****Cohort 2**

Prediction of diagnosis using model trained on cohort 1 (See Figure 6)

FIG. 2

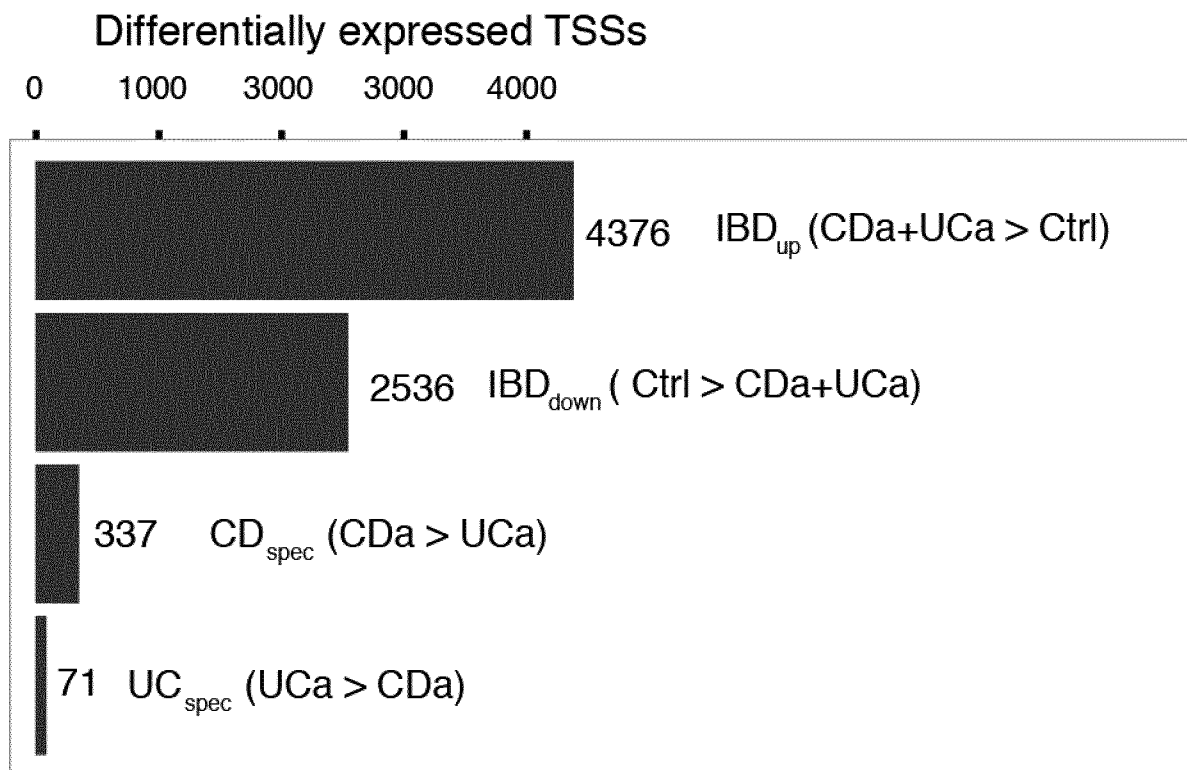


FIG. 3

Classification workflow

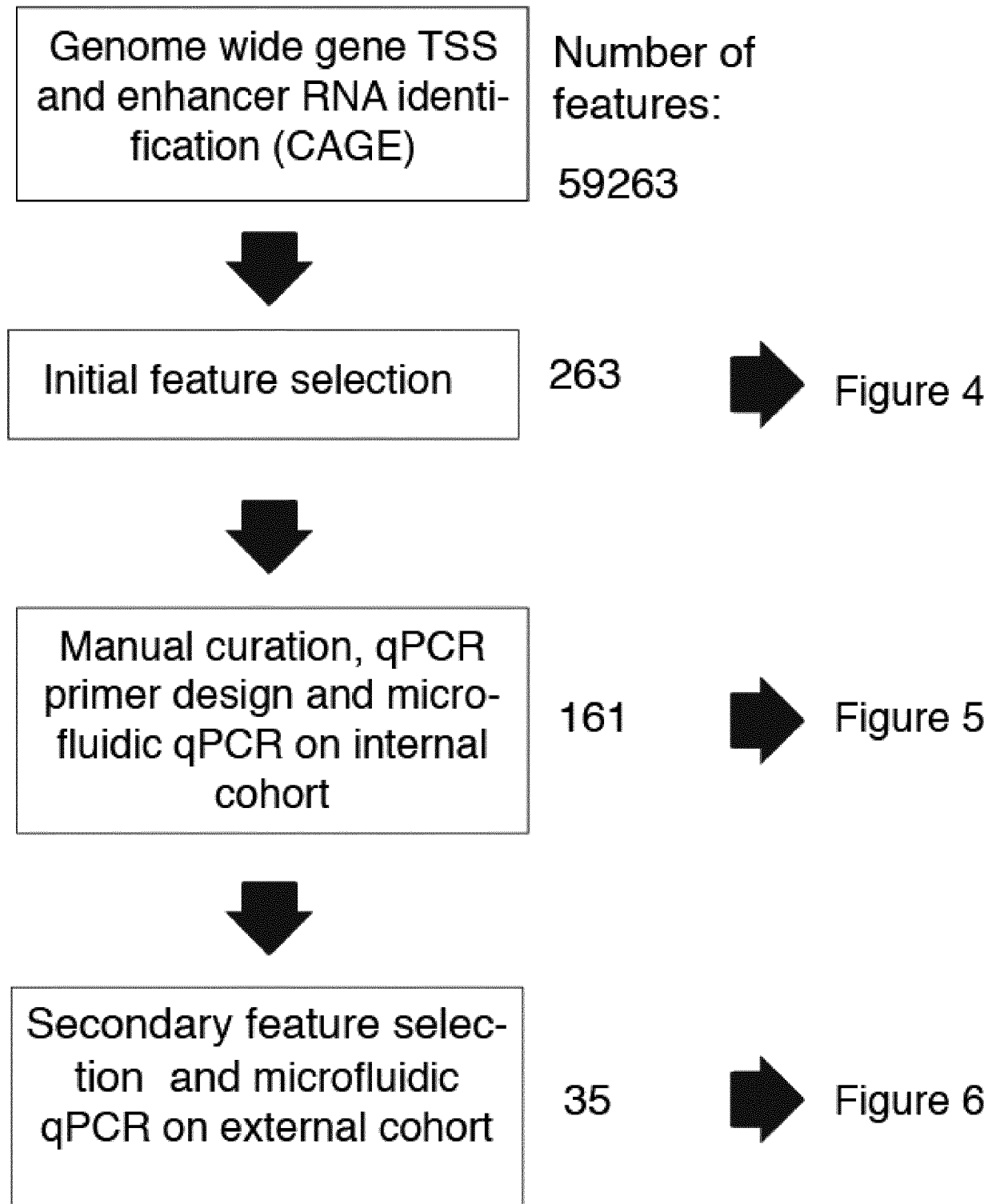


FIG. 4

Classification based on CAGE,
cohort 1 (20 CD, 25 UC, 29 Ctrl subjects), 263 features

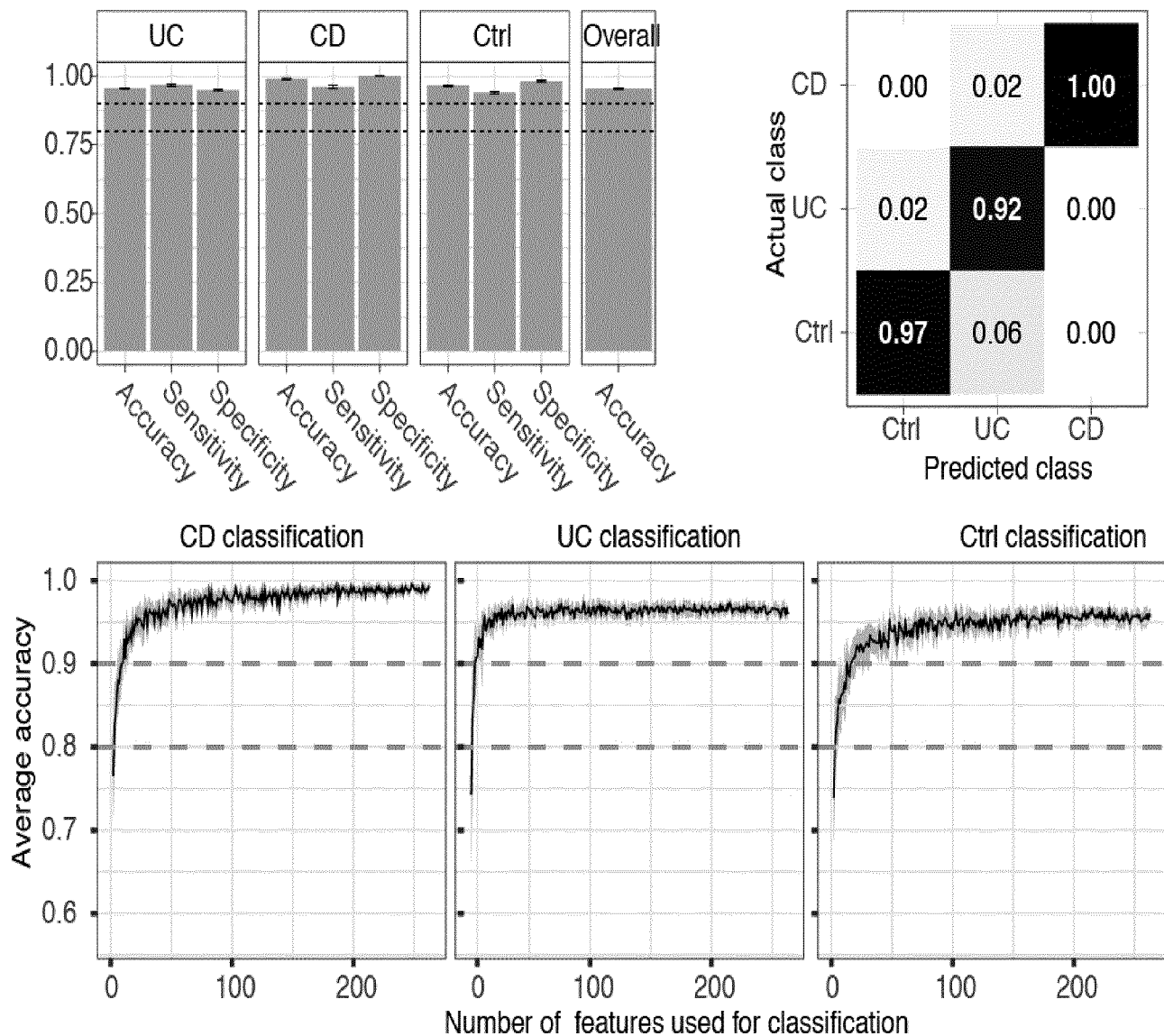


FIG. 5

Classification based on qPCR,
cohort 1 (20 CD, 25 UC, 29 Ctrl subjects), 161 features

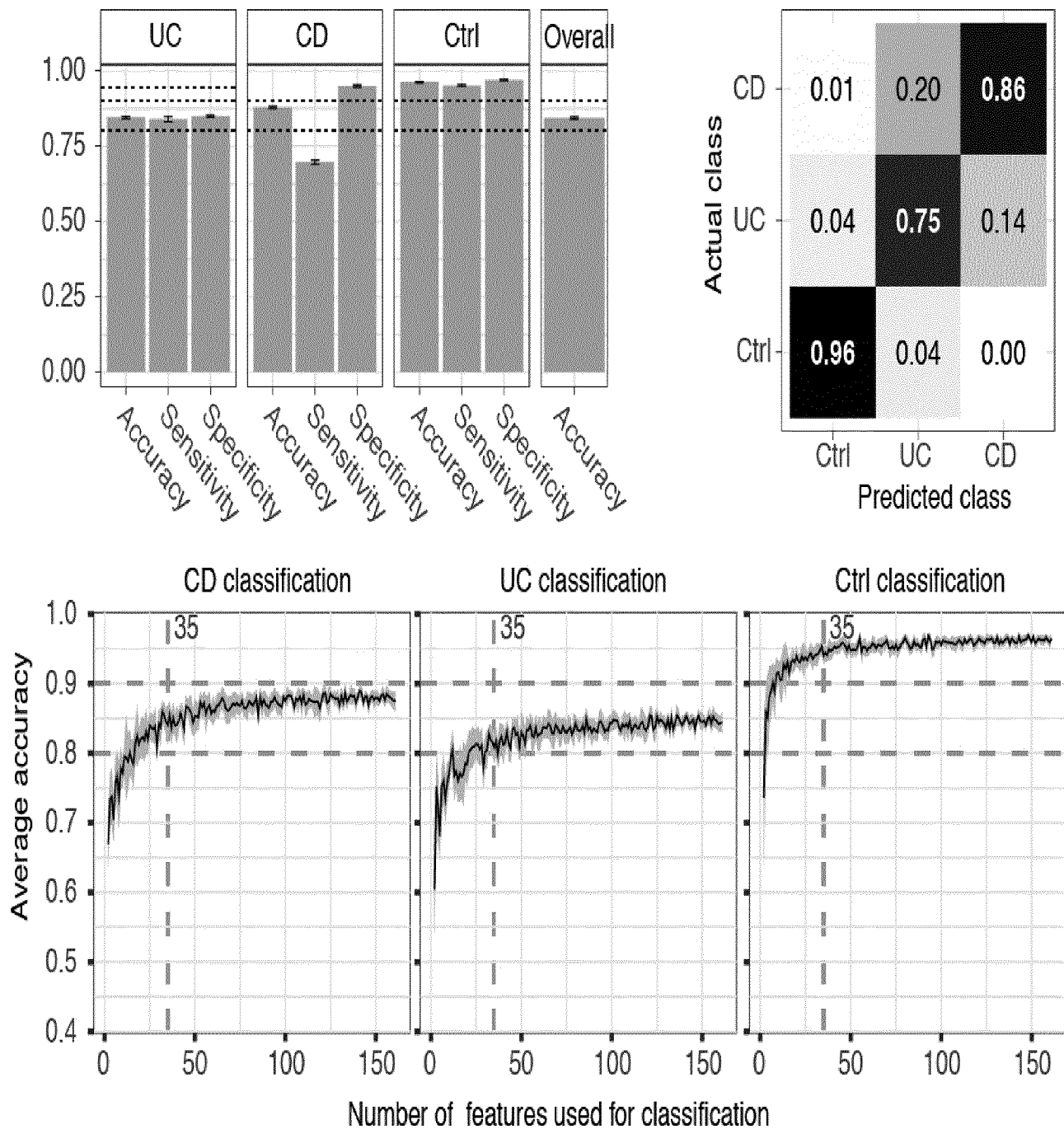


FIG. 6

A

Classification based on qPCR, trained on cohort 1
and evaluated on cohort 2 (18 CD, 37 UC, 46 Ctrl subjects)

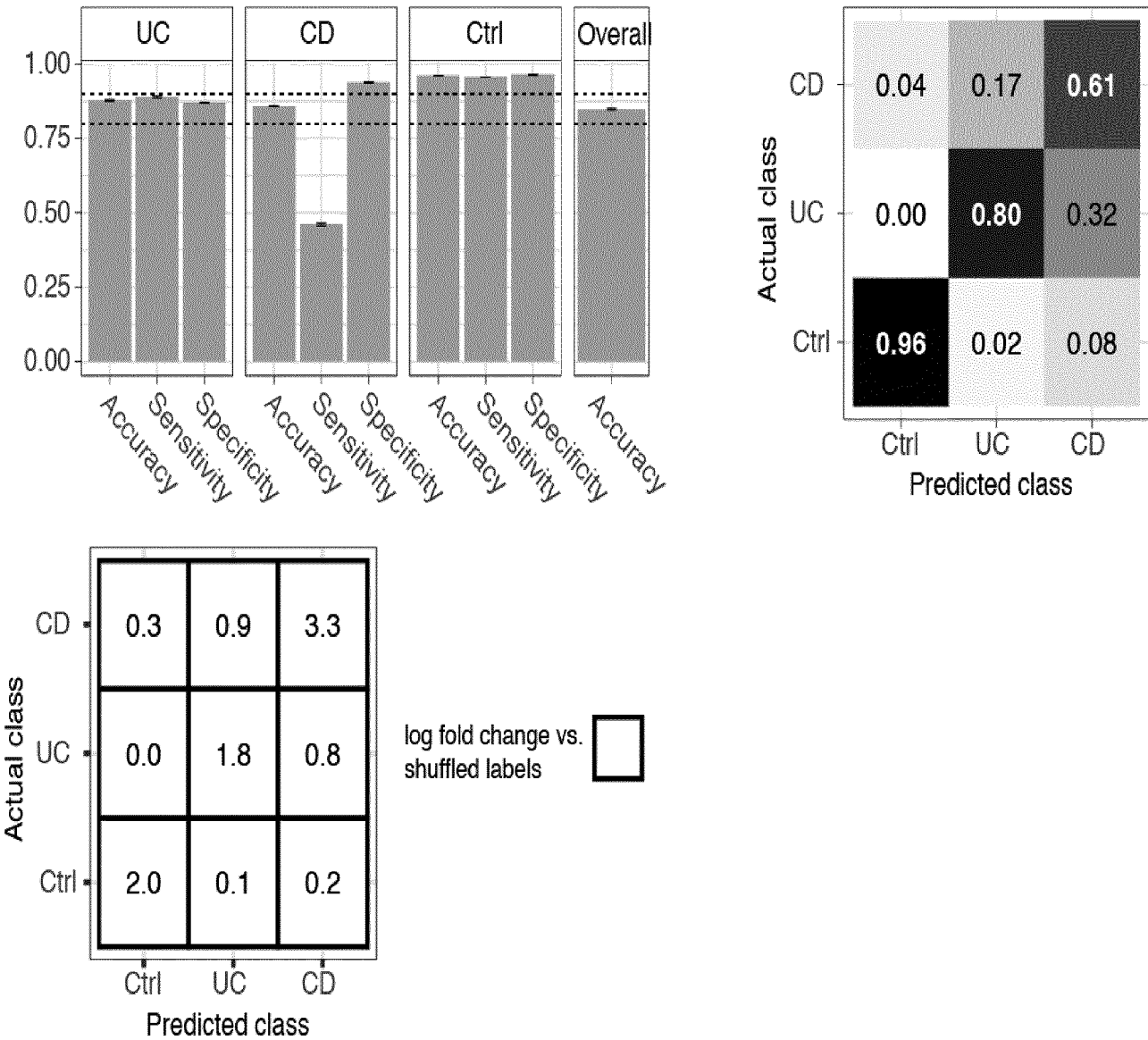


FIG. 6 (CONT.)

B

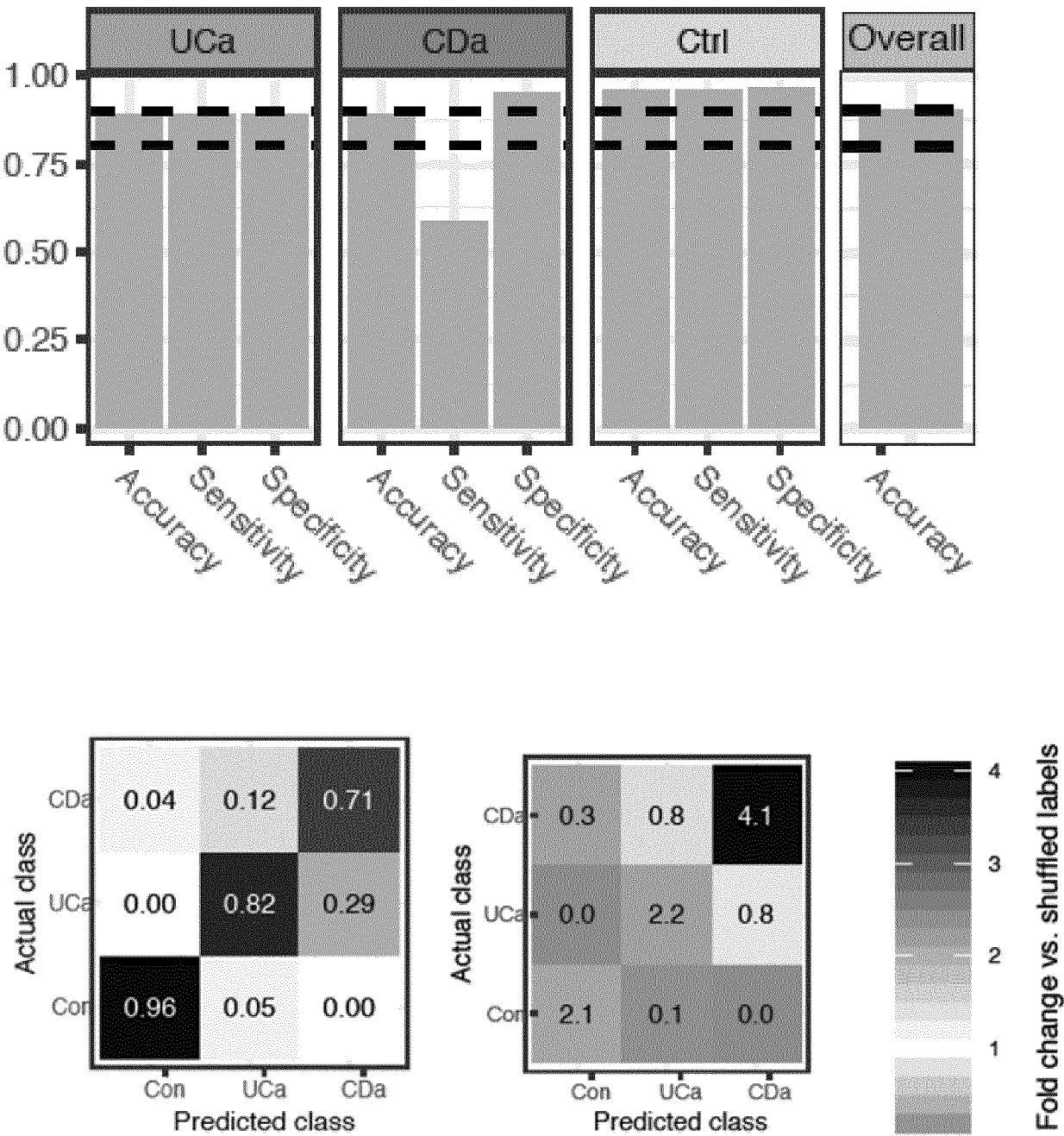


FIG. 7

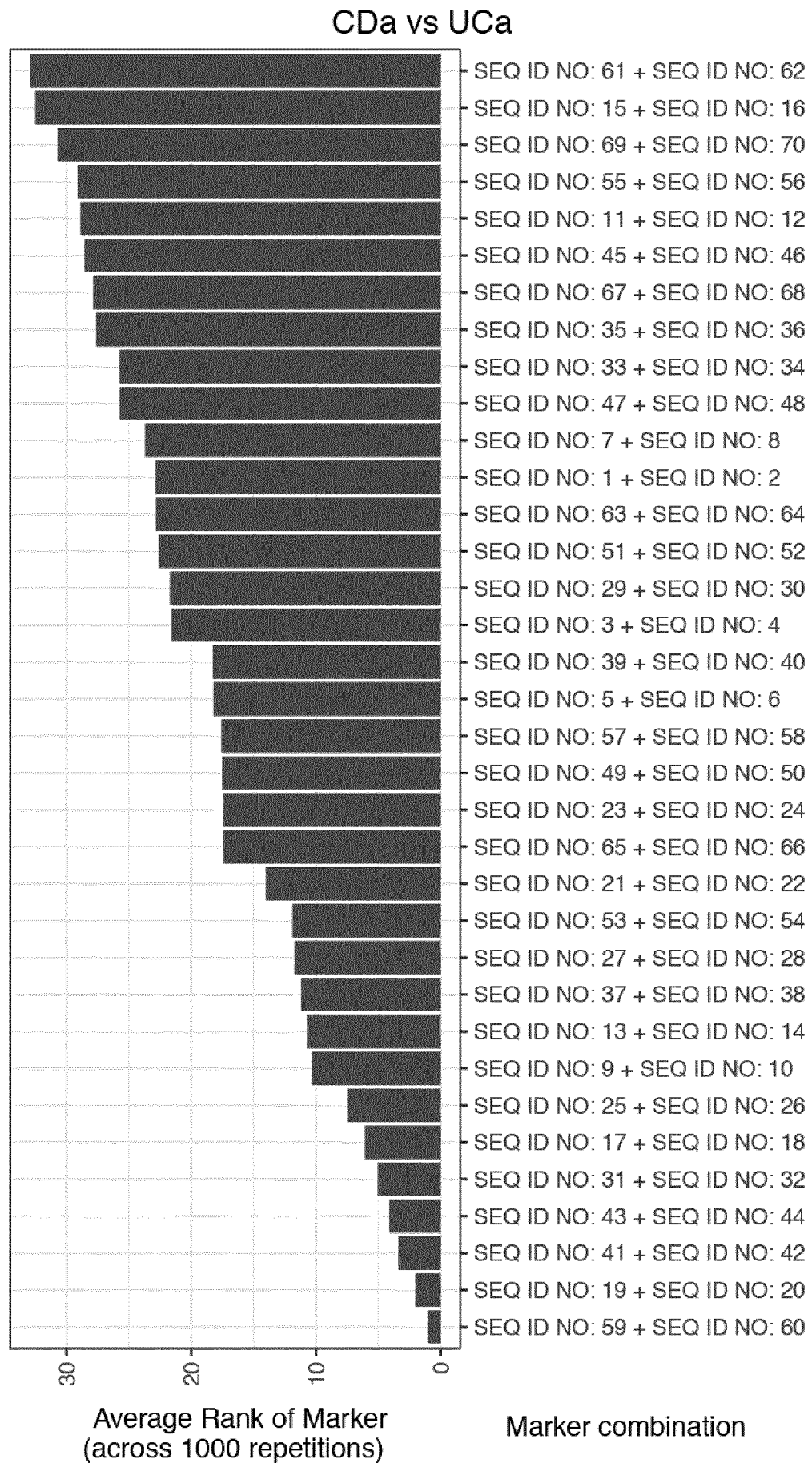


FIG. 8

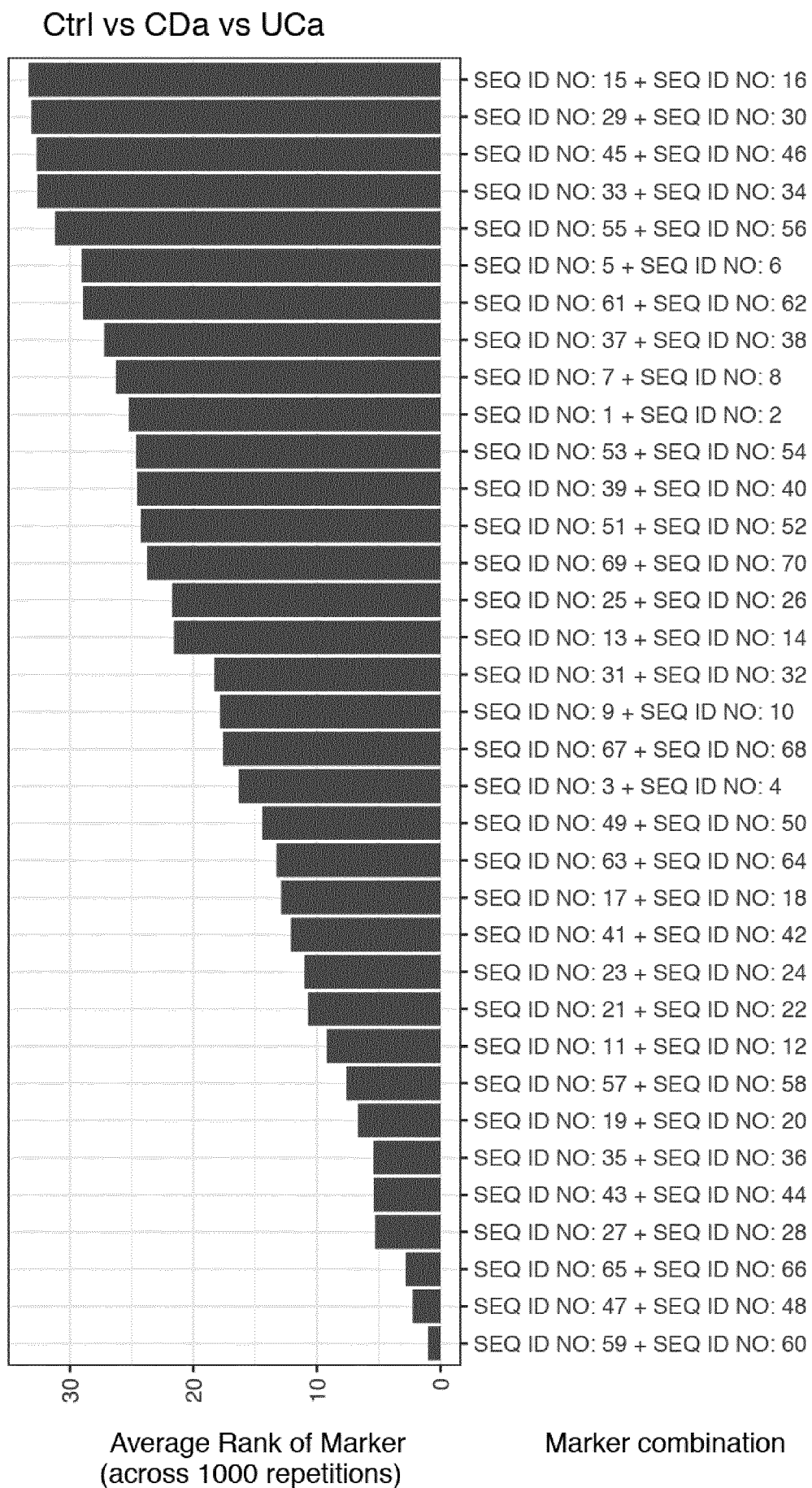
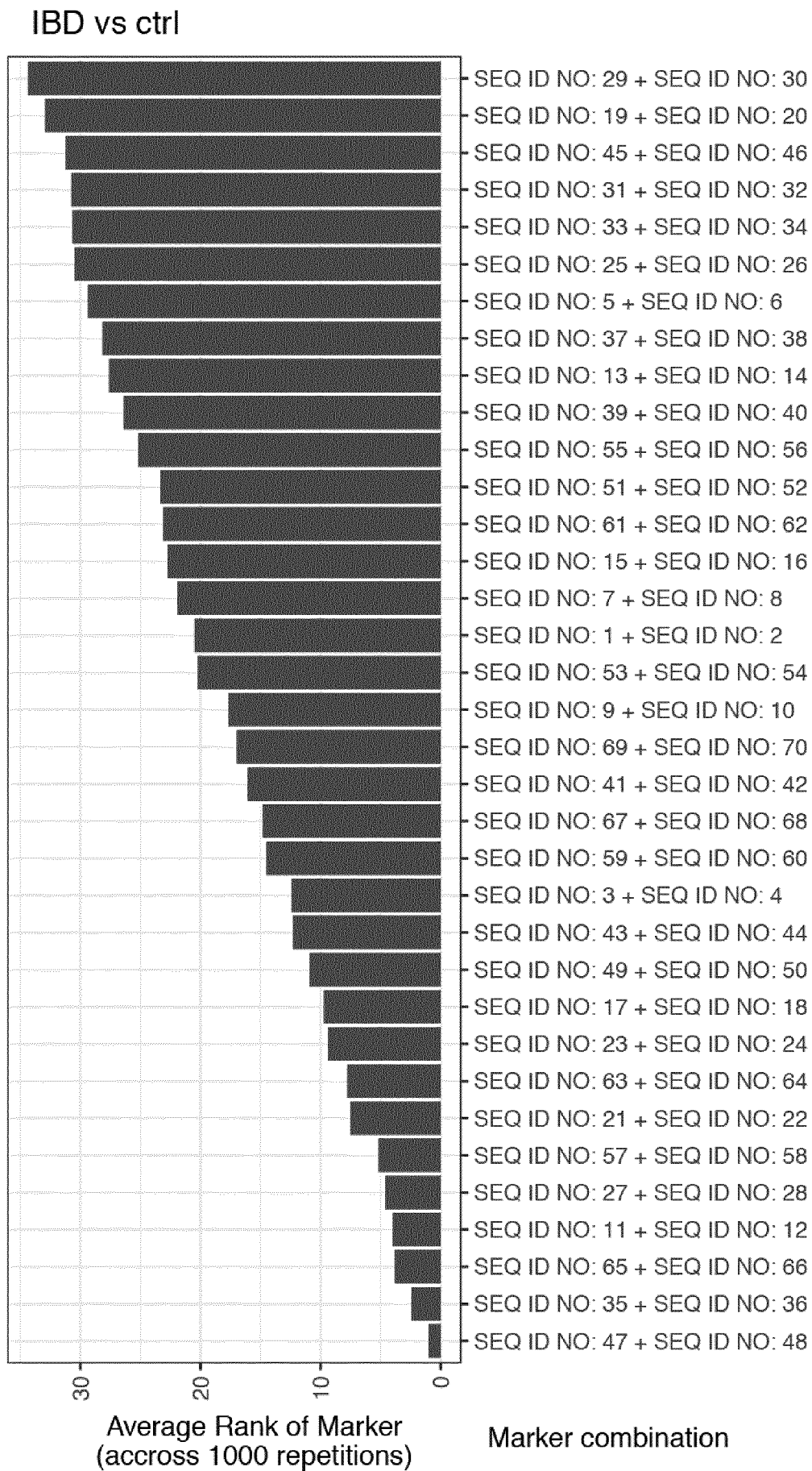


FIG. 9



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/068244

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, Sequence Search, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Vitezic: "Genome-Wide Discovery of Inflammatory Bowel Disease-Specific Transcriptional Enhancers and Promoters Identifies Powerful Diagnostic Biomarkers", Gastroenterology, 1 April 2015 (2015-04-01), XP055407110, Retrieved from the Internet: URL: http://www.gastrojournal.org/article/S0016-5085(15)31460-8/pdf [retrieved on 2017-09-15] abstract	1-10,13
X	WO 01/29269 A2 (UNIV CASE WESTERN RESERVE [US]) 26 April 2001 (2001-04-26) page 5 ----- -/-	1-10,13



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 July 2018

Date of mailing of the international search report

21/09/2018

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Dolce, Luca

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2018/068244

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PAPA GOBBI RODRIGO ET AL: "A galectin-specific signature in the gut delineates Crohn's disease and ulcerative colitis from other human inflammatory intestinal disorders", BIOFACTORS (OXFORD, ENGL,, vol. 42, no. 1, 1 January 2016 (2016-01-01), pages 93-105, XP009193786, ISSN: 1872-8081, DOI: 10.1002/BIOF.1252 figures 1-5 -----	1-10,13
X	VON STEIN P ET AL: "Multigene Analysis Can Discriminate Between Ulcerative Colitis, Crohn's Disease, and Irritable Bowel Syndrome", GASTROENTEROLOGY, ELSEVIER, US, vol. 134, no. 7, 1 June 2008 (2008-06-01), pages 1869-1881, XP022756831, ISSN: 0016-5085, DOI: 10.1053/J.GASTRO.2008.02.083 [retrieved on 2008-03-02] tables 1, 2 -----	1-10,13
X	J. T. BJERRUM ET AL: "Assessment of the validity of a multigene analysis in the diagnostics of inflammatory bowel disease", JOURNAL OF INTERNAL MEDICINE, vol. 275, no. 5, 1 May 2014 (2014-05-01), pages 484-493, XP055407111, GB ISSN: 0954-6820, DOI: 10.1111/joim.12160 figure 1 -----	1-10,13
X	WO 2009/082298 A1 (INDEX DIAGNOSTICS AB [SE]; VON STEIN PETRA [SE]; KOUZNETSOV NIKOLAI [S] 2 July 2009 (2009-07-02) page 3 - page 4 -----	1-10,13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2018/068244

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-10, 13(all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-10, 13(all partially)

methods and products all based on the marker with SEQ ID NO: 71 in combination with 1, 2, 3, 4, 5, 6, 7, 8 or 9 further markers of claim 1

2-35. claims: 1-10, 13(all partially)

same as above for each of the remaining markers of claim 1

36. claims: 11, 12, 14, 15

methods to identify differentially expressed genomic regions in IBD, CD, UC and related computer programs

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2018/068244

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0129269	A2	26-04-2001	AU 784861 B2 06-07-2006
		CA 2356207 A1 26-04-2001	
		EP 1287162 A2 05-03-2003	
		EP 2319939 A2 11-05-2011	
		WO 0129269 A2 26-04-2001	

WO 2009082298	A1	02-07-2009	CA 2747253 A1 02-07-2009
		DK 2223121 T3 22-10-2012	
		EP 2223121 A1 01-09-2010	
		EP 2562544 A1 27-02-2013	
		ES 2391792 T3 29-11-2012	
		JP 2011507509 A 10-03-2011	
		US 2011183337 A1 28-07-2011	
		WO 2009082298 A1 02-07-2009	
