

CLAIMS

WHAT IS CLAIMED IS:

1. A method for detecting a colon cell proliferative disorder in a subject, comprising:
 - a) measuring an amount of an autoantibody from a predetermined autoantibody panel comprising autoantibodies to 3 or more antigens selected from the group consisting of NME5, USP16, UBE2S, RNF41, CD20, ANKHD1, TXNL1, NAT6, Supt6h, PRDM8, OTUD5, PNKP, SRSF7, ASB9, NXN, ZBTB21, EYA1, GSPT1, MLIP, RBM38, ARMC5, TP53, BRD9, CDK4, PRMT6, PCOLCE, and SDCBP, in a biological sample obtained from the subject to provide an autoantibody profile of the subject;
 - b) detecting a methylation status of one or more nucleic acid molecules in the biological sample to provide a methylation profile of the subject, or measuring an amount of one or more proteins in the biological sample to provide a protein profile of the subject; and
 - c) processing the autoantibody profile and the methylation profile or the protein profile using a machine learning model trained to be capable of distinguishing between subjects with the colon cell proliferative disorder and subjects without the colon cell proliferative disorder to provide an output value associated with presence of the colon cell proliferative disorder, thereby indicating the presence of the colon cell proliferative disorder in the subject.
2. The method of claim 1, wherein the autoantibody profile is associated with the colon cell proliferative disorder and provides classification of the subject as having the colon cell proliferative disorder.
3. The method of claim 1 or 2, wherein the methylation profile is associated with the colon cell proliferative disorder and provides classification of the subject as having the colon cell proliferative disorder.
4. The method of claim 1 or 2, wherein the protein profile is associated with the colon cell proliferative disorder and provides classification of the subject as having the colon cell proliferative disorder.
5. The method of any one of claims 1 to 4, wherein the methylation profile is combined with the autoantibody profile in the machine learning model to distinguish between subjects with the colon cell proliferative disorder and subjects without the colon cell proliferative disorder.

6. The method of any one of claims 1 to 4, wherein the protein profile is combined with the autoantibody profile in the machine learning model to distinguish between subjects with the colon cell proliferative disorder and subjects without the colon cell proliferative disorder.
7. The method of any one of claims 1 to 6, wherein the biological sample obtained from the subject is selected from the group consisting of body fluids, stool, colonic effluent, urine, blood plasma, blood serum, whole blood, isolated blood cells, cells isolated from the blood, tissue biopsy, and combinations thereof.
8. The method of any one of claims 1 to 7, wherein the colon cell proliferative disorder is selected from the group consisting of adenoma (adenomatous polyps), polyposis disorder, Lynch syndrome, sessile serrated adenoma (SSA), advanced adenoma, colorectal dysplasia, colorectal adenoma, colorectal cancer, colon cancer, rectal cancer, colorectal carcinoma, colorectal adenocarcinoma, carcinoid tumor, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), lymphoma, and sarcoma.
9. The method of any one of claims 1 to 8, wherein the panel is configured to indicate advanced adenoma and comprises: 1) IgM autoantibodies to at least 3 antigens selected from the group consisting of NME5, USP16, UBE2S, RNF41, CD20, and SDCBP; 2) IgM autoantibodies to at least one antigen selected from the group consisting of UBE2S, NME5, and CD20; 3) IgG autoantibodies to at least 3 antigens selected from the group consisting of ANKHD1, TXNL1, NAT6, Supt6h, PRDM8, OTUD5, PNKP, SRSF7, PCOLCE, and ASB9; 4) IgG autoantibodies to at least one antigen selected from the group consisting of ASB9, NAT6, Supt6h, and PRDM8; or a combination thereof.
10. The method of any one of claims 1 to 9, wherein the panel is configured to indicate colorectal cancer and comprises: 1) IgM autoantibodies to at least 3 antigens selected from the group consisting of PELO, CDK4, MTP1, PRMT6 ZBTB2, and PCOLCE; 2) IgM autoantibodies to at least one antigen selected from the group consisting of CDK4, MTCP1, and PCOLCE; 3) IgG autoantibodies to at least 3 antigens selected from the group consisting of TSSC4, BRD9, BCCIP, and TP53; 4) IgG autoantibodies to TP53; or a combination thereof.
11. A method for determining an autoantibody profile of a subject, comprising:
 - a) measuring an amount of an autoantibody from a predetermined panel of autoantibodies comprising autoantibodies to 3 or more antigens selected from the group consisting of NME5, USP16, UBE2S, RNF41, CD20, ANKHD1, TXNL1, NAT6, Supt6h, PRDM8,

OTUD5, PNKP, SRSF7, ASB9, NXN, ZBTB21, EYA1, GSPT1, MLIP, RBM38, ARMC5, TP53, BRD9, CDK4, PRMT6, PCOLCE, and SDCBP, in a biological sample obtained from a subject to provide the autoantibody profile of the subject.

12. The method of claim 11, wherein the autoantibody profile is associated with a colon cell proliferative disorder and provides classification of the subject as having the colon cell proliferative disorder.

13. The method of claim 11 or 12, wherein the biological sample obtained from the subject is selected from the group consisting of body fluids, stool, colonic effluent, urine, blood plasma, blood serum, whole blood, isolated blood cells, cells isolated from the blood, tissue biopsy, and combinations thereof.

14. The method of claim 11 or 12, wherein the colon cell proliferative disorder is selected from the group consisting of adenoma (adenomatous polyps), polyposis disorder, Lynch syndrome, sessile serrated adenoma (SSA), advanced adenoma, colorectal dysplasia, colorectal adenoma, colorectal cancer, colon cancer, rectal cancer, colorectal carcinoma, colorectal adenocarcinoma, carcinoid tumor, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), lymphoma, and sarcoma.

15. A method for detecting a colon cell proliferative disorder in a subject, comprising:

- a) measuring an amount of an autoantibody from a predetermined autoantibody panel comprising autoantibodies to 3 or more antigens selected from the group consisting of NME5, USP16, UBE2S, RNF41, CD20, ANKHD1, TXNL1, NAT6, Supt6h, PRDM8, OTUD5, PNKP, SRSF7, ASB9, NXN, ZBTB21, EYA1, GSPT1, MLIP, RBM38, ARMC5, TP53, BRD9, CDK4, PRMT6, PCOLCE, and SDCBP, in a biological sample obtained from the subject to provide an autoantibody profile of the subject; and
- b) processing the autoantibody profile using a machine learning model trained to be capable of distinguishing between subjects with the colon cell proliferative disorder and subjects without the colon cell proliferative disorder to provide an output value associated with presence of the colon cell proliferative disorder, thereby indicating the presence of the colon cell proliferative disorder in the subject.

16. The method of claim 15, wherein the autoantibody profile is associated with a colon cell proliferative disorder and provides classification of the subject as having the colon cell proliferative disorder.

17. The method of claim 15 or 16, wherein the biological sample obtained from the subject is selected from the group consisting of body fluids, stool, colonic effluent, urine, blood plasma, blood serum, whole blood, isolated blood cells, cells isolated from the blood, tissue biopsy, and combinations thereof.

18. The method of claim 15 or 16, wherein the colon cell proliferative disorder is selected from the group consisting of adenoma (adenomatous polyps), polyposis disorder, Lynch syndrome, sessile serrated adenoma (SSA), advanced adenoma, colorectal dysplasia, colorectal adenoma, colorectal cancer, colon cancer, rectal cancer, colorectal carcinoma, colorectal adenocarcinoma, carcinoid tumor, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), lymphoma, and sarcoma.

19. The method of any one of claims 15 to 17, wherein the panel is configured to indicate advanced adenoma and comprises: 1) IgM autoantibodies to at least 3 antigens selected from the group consisting of NME5, USP16, UBE2S, RNF41, CD20, and SDCBP; 2) IgM autoantibodies to at least one antigen selected from the group consisting of UBE2S, NME5, and CD20; 3) IgG autoantibodies to at least 3 antigens selected from the group consisting of ANKHD1, TXNL1, NAT6, Supt6h, PRDM8, OTUD5, PNKP, SRSF7, PCOLCE, and ASB9; 4) IgG autoantibodies to at least one antigen selected from the group consisting of ASB9, NAT6, Supt6h, and PRDM8; or a combination thereof.

20. The method of any one of claims 15 to 17, wherein the panel is configured to indicate colorectal cancer and comprises: 1) IgM autoantibodies to at least 3 antigens selected from the group consisting of PELO, CDK4, MTP1, PRMT6 ZBTB2, and PCOLCE; 2) IgM autoantibodies to at least one antigen selected from the group consisting of CDK4, MTCP1, and PCOLCE; 3) IgG autoantibodies to at least 3 antigens selected from the group consisting of TSSC4, BRD9, BCCIP, and TP53; 4) IgG autoantibodies to TP53; or a combination thereof.

21. The method of any one of claims 15 to 20, further comprising detecting a methylation status of one or more nucleic acid molecules in the biological sample to provide a methylation profile of the subject.

22. The method of claim 21, further comprising processing the methylation profile using the machine learning model.

23. The method of any one of claims 15 to 22, further comprising measuring an amount of one or more proteins in the biological sample to provide a protein profile of the subject.

24. The method of claim 23, further comprising processing the protein profile using the machine learning model.

25. A predetermined autoantibody panel characteristic of a colon cell proliferative disorder comprising autoantibodies to 3 or more antigens selected from the group consisting of NME5, USP16, UBE2S, RNF41, CD20, ANKHD1, TXNL1, NAT6, Supt6h, PRDM8, OTUD5, PNKP, SRSF7, ASB9, NXN, ZBTB21, EYA1, GSPT1, MLIP, RBM38, ARMC5, TP53, BRD9, CDK4, PRMT6, PCOLCE, and SDCBP.

26. The panel of claim 25, wherein the 3 or more autoantibodies are IgG autoantibodies, IgM autoantibodies, or a combination thereof.

27. The panel of claim 25 or 26, wherein the panel is configured to distinguish healthy subjects, subjects with benign colon polyp, subjects with advanced adenoma, or subjects with colorectal cancer.

28. The panel of any one of claims 25 to 27, wherein the panel is configured to indicate advanced adenoma and comprises: 1) IgM autoantibodies to at least 3 antigens selected from the group consisting of NME5, USP16, UBE2S, RNF41, CD20, and SDCBP; 2) IgM autoantibodies to at least one antigen selected from the group consisting of UBE2S, NME5, and CD20; 3) IgG autoantibodies to at least 3 antigens selected from the group consisting of ANKHD1, TXNL1, NAT6, Supt6h, PRDM8, OTUD5, PNKP, SRSF7, PCOLCE, and ASB9; 4) IgG autoantibodies to at least one antigen selected from the group consisting of ASB9, NAT6, Supt6h, and PRDM8; or a combination thereof.

29. The panel of any one of claims 25 to 27, wherein the panel is configured to indicate colorectal cancer and comprises: 1) IgM autoantibodies to at least 3 antigens selected from the group consisting of PELO, CDK4, MTP1, PRMT6 ZBTB2, and PCOLCE; 2) IgM autoantibodies to at least one antigen selected from the group consisting of CDK4, MTCP1, and PCOLCE; 3) IgG autoantibodies to at least 3 antigens selected from the group consisting of TSSC4, BRD9, BCCIP, and TP53; 4) IgG autoantibodies to TP53; or a combination thereof.

30. The panel of any one of claims 25 to 27, wherein the colon cell proliferative disorder is selected from the group consisting of adenoma (adenomatous polyps), polyposis disorder, Lynch syndrome, sessile serrated adenoma (SSA), advanced adenoma, colorectal dysplasia, colorectal adenoma, colorectal cancer, colon cancer, rectal cancer, colorectal carcinoma, colorectal adenocarcinoma,

carcinoid tumor, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), lymphoma, and sarcoma.

31. A classifier configured to distinguish a population of subjects with a colon cell proliferative disorder from subjects without the colon cell proliferative disorder, comprising:

- a) sets of measured values representative of autoantibodies from a predetermined autoantibody panel characteristic of the colon cell proliferative disorder,
- b) wherein the measured values are obtained from autoantibody expression data from subjects having the colon cell proliferative disorder and subjects not having the colon cell proliferative disorder,
- c) wherein the measured values are used to generate a set of features corresponding to properties of the autoantibodies, wherein the set of features are inputted to a machine learning or statistical model, and
- d) wherein the model provides a feature vector useful as the classifier capable of distinguishing the population of subjects having the colon cell proliferative disorder from subjects without the colon cell proliferative disorder.

32. The classifier of claim 31, wherein the predetermined autoantibody panel comprises autoantibodies to antigens selected from the group consisting of NME5, USP16, UBE2S, RNF41, CD20, ANKHD1, TXNL1, NAT6, Supt6h, PRDM8, OTUD5, PNKP, SRSF7, ASB9, PRDM8, NXN, ZBTB21, EYA1, GSPT1, MLIP, RBM38, ARMC5, TP53, BRD9, CDK4, PRMT6, PCOLCE, and SDCBP.

33. The classifier of claim 31 or 32, wherein the autoantibodies are IgG autoantibodies, IgM autoantibodies, or a combination thereof.

34. The classifier of any one of claims 31 to 33, wherein the panel is configured to distinguish healthy subjects, subjects with benign colon polyp, subjects with advanced adenoma, or subjects with colorectal cancer.

35. The classifier of any one of claims 31 to 33, wherein the panel is configured to indicate advanced adenoma and comprises: 1) IgM autoantibodies to at least 3 antigens selected from the group consisting of NME5, USP16, UBE2S, RNF41, CD20, and SDCBP; 2) IgM autoantibodies to at least one antigen selected from the group consisting of UBE2S, NME5, and CD20; 3) IgG autoantibodies to at least 3 antigens selected from the group consisting of ANKHD1, TXNL1, NAT6, Supt6h, PRDM8, OTUD5, PNKP, SRSF7, PCOLCE, and ASB9; 4) IgG autoantibodies to

at least one antigen selected from the group consisting of ASB9, NAT6, Supt6h, and PRDM8; or a combination thereof.

36. The classifier of any one of claims 31 to 33, wherein the panel is configured to indicate colorectal cancer and comprises: 1) IgM autoantibodies to at least 3 antigens selected from the group consisting of PELO, CDK4, MTP1, PRMT6 ZBTB2, and PCOLCE; 2) IgM autoantibodies to at least one antigen selected from the group consisting of CDK4, MTCP1, and PCOLCE; 3) IgG autoantibodies to at least 3 antigens selected from the group consisting of TSSC4, BRD9, BCCIP, and TP53; 4) IgG autoantibodies to TP53; or a combination thereof.

37. The classifier of any one of claims 31 to 33, wherein the colon cell proliferative disorder is selected from the group consisting of adenoma (adenomatous polyps), polyposis disorder, Lynch syndrome, sessile serrated adenoma (SSA), advanced adenoma, colorectal dysplasia, colorectal adenoma, colorectal cancer, colon cancer, rectal cancer, colorectal carcinoma, colorectal adenocarcinoma, carcinoid tumor, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), lymphoma, and sarcoma.

38. A system comprising a machine learning model classifier for detecting a colon cell proliferative disorder comprising:

- a) a computer-readable medium comprising a classifier operable to classify the subjects based at least in part on a predetermined autoantibody panel; and
- b) one or more processors for executing instructions stored on the computer-readable medium.

39. The system of claim 38, comprising the classifier of claim 31 loaded into a memory of a computer system, wherein the machine learning model is trained using training vectors obtained from training biological samples, wherein a first subset of the training biological samples identified as having a colon cell proliferative disorder, and wherein a second subset of the training biological samples identified as not having a colon cell proliferative disorder.

40. The system of claim 38 or 39, wherein the predetermined autoantibody panel comprises autoantibodies to 3 or more antigens selected from the group consisting of NME5, USP16, UBE2S, RNF41, CD20, ANKHD1, TXNL1, NAT6, Supt6h, PRDM8, OTUD5, PNKP, SRSF7, ASB9, PRDM8, NXN, ZBTB21, EYA1, GSPT1, MLIP, RBM38, ARMC5, TP53, BRD9, CDK4, PRMT6, PCOLCE, and SDCBP.

41. The system of claim 38 or 39, wherein the classifier is selected from the group consisting of a deep learning classifier, a neural network classifier, a linear discriminant analysis (LDA) classifier,

a quadratic discriminant analysis (QDA) classifier, a support vector machine (SVM) classifier, a random forest (RF) classifier, a K nearest neighbor classifier, a linear kernel support vector machine classifier, a first or second order polynomial kernel support vector machine classifier, a ridge regression classifier, an elastic net algorithm classifier, a sequential minimal optimization algorithm classifier, a naïve Bayes algorithm classifier, and a principal component analysis classifier.