

(a) analyzing a sample obtained from said individual to determine the presence, level or genotype of one or more markers selected from the group consisting of a serological marker, a genetic marker, an inflammation marker, and a combination thereof in said sample to obtain a marker profile;

5 (b) applying a regression analysis to said marker profile to obtain a decision whether said marker profile is an IBD sample or a nonIBD sample;

(c) applying a decision tree or set of rules to said sample designated as an IBD sample to determine if said IBD sample is an inconclusive sample; and

10 (d) if the sample is not inconclusive, but an IBD sample, applying a second regression analysis to said IBD sample to determine a clinical subtype.

79. A method for diagnosing inflammatory bowel disease (IBD) and/or a clinical subtype thereof in an individual, said method comprising:

15 (a) analyzing a sample obtained from said individual to determine the presence or level or genotype of at least each of the following markers to obtain a marker profile: (i) the presence or level of each of the serological markers ASCA-A, ASCA-G, ANCA, pANCA, anti-OmpC antibody, anti-CBir1 antibody, anti-FlaX antibody, and anti-A4-Fla2 antibody; (ii) the presence or level of each of the inflammation markers VEGF, ICAM, VCAM, SAA, and CRP; and (iii) the genotype of each of the genetic markers ATG16L1, ECM1, NKX2-3, and STAT3;

20 (b) applying a first random forest statistical analysis to said marker profile to compute a first model score and comparing said first model score to a first cut-off value to obtain a decision whether said sample is an IBD sample or a non-IBD sample;

(c) if said sample is an IBD sample, then applying a decision tree to said IBD sample to determine if said IBD sample is or is not an inconclusive sample,  
25 wherein said IBD sample is an inconclusive sample when said IBD sample has an ANCA level greater than a quartile score of 3 ( $> Q3$ ), is pANCA2 positive, and has a level of anti-CBir1 antibody or anti-A4-Fla2 antibody or anti-FlaX antibody  $> Q3$ , or

wherein said IBD sample is an inconclusive sample when said IBD sample is pANCA2 positive and expresses two out of three markers selected from anti-CBir1 antibody, anti-A4-Fla2 antibody, and anti-FlaX antibody  $> Q3$ , and  
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wherein the presence or level of pANCA is used to determine the value of pANCA2; and

(d) if said IBD sample is not an inconclusive sample, then applying a second random forest statistical analysis to said IBD sample to compute a second model score

and comparing said second model score to a second cut-off value to determine a clinical subtype of IBD.

5        80.     The method of claim 79, wherein the presence or level of each of said serological markers or inflammation markers is independently detected with a hybridization assay, amplification-based assay, immunoassay, or immunohistochemical assay.

81.     The method of claim 79, wherein the genotype of each of said genetic markers is independently detected by genotyping for the presence or absence of a single nucleotide polymorphism (SNP) in each of said genetic markers.

10       82.     The method of claim 81, wherein said SNP is rs2241880 for ATG16L1, rs3737240 for ECM1, rs10883365 for NKX2-3, and/or rs744166 for STAT3.

83.     The method of claim 79, wherein the clinical subtype of IBD is Crohn's disease (CD) or ulcerative colitis (UC).

15       84.     The method of claim 79, wherein said second random forest statistical analysis is based upon (i) the presence or level of ASCA-A, ASCA-G, ANCA, pANCA, anti-OmpC antibody, anti-CBir1 antibody, anti-FlaX antibody, anti-A4-Fla2 antibody, and VEGF in said sample and (ii) the genotype of ECM1 and STAT3 in said sample.

85.     The method of claim 79, wherein said sample is selected from the group consisting of serum, plasma, whole blood, and stool.

20       86.     The method of claim 79, wherein when pANCA values are 0 or +1, the pANCA2 value is negative.

87.     The method of claim 79, wherein when pANCA values are +2, +3 or +4, the pANCA2 value is positive.

88.     The method of claim 86, wherein in said pANCA2 negative sample, further comprising:

25       (a)     determining whether the pANCA2 negative sample is directly predictive of Crohn's disease by measuring a serum marker panel, wherein the serum marker panel is a member of the group consisting of ASCA-IgA, ASCA-IgG, and OmpC-IgA and comparing each of the serum markers of the serum marker panel to a cutoff value to determine if the sample is consistent with Crohn's disease; or

(b) determining whether the pANCA2 negative sample is consistent with Crohn's disease by measuring a CD count panel, wherein the CD count panel is a member of the group consisting of ASCA-IgA, ASCA-IgG, OmpC-IgA, CBir1-IgG, A4-Fla2-IgG and FlaX-IgG to form a CD count value, wherein when the CD count value is greater than or equal to 2, the sample is consistent with Crohn's disease; or

(c) determining whether the pANCA2 negative sample having a pANCA value of zero is consistent or inconsistent with IBD by measuring ANCA ELISA and comparing the ANCA ELISA value to a reference value and considering the CD count value to determine whether the sample is consistent or inconsistent with IBD; or

(d) determining whether the pANCA2 negative sample having a pANCA value of zero is consistent with IBD or is inconclusive of IBD by measuring ANCA ELISA and comparing the ANCA ELISA value and considering the CD count value to determine whether the sample is consistent or inconsistent with IBD or is consistent with IBD and inconclusive for Crohn's disease or ulcerative colitis; or

(e) determining whether the pANCA2 negative sample having a pANCA value of one is consistent or inconsistent with IBD by measuring ANCA ELISA and comparing the ANCA ELISA value to a cut-off value to determine whether the sample is consistent with IBD or is inconsistent with IBD.

89. The method of claim 88, wherein in part (a) above, if the value for ASCA-IgA is greater than or equal to 69 EU/mL, then designating the sample as being consistent with Crohn's disease.

90. The method of claim 88, wherein in part (a) above, if the value of ASCA-IgG is greater than or equal to 40 EU/mL, then designating the sample as being consistent with Crohn's disease.

91. The method of claim 88, wherein in part (a) above, if the value for OmpC-IgA is greater than or equal to 60 EU/mL, then designating the sample as being consistent with Crohn's disease.

92. The method of claim 88, wherein in part (b) above, further comprising assigning the CD count value by determining if:

i. ASCA-IgA is greater than or equal to 8.5 EU/mL, then adding +1 to the CD count value;

ii. ASCA-IgG is greater than or equal to 17.8 EU/mL, then adding +1 to the CD count value;

iii. OmpC-IgA is greater than or equal to 10.9 EU/mL, then adding +1 to the CD count value;

5 iv. 2 or more flagellin markers are above their respective reference ranges, then adding +1 to the CD count value;

v. any flagellin is greater than or equal to 100 EU/mL, then adding +1 to the CD count value;

and if the total CD count value is greater than or equal to 2, then designating  
10 that the sample is consistent with Crohn's disease.

93. The method of claim 92, wherein the reference value for CBir1-IgG is greater than or equal to 78.4 EU/mL.

94. The method of claim 92, wherein the reference value for A4-Fla2-IgG is greater than or equal to 44.8 EU/mL.

15 95. The method of claim 92, wherein the reference value for FlaX-IgG is greater than or equal to 33.4 EU/mL.

96. The method of claim 88, wherein in part (c) above, if pANCA is zero (not detected), further comprising:

20 i. designating the sample as being inconsistent with IBD if ANCA ELISA is less than 20 EU/mL; or

ii. designating the sample as being consistent with ulcerative colitis if ANCA ELISA is greater than 27.4 EU/mL; or

iii. designating the sample as being inconsistent with IBD if ANCA ELISA is greater than or equal to 20 and less than or equal to 27.4 EU/mL and the CD count  
25 value is zero; or

iv. designating the sample as being consistent with IBD but inconclusive for Crohn's disease or ulcerative colitis if ANCA ELISA is greater than or equal to 20 and less than or equal to 27.4 EU/mL and the CD count value is one.

97. The method of claim 88, wherein when pANCA is one, further  
30 comprising:

i. designating the sample as being inconsistent with IBD if ANCA ELISA is less than 13.7 EU/mL; or

ii. designating that the sample as being consistent with ulcerative colitis if ANCA ELISA is greater than or equal to 13.7 EU/mL.

**98.** A method for diagnosing inflammatory bowel disease (IBD) and/or a clinical subtype thereof in an individual, said method comprising:

5 (a) analyzing a sample obtained from said individual to determine the presence or level or genotype of at least each of the following markers to obtain a marker profile: (i) the presence or level of each of the serological markers ASCA-A, ASCA-G, ANCA, pANCA, anti-OmpC antibody, anti-CBir1 antibody, anti-FlaX antibody, and anti-A4-Fla2 antibody; (ii) the presence or level of each of the inflammation markers VEGF, ICAM, VCAM, SAA, and CRP; and (iii) the genotype of each of the genetic markers ATG16L1, ECM1, NKX2-3, and STAT3;

10 (b) applying a first random forest statistical analysis to said marker profile to determine whether said sample is an IBD sample or a non-IBD sample with a sensitivity of at least 70%;

15 (c) if said sample is an IBD sample, then applying a decision tree to said IBD sample to determine if said IBD sample is or is not an inconclusive sample,

wherein said IBD sample is an inconclusive sample when said IBD sample has an ANCA level greater than a quartile score of 3 ( $> Q3$ ), is pANCA2 positive, and has a level of anti-CBir1 antibody or anti-A4-Fla2 antibody or anti-FlaX antibody  $> Q3$ , or

20 wherein said IBD sample is an inconclusive sample when said IBD sample is pANCA2 positive and expresses two out of three markers selected from anti-CBir1 antibody, anti-A4-Fla2 antibody, and anti-FlaX antibody  $> Q3$ , and

wherein the presence or level of pANCA is used to determine the value of pANCA2; and

25 (d) if said IBD sample is not an inconclusive sample, then applying a second random forest statistical analysis to said IBD sample to determine a clinical subtype of IBD with a sensitivity of at least 85% for Crohn's disease (CD) and a sensitivity of at least 95% for ulcerative colitis (UC).

**99.** The method of claim 98, wherein the presence or level of each of said serological markers or inflammation markers is independently detected with a hybridization assay, amplification-based assay, immunoassay, or immunohistochemical assay.

100. The method of claim 98, wherein the genotype of each of said genetic markers is independently detected by genotyping for the presence or absence of a single nucleotide polymorphism (SNP) in each of said genetic markers.

5 101. The method of claim 100, wherein said SNP is rs2241880 for ATG16L1, rs3737240 for ECM1, rs10883365 for NKX2-3, and/or rs744166 for STAT3.

102. The method of claim 98, wherein said second random forest statistical analysis is based upon (i) the presence or level of ASCA-A, ASCA-G, ANCA, pANCA, anti-OmpC antibody, anti-CBir1 antibody, anti-FlaX antibody, anti-A4-Fla2 antibody, and VEGF in said sample and (ii) the genotype of ECM1 and STAT3 in said sample.

10 103. The method of claim 98, wherein said sample is selected from the group consisting of serum, plasma, whole blood, and stool.

104. The method of claim 98, wherein when pANCA values are 0 or +1, the pANCA2 value is negative.

15 105. The method of claim 98, wherein when pANCA values are +2, +3 or +4, the pANCA2 value is positive.

106. The method of claim 104, wherein in said pANCA2 negative sample, further comprising:

20 (a) determining whether the pANCA2 negative sample is directly predictive of Crohn's disease by measuring a serum marker panel, wherein the serum marker panel is a member of the group consisting of ASCA-IgA, ASCA-IgG, and OmpC-IgA and comparing each of the serum markers of the serum marker panel to a cutoff value to determine if the sample is consistent with Crohn's disease; or

25 (b) determining whether the pANCA2 negative sample is consistent with Crohn's disease by measuring a CD count panel, wherein the CD count panel is a member of the group consisting of ASCA-IgA, ASCA-IgG, OmpC-IgA, CBir1-IgG, A4-Fla2-IgG and FlaX-IgG to form a CD count value, wherein when the CD count value is greater than or equal to 2, the sample is consistent with Crohn's disease; or

30 (c) determining whether the pANCA2 negative sample having a pANCA value of zero is consistent or inconsistent with IBD by measuring ANCA ELISA and comparing the ANCA ELISA value to a reference value and considering the CD count value to determine whether the sample is consistent or inconsistent with IBD; or

(d) determining whether the pANCA2 negative sample having a pANCA value of zero is consistent with IBD or is inconclusive of IBD by measuring ANCA ELISA and comparing the ANCA ELISA value and considering the CD count value to determine whether the sample is consistent or inconsistent with IBD or is consistent with IBD and inconclusive for Crohn's disease or ulcerative colitis; or

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(e) determining whether the pANCA2 negative sample having a pANCA value of one is consistent or inconsistent with IBD by measuring ANCA ELISA and comparing the ANCA ELISA value to a cut-off value to determine whether the sample is consistent with IBD or is inconsistent with IBD.

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**107.** The method of claim 98, wherein in part (b) said IBD sample or non-IBD sample is determined with a specificity of at least 90%.

**108.** The method of claim 98, wherein in part (d) said clinical subtype of IBD is determined with a specificity of at least 80% for CD or UC.