METHODS FOR ASSESSING MUCOSAL HEALING IN CROHN'S DISEASE PATIENTS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Application No. 62/512,947 filed May 31, 2017, and U.S. Provisional Application No. 62/561,459, filed September 21, 2017, the disclosures of which are incorporated herein by references in their entirety for all purposes.

BACKGROUND

[0002] Crohn's disease (CD) recurs in a majority of patients after intestinal resection, with new lesions developing at the anastomosis in 70-90% of patients within 1 year of surgery. Mucosal healing (MH), typically defined as absence of ulcers on visual endoscopic examination, is a desired clinical endpoint that has become the primary therapeutic target in CD. Ileocolonoscopy, currently the gold standard for assessing MH, is however an invasive and time consuming procedure with poor patient acceptance. This limits the practical feasibility for serial monitoring of mucosal disease activity and the MH status in response to treatment. Non-invasive monitoring of post-operative disease recurrence would be useful in the clinical management of such patients but is particularly challenging due to low disease burden after removal of macroscopically involved intestine. In particular, non-invasive alternative tests could provide an attractive option as adjuncts or surrogates for endoscopy for inflammatory bowel disease (IBD) patient management, with particular utility in patients with CD given its transmural nature and lack of optimal endoscopic accessibility of the small bowel. The present disclosure addresses this and other needs and provides related advantages.

BRIEF SUMMARY

[0002a] In one aspect, the present disclosure provides a method for assessing mucosal healing in a patient with Crohn's Disease (CD), the method comprising: providing a serum sample from a patient;
detecting in the serum sample an expression level of each of the following biomarkers: Ang1, Ang2, CEACAM1, VCAM1, TGFα, CRP, SAA1, MMP-1, MMP-2, MMP-3, MMP-9, EMMPRIN, and IL-7; and applying a mathematical algorithm to the expression levels of the biomarkers, thereby producing a Mucosal Healing Index (MHI) score for the patient.

[0003] In one example, the present disclosure provides a method for assessing mucosal healing in a patient with Crohn's Disease (CD). The method includes providing a serum

sample from a patient. The method further includes detecting in the serum sample an expression level of each of two or more biomarkers selected from the group consisting of Ang1, Ang2, CEACAM1, VCAM1, TGFα, CRP, SAA1, MMP-1, MMP-2, MMP-3, MMP-9, EMMPRIN, and IL-7. The method further includes applying a mathematical algorithm to the expression levels of the two or more biomarkers, thereby producing a Mucosal Healing Index (MHI) score for the patient. In certain examples, the MHI score has a scale from 0 to 100.

[0004] In some examples, the detecting includes contacting the serum sample with a binding partner for each of the two or more biomarkers and detecting binding between each biomarker and its respective binding partner. In certain examples, each binding partner is an antibody. In some examples, the detecting includes measuring an expression level of each of the biomarkers in the group consisting of Ang1, Ang2, CEACAM1, VCAM1, TGFα, CRP, SAA1, MMP-1, MMP-2, MMP-3, MMP-9, EMMPRIN, and IL-7. In certain examples, the method further includes determining that the patient has a high probability of being in remission or having mild endoscopic disease when the MHI score is less than or equal to 40. In certain examples, the high probability of being in remission or having mild endoscopic disease is greater than or equal to 92%. In some examples, the remission corresponds to a Crohn's Disease Endoscopic Index of Severity (CDEIS) of less than 3 (CDEIS < 3). In some examples, the mild endoscopic disease corresponds to a CDEIS of between 3-8 (CDEIS 3-8). In certain examples, the method further includes determining that the patient has a high probability of having endoscopically active disease when the MHI score is greater than or equal to 50. In certain examples, the high probability of having endoscopically active disease is greater than or equal to 87%. In some examples, the endoscopically active disease corresponds to a CDEIS of greater than or equal to 3 (CDEIS ≥ 3). In some examples, the method further includes determining that the patient has a moderate probability of having endoscopically active disease when the MHI score is between 40 and 50. In some examples, the moderate probability of having endoscopically active disease is greater than or equal to 78%.

[0005] In certain examples, the mathematical algorithm includes two or more models relating the expression levels of the biomarkers to an endoscopic score. In certain examples, one or more of the two or more models are derived by using classification and regression trees, and/or one or more of the two or more models are derived by using ordinary least squares regression. In certain examples, one or more of the two or more models are derived by using classification and regression trees, and/or one or more of the two or more models are

derived by using ordinary least squares regression to model diagnostic sensitivity. In certain examples, one or more of the two or more models are derived by using classification and regression trees, and/or one or more of the two or more models are derived by using ordinary least squares regression to model diagnostic specificity. In certain examples, one or more of the two or more models are derived by using classification and regression trees, and/or one or more of the two or more models are derived by using ordinary least squares regression to model diagnostic specificity. In certain examples, one or more of the two or more models are derived by using classification and regression trees to model diagnostic specificity, and/or one or more of the two or more models are derived by using ordinary least squares regression. In certain examples, one or more of the two or more models are derived by using classification and regression trees to model diagnostic sensitivity, and/or one or more of the two or more models are derived by using ordinary least squares regression. In certain examples, one or more of the two or more models are derived by using classification and regression trees to model diagnostic specificity, and/or one or more of the two or more models are derived by using ordinary least squares regression to model diagnostic sensitivity.

[0006] In certain examples, one or more of the two or more models are derived by using random forest learning classification, and/or one or more of the two or more models are derived by using quantile classification. In certain examples, one or more of the two or more models are derived by using random forest learning classification to model diagnostic sensitivity, and/or one or more of the two or more models are derived by using quantile classification. In certain examples, one or more of the two or more models are derived by using random forest learning classification to model diagnostic specificity, and/or one or more of the two or more models are derived by using quantile classification. In certain examples, one or more of the two or more models are derived by using random forest learning classification, and/or one or more of the two or more models are derived by using quantile classification to model diagnostic sensitivity. In certain examples, one or more of the two or more models are derived by using random forest learning classification, and/or one or more of the two or more models are derived by using quantile classification to model diagnostic specificity. In certain examples, one or more of the two or more models are derived by using random forest learning classification to model diagnostic specificity, and/or one or more of the two or more models are derived by using quantile classification to model diagnostic sensitivity. In certain examples, one or more of the two or more models are derived by using random forest learning classification to model diagnostic specificity, and/or

one or more of the two or more models are derived by using quantile classification to model diagnostic sensitivity. In certain examples, one or more of the two or more models are derived by using logistic regression to model diagnostic sensitivity, and one or more of the two or more models are derived by using logistic regression to model diagnostic specificity.

[0007] In some examples, the patient is receiving biologic or non-biologic therapy. In some examples, the method assesses mucosal healing by determining the efficacy of the therapy. In certain examples, the method assesses mucosal healing at colonic, ileocolonic, and/or ileal disease locations in the patient. In certain examples, the method assesses mucosal healing in the patient after surgery. In some examples, the method assesses mucosal healing by identifying post-operative, endoscopic recurrence in the patient. In certain examples, the method assesses mucosal healing by predicting or monitoring the mucosal status in the patient.

[0008] In another example, the disclosure provides a method for assessing mucosal healing in a patient with CD. The method includes: (a) detecting the expression of the following biomarkers in a serum sample from the patient: Ang1; Ang2; CEACAM1; VCAM1; TGFα; CRP; SAA1; MMP-1; MMP-2; MMP-3; MMP-9; EMMPRIN; and IL-7. The method further includes: (b) applying a mathematical algorithm to the expression of the biomarkers in step (a) to produce an MHI for the patient, wherein the MHI is a scale of 0-100, wherein the patient is in remission or has mild endoscopic disease when the MHI is between 0-40, and wherein the patient has endoscopically active disease when the MHI is between 50-100.

[0009] In some examples, the patient is receiving biologic or non-biologic therapy. In certain examples, the method assesses mucosal healing by determining the efficacy of the therapy. In certain examples, the method assesses mucosal healing at colonic, ileocolonic, and/or ileal disease locations in the patient. In some examples, the method assesses mucosal healing by identifying post-operative, endoscopic recurrence in the patient. In some examples, the remission corresponds to a CDEIS of less than 3 (CDEIS < 3). In certain examples, the mild endoscopic disease corresponds to a CDEIS of between 3-8 (CDEIS 3-8). In some examples, the endoscopically active disease corresponds to a CDEIS of greater than or equal to 3 (CDEIS ≥ 3). In certain examples, the method assesses mucosal healing by predicting or monitoring the mucosal status in the patient.

[0010] In another example, the disclosure is to a method of evaluating the efficacy of a therapy administered to a patient with CD. The method includes providing a serum sample

from the patient. The method further includes detecting in the serum sample an expression level of each of two or more biomarkers selected from the group consisting of Ang1, Ang2, CEACAM1, VCAM1, TGFα, CRP, SAA1, MMP-1, MMP-2, MMP-3, MMP-9, EMMPRIN, and IL-7. The method further includes applying a mathematical algorithm to the expression levels of the two or more biomarkers, thereby producing an MHI score for the patient. The method further includes adjusting the therapy in response to the MHI score.

[0011] In some examples, the detecting includes contacting the serum sample with a binding partner for each of the two or more biomarkers and detecting binding between each biomarker and its respective binding partner. In certain examples, each binding partner is an antibody. In some examples, the adjusting includes decreasing the therapy when the MHI score is less than or equal to 40 on a scale from 0 to 100. In certain examples, the adjusting includes increasing the therapy when the MHI score is greater than or equal to 50 on a scale from 0 to 100. In certain examples, the therapy comprises one or more biologic agents, conventional drugs, nutritional supplements, or combinations thereof.

[0012] In another example, the disclosure is to a method of detecting in a patient with Crohn's disease an expression level of two or more biomarkers selected from the group consisting of Ang1, Ang2, CEACAM1, VCAM1, TGFα, CRP, SAA1, MMP-1, MMP-2, MMP-3, MMP-9, EMMPRIN, and IL-7. The method includes obtaining a serum sample from the patient. The method further includes detecting the expression level of each of the two or more biomarkers in the serum sample by contacting the serum sample with a binding partner for each of the two or more biomarkers and detecting binding between each biomarker and its respective binding partner. In some examples, each binding partner is an antibody.

[0013] In another example, the disclosure is to a method for assessing mucosal healing in a patient with Crohn's disease. The method includes obtaining a serum sample from the patient. The method further includes detecting the expression level of each of the two or more biomarkers in the serum sample by contacting the serum sample with a binding partner for each of the two or more biomarkers and detecting binding between each biomarker and its respective binding partner. Each of the two or more biomarkers can independently be Ang1, Ang2, CEACAM1, VCAM1, TGFα, CRP, SAA1, MMP-1, MMP-2, MMP-3, MMP-9, EMMPRIN, or IL-7. The method further includes applying a mathematical algorithm to the expression levels of the two or more biomarkers, thereby producing an MHI score for the patient.

[0014] In some examples, each binding partner is an antibody. In certain examples, the method further includes determining that the patient has a high probability of being in remission or having mild endoscopic disease when the MHI score is less than or equal to 40 on a scale from 0 to 100. In certain examples, the method further includes determining that the patient has a high probability of having endoscopically active disease when the MHI score is greater than or equal to 50 on a scale from 0 to 100.

[0015] In another example, the disclosure is to a method for assessing mucosal heling in a patient with Crohn's disease and treating Crohn's disease in the patient. The method includes obtaining a serum sample from a patient. The method further includes detecting in the serum sample an expression level of each of two or more biomarkers selected from the group consisting of Angl, Ang2, CEACAM1, VCAM1, TGFα, CRP, SAA1, MMP-1, MMP-2, MMP-3, MMP-9, EMMPRIN, and IL-7. The method further includes applying a mathematical algorithm to the expression levels of the two or more biomarkers, thereby producing an MHI score for the patient. The method further includes diagnosing the patient with a high probability of having endoscopically active disease when the MHI score is greater than or equal to 50 on a scale from 0 to 100. The method further includes administering an effective amount of a therapeutic agent to the diagnosed patient. In some examples, the therapeutic agent includes one or more biologic agents, conventional drugs, nutritional supplements, or combinations thereof.

[0016] In another example, the disclosure is to a method of treating a patient with Crohn's Disease. The method includes administering an effective amount of a therapeutic agent to a patient diagnosed with a high probability of having endoscopically active disease according to a disclosed method. In some examples, the therapeutic agent comprises one or more biologic agents, conventional drugs, nutritional supplements, or combinations thereof.

[0017] In another example, the disclosure provides a kit including two or more binding partners Each of the two or more binding partners is attached to one or more solid supports. Each of the two or more binding partners is also capable of binding a different analyte selected from the group consisting of Angl, Ang2, CEACAM1, VCAM1, TGFα, CRP, SAA1, MMP-1, MMP-2, MMP-3, MMP-9, EMMPRIN, and IL-7.

[0018] In some examples, each of the two or more binding partners is covalently attached to one or more solid supports. In certain examples, each of the two or more binding partners is attached to a different solid support. In some examples, the kit further includes

instructions for contacting the one or more solid supports with a serum sample from a patient. The instructions can further be for detecting in the serum sample an expression level of each of analytes bound by the one or more binding partners. The instructions can further be for applying a mathematical algorithm to the expression levels of the analytes, thereby producing an MHI score for the patient. In certain examples, the MHI score has a scale from 0 to 100.

[0019] In some examples, the instructions can further be for determining that the patient has a high probability of being in remission or having mild endoscopic disease when the MHI score is less than or equal to 40. In certain examples, the high probability of being in remission or having mild endoscopic disease is greater than or equal to 92%. In certain examples, the remission corresponds to a CDEIS of less than 3 (CDEIS < 3). In some examples, the mild endoscopic disease corresponds to a CDEIS of between 3-8 (CDEIS 3-8). In certain examples, the instructions can further be for determining that the patient has a high probability of having endoscopically active disease when the MHI score is greater than or equal to 50. In some examples, the high probability of having endoscopically active disease is greater than or equal to 87%. In certain examples, the endoscopically active disease corresponds to a CDEIS of greater than or equal to 3 (CDEIS ≥ 3). In certain examples, the instructions can further be for determining that the patient has a moderate probability of having endoscopically active disease when the MHI score is between 40 and 50. In some examples, the moderate probability of having endoscopically active disease is greater than or equal to 78%.

[0020] In some examples, the patient is receiving biologic or non-biologic therapy. In certain examples, the kit assesses mucosal healing by determining the efficacy of the therapy. In certain examples, the kit assesses mucosal healing at colonic, ileocolonic, and/or ileal disease locations in the patient. In some examples, the kit assesses mucosal healing in the patient after surgery. In some examples, the kit assesses mucosal healing by identifying post-operative, endoscopic recurrence in the patient. In certain examples, the kit assesses mucosal healing by predicting or monitoring the mucosal status in the patient.

[0021] Other objects, features, and advantages of the present disclosure will be apparent to one of skill in the art from the following detailed description and figures.

WHAT IS CLAIMED IS:

1. A method for assessing mucosal healing in a patient with Crohn's Disease (CD), the method comprising:

providing a serum sample from a patient;

detecting in the serum sample an expression level of each of the following biomarkers: Ang1, Ang2, CEACAM1, VCAM1, TGFα, CRP, SAA1, MMP-1, MMP-2, MMP-3, MMP-9, EMMPRIN, and IL-7; and

applying a mathematical algorithm to the expression levels of the biomarkers, thereby producing a Mucosal Healing Index (MHI) score for the patient.

2. The method of claim 1, wherein the detecting comprises contacting the serum sample with a binding partner for each of the biomarkers and detecting binding between each biomarker and its respective binding partner.

3. The method of claim 2, wherein each binding partner is an antibody.

4. The method of any one of claims 1-3, further comprising:

determining that the patient has a high probability of being in remission or having mild endoscopic disease when the MHI score is less than or equal to 40 on a scale from 0 to 100.

5. The method of claim 4, wherein the high probability of being in remission or having mild endoscopic disease is greater than or equal to 92%.

6. The method of claim 4 or 5, wherein the remission corresponds to a Crohn's Disease Endoscopic Index of Severity (CDEIS) of less than 3 (CDEIS < 3).

7. The method of claim 4 or 5, wherein the mild endoscopic disease corresponds to a CDEIS of between 3-8 (CDEIS 3-8).

8. The method of any one of claims 1-7, further comprising:

determining that the patient has a high probability of having endoscopically active disease when the MHI score is greater than or equal to 50 on a scale from 0 to 100.

9. The method of claim 8, wherein the high probability of having endoscopically active disease is greater than or equal to 87%.

10. The method of claim 8 or 9, wherein the endoscopically active disease corresponds to a CDEIS of greater than or equal to 3 (CDEIS $\geq$ 3).

11. The method of any one of claims 1-10, further comprising:

determining that the patient has a moderate probability of having endoscopically active disease when the MHI score is between 40 and 50 on a scale from 0 to 100.

12. The method of claim 11, wherein the moderate probability of having endoscopically active disease is greater than or equal to 78%.

13. The method of any one of claims 1-12, wherein the mathematical algorithm comprises two or more models relating the expression levels of the biomarkers to an endoscopic score.

14. The method of claim 13, wherein one or more of the two or more models are derived by using classification and regression trees, and/or one or more of the two or more models are derived by using ordinary least squares regression to model diagnostic specificity.

15. The method of claim 13, wherein one or more of the two or more models are derived by using random forest learning classification, and/or one or more of the two or more models are derived by using quantile classification.

16. The method of claim 13, wherein one or more of the two or more models are derived by using logistic regression to model diagnostic sensitivity, and/or one or more of the two or more models are derived by using logistic regression to model diagnostic specificity.

17. The method of any one of claims 1-16, wherein the patient is receiving biologic or non-biologic therapy.

18. The method of claim 17, wherein the method assesses mucosal healing by determining the efficacy of the therapy.

19. The method of any one of claims 1-18, wherein the method assesses mucosal healing at colonic, ileocolonic, and/or ileal disease locations in the patient.

20. The method of any one of claims 1-19, wherein the method assesses mucosal healing in the patient after surgery.

21. The method of claim 20, wherein the method assesses mucosal healing by identifying post-operative, endoscopic recurrence in the patient.

22. The method of any one of claims 1-21, wherein the method assesses mucosal healing by predicting or monitoring the mucosal status in the patient.

23. A method for assessing mucosal healing in a patient with CD, the method comprising:

(a) detecting the expression of the following biomarkers in a serum sample from the patient: Ang1; Ang2; CEACAM1; VCAM1; TGFα; CRP; SAA1; MMP-1; MMP-2; MMP-3; MMP-9; EMMPRIN; and IL-7; and

(b) applying a mathematical algorithm to the expression of the biomarkers in step (a) to produce an MHI for the patient,

wherein the MHI is a scale of 0-100,

wherein the patient is in remission or has mild endoscopic disease when the MHI is between 0-40, and

wherein the patient has endoscopically active disease when the MHI is between 50-100.

24. The method of claim 23, wherein the patient is receiving biologic or non-biologic therapy.

25. The method of claim 24, wherein the method assesses mucosal healing by determining the efficacy of the therapy.

26. The method of any one of claims 23-25, wherein the method assesses mucosal healing at colonic, ileocolonic, and/or ileal disease locations in the patient.

27. The method of any one of claims 23-26, wherein the method assesses mucosal healing in the patient after surgery.

28. The method of claim 27, wherein the method assesses mucosal healing by identifying post-operative, endoscopic recurrence in the patient.

29. The method of any one of claims 23-28, wherein the remission corresponds to a Crohn's Disease Endoscopic Index of Severity (CDEIS) of less than 3 (CDEIS < 3).

30. The method of any one of claims 23-28, wherein the mild endoscopic disease corresponds to a CDEIS of between 3-8 (CDEIS 3-8).

31. The method of any one of claims 23-28, wherein the endoscopically active disease corresponds to a CDEIS of greater than or equal to 3 (CDEIS ≥ 3).

32. The method of any one of claims 23-31, wherein the method assesses mucosal healing by predicting or monitoring the mucosal status in the patient.