

screening would lead to the recommendation of a follow up LDCT screening in order to achieve mortality benefits.

[0015] Lung cancer screening is a joint decision-making process between the patient and provider that should take place in addition to smoking cessation counseling (in current smokers). The risks, benefits, and evidence level of each screening modality should be discussed, as well as advice on where screening should be conducted (High-quality lung cancer and treatment center that employs Lung-RADS standardized categorization). In cases where the risk of lung cancer is particularly high (e.g., screening eligible current heavy smoker, with history of COPD and a strong family history of lung cancer), the physician may modify guidance to strongly suggest LDCT as a screening modality (as it is the gold standard), and screening to be performed at a Screening Center of Excellence (to ensure the highest level of sensitivity and specificity is achieved).

[0016] While it is well established that lung cancer screening with LDCT benefits reduce lung cancer mortality rates, available data indicate that uptake of lung cancer screening is low with studies showing that as few as 14% of individuals eligible for lung cancer screening had been screened in the previous years. (Zahnd et al. “Lung Cancer Screening Utilization: A Behavioral Risk Factor Surveillance System Analysis.” Am J Prev Med 2019;57:250-5). With an estimated over 130 thousand people in the US projected to die of lung cancer in 2021, (<https://seer.cancer.gov/statfacts/html/lungb.html>) additional clinical care paths to advise patients’ risk for lung cancer are needed. There is no current clinically accepted standard of care for assessing a patient’s risk for future lung cancer diagnosis.

[0017] As described above, physicians may recommend differing lung cancer screening modalities or referral to a Screening Center of Excellence for lung cancer based on individual patients’ risk level; however, screening tools are limited to detecting current lung cancer, not future risk. A variety of clinical risk calculators for future lung risk have been developed that can predict an individual’s lung cancer risk from a combination of demographic, personal and family health history, lifestyle, and carcinogen exposure level; however, these calculators are routinely not validated/replicated in independent cohorts, involve patient self-report information, and many require non-standard clinical outputs. No clinical risk calculators are currently widely used as standard of care in clinical practice. Accordingly, a need exists for biomarkers, methods, devices, reagents, systems, and kits to evaluate an individual’s lung cancer risk.

SUMMARY

[0018] The present application discloses biomarkers, methods, devices, reagents, systems, and kits to evaluate an individual’s risk for lung cancer diagnosis within a specified

time frame. In one example, the objective of the presently disclosed lung cancer risk test is to create a model that predicts a current or former smoker's risk for a lung cancer diagnosis within 5 years of blood draw.

[0019] Benefits of the presently disclosed lung cancer risk test include: a convenient way to gain personalized knowledge of the degree of risk for a future lung cancer diagnosis without reliance on self-reported demographics or genetic background information; the test result may influence compliance with lung cancer screening guidelines allowing for the potential for earlier identification of lung cancer, and thus improved chance of lung cancer survival; the test may influence positive behavior changes in modifiable risk-related behaviors (e.g., smoking cessation, dietary change, weight loss); and the test may aid healthcare provider lung cancer screening decisions/recommendations or patient's lung screening preferences based on the test result (e.g., for patients in high-risk category to initially undertake LDCT screening methodology that is considered the gold standard versus another lesser sensitive methodology such as chest radiography). The lung cancer risk test may include identifying subjects that have lung cancer at the time of sampling.

[0019a] In one aspect, the disclosure provides a method comprising:

- a) measuring the level of PH protein and the level of at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, SP-D, HE4, PSP-94, FUT5 and CRLF1 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of PH and the level of the at least one, two, three, four, five, or six proteins.

[0019b] In one aspect, the disclosure provides a method comprising:

- a) measuring the level of FUT5 protein and the level of at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, SP-D, HE4, PSP-94, PH and CRLF1 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of FUT5 and the level of the at least one, two, three, four, five, or six proteins.

[0019c] In one aspect, the disclosure provides a method comprising:

- a) measuring the level of CRLF1 protein and the level of at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, SP-D, HE4, PSP-94, PH and FUT5 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of CRLF1 and the level of the at least one, two, three, four, five, or six proteins.

[0019d] In one aspect, the disclosure provides a method comprising:

- a) measuring the level of PSP-94 protein and the level of at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, SP-D, HE4, PH, FUT5 and CRLF1 in a sample from a human subject; and

b) identifying the human subject as being at risk for developing lung cancer based on the level of PSP-94 and the level of the at least one, two, three, four, five, or six proteins.

[0019e] In one aspect, the disclosure provides a method comprising:

- a) measuring the level of at least three, four, five, six, or seven proteins selected from the group consisting of PH, MMP-12, SP-D, HE4, PSP-94, FUT5 and CRLF1 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of the at least three, four, five, six, or seven proteins.

[0019f] In one aspect, the disclosure provides a kit comprising N protein capture reagents, wherein N is at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, or at least 7, and wherein at least one of the N protein capture reagents specifically binds to a protein selected from PH, PSP-94, MMP-12, SP-D, HE4, FUT5 and CRLF1.

[0019g] In one aspect, the disclosure provides the kit as disclosed herein, for use in detecting the N biomarker proteins in a sample from a subject.

[0020] The following numbered paragraphs [0021] - [00116] contain statements of broad combinations of the inventive technical features herein disclosed:

[0021] 1. A method comprising:

- a) measuring the level of PSP-94 protein and the level of at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, SP-D, HE4, PH, FUT5 and CRLF1 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of PSP-94 and the level of the at least one, two, three, four, five, or six proteins.

[0022] 2. A method comprising:

- a) measuring the level of PH protein and the level of at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, SP-D, HE4, PSP-94, FUT5 and CRLF1 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of PH and the level of the at least one, two, three, four, five, or six proteins.

[0023] 3. A method comprising:

- a) measuring the level of FUT5 protein and the level of at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, SP-D, HE4, PSP-94, PH and CRLF1 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of FUT5 and the level of the at least one, two, three, four, five, or six proteins.

[0024] 4. A method comprising:

- a) measuring the level of CRLF1 protein and the level of at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, SP-D, HE4, PSP-94, PH and FUT5 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of CRLF1 and the level of the at least one, two, three, four, five, or six proteins.

[0025] 5. A method comprising:

- a) contacting a sample from a human subject with a set of capture reagents, wherein each capture reagent has affinity for a different protein of the set of proteins comprising PSP-94 protein, and at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, SP-D, HE4, PH, FUT5 and CRLF1; and
- b) measuring the level of each protein of the set of proteins with the set of capture reagents.

[0026] 6. A method comprising:

- a) contacting a sample from a human subject with a set of capture reagents, wherein each capture reagent has affinity for a different protein of the set of proteins comprising PH protein, and at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, SP-D, HE4, PSP-94, FUT5 and CRLF1; and
- b) measuring the level of each protein of the set of proteins with the set of capture reagents.

[0027] 7. A method comprising:

- a) contacting a sample from a human subject with a set of capture reagents, wherein each capture reagent has affinity for a different protein of the set of proteins comprising FUT5 protein, and at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, SP-D, HE4, PSP-94, PH and CRLF1; and
- b) measuring the level of each protein of the set of proteins with the set of capture reagents.

[0028] 8. A method comprising:

- a) contacting a sample from a human subject with a set of capture reagents, wherein each capture reagent has affinity for a different protein of the set of proteins comprising CRLF1 protein, and at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, SP-D, HE4, PSP-94, PH and FUT5; and
- b) measuring the level of each protein of the set of proteins with the set of capture reagents.

[0029] 9. The method of example 1 or example 5, wherein the method comprises measuring PSP-94 and MMP-12; PSP-94 and SP-D; PSP-94 and HE4; PSP-94 and PH; PSP-94 and FUT5; or PSP-94 and CRLF1.

[0030] 10. The method of example 1 or example 5, wherein the method comprises measuring PSP-94, MMP-12 and SP-D; PSP-94, MMP-12 and HE4; PSP-94, MMP-12 and PH;

PSP-94, MMP-12 and FUT5; PSP-94, MMP-12 and CRLF1; PSP-94, SP-D and HE4; PSP-94, SP-D and PH; PSP-94, SP-D and FUT5; PSP-94, SP-D and CRLF1; PSP-94, HE4 and PH; PSP-94, HE4 and FUT5; PSP-94, HE4 and CRLF1; PSP-94, PH and FUT5; PSP-94, PH and CRLF1; or PSP-94, FUT5 and CRLF1.

[0031] 11. The method of example 2 or example 6, wherein the method comprises measuring PH and MMP-12; PH and SP-D; PH and HE4; PH and PSP-94; PH and FUT5; or PH and CRLF1.

[0032] 12. The method of example 2 or example 6, wherein the method comprises measuring PH, MMP-12 and SP-D; PH, MMP-12 and HE4; PH, MMP-12 and PSP-94; PH, MMP-12 and FUT5; PH, MMP-12 and CRLF1; PH, SP-D and HE4; PH, SP-D and PSP-94; PH, SP-D and FUT5; PH, SP-D and CRLF1; PH, HE4 and PSP-94; PH, HE4 and FUT5; PH, HE4 and CRLF1; PH, PSP-94 and FUT5; PH, PSP-94 and CRLF1; or PH, FUT5 and CRLF1.

[0033] 13. The method of example 3 or example 7, wherein the method comprises measuring FUT5 and MMP-12; FUT5 and SP-D; FUT5 and HE4; FUT5 and PSP-94; FUT5 and PH; or FUT5 and CRLF1.

[0034] 14. The method of example 3 or example 7, wherein the method comprises measuring FUT5, MMP-12 and SP-D; FUT5, MMP-12 and HE4; FUT5, MMP-12 and PSP-94; FUT5, MMP-12 and PH; FUT5, MMP-12 and CRLF1; FUT5, SP-D and HE4; FUT5, SP-D and PSP-94; FUT5, SP-D and PH; FUT5, SP-D and CRLF1; FUT5, HE4 and PSP-94; FUT5, HE4 and PH; FUT5, HE4 and CRLF1; FUT5, PSP-94 and PH; FUT5, PSP-94 and CRLF1; or FUT5, PH and CRLF1.

[0035] 15. The method of example 4 or example 8, wherein the method comprises measuring CRLF1 and MMP-12; CRLF1 and SP-D; CRLF1 and HE4; CRLF1 and PSP-94; CRLF1 and PH; or CRLF1 and FUT5.

[0036] 16. The method of example 4 or example 8, wherein the method comprises measuring CRLF1, MMP-12 and SP-D; CRLF1, MMP-12 and HE4; CRLF1, MMP-12 and PSP-94; CRLF1, MMP-12 and PH; CRLF1, MMP-12 and FUT5; CRLF1, SP-D and HE4; CRLF1, SP-D and PSP-94; CRLF1, SP-D and PH; CRLF1, SP-D and FUT5; CRLF1, HE4 and PSP-94; CRLF1, HE4 and PH; CRLF1, HE4 and FUT5; CRLF1, PSP-94 and PH; CRLF1, PSP-94 and FUT5; or CRLF1, PH and FUT5.

[0037] 17. The method of example 1 or example 5, wherein the method comprises measuring PSP-94 and PH and at least one of the following proteins selected from MMP-12, SP-D, HE4, FUT5 and CRLF1.

- [0038]** 18. The method of example 1 or example 5, wherein the method comprises measuring PSP-94 and FUT5 and at least one of the following proteins selected from MMP-12, SP-D, HE4, PH and CRLF1.
- [0039]** 19. The method of example 1 or example 5, wherein the method comprises measuring PSP-94 and CRLF1 and at least one of the following proteins selected from MMP-12, SP-D, HE4, PH and FUT5.
- [0040]** 20. The method of example 2 or example 6, wherein the method comprises measuring PH and FUT5 and at least one of the following proteins selected from MMP-12, SP-D, HE4, PSP-94 and CRLF1.
- [0041]** 21. The method of example 2 or example 6, wherein the method comprises measuring PH and CRLF1 and at least one of the following proteins selected from MMP-12, SP-D, HE4, PSP-94 and FUT5.
- [0042]** 22. The method of example 3 or example 7, wherein the method comprises measuring FUT5 and CRLF1 and at least one of the following proteins selected from MMP-12, SP-D, HE4, PSP-94 and PH.
- [0043]** 23. A method comprising:
- a) contacting a sample from a human subject with two capture reagents, wherein one capture reagent has affinity for a PSP-94 protein and the second capture reagent has affinity for a PH protein; and
 - b) measuring the level of each protein with the two capture reagents.
- [0044]** 24. A method comprising:
- a) contacting a sample from a human subject with two capture reagents, wherein one capture reagent has affinity for a PSP-94 protein and the second capture reagent has affinity for a FUT5 protein; and
 - b) measuring the level of each protein with the two capture reagents.
- [0045]** 25. A method comprising:
- a) contacting a sample from a human subject with two capture reagents, wherein one capture reagent has affinity for a PSP-94 protein and the second capture reagent has affinity for a CRLF1 protein; and
 - b) measuring the level of each protein with the two capture reagents.
- [0046]** 26. A method comprising:
- a) contacting a sample from a human subject with two capture reagents, wherein one capture reagent has affinity for a PH protein and the second capture reagent has affinity for a FUT5 protein; and
 - b) measuring the level of each protein with the two capture reagents.

- a) contacting a sample from a human subject with three capture reagents, wherein each of the three capture reagents has affinity for a protein selected from PSP-94, PH, and FUT5; and
- b) measuring the level of each protein with the three capture reagents.

[0056] 36. A method comprising:

- a) contacting a sample from a human subject with three capture reagents, wherein each of the three capture reagents has affinity for a protein selected from PSP-94, PH, and CRLF1; and
- b) measuring the level of each protein with the three capture reagents.

[0057] 37. A method comprising:

- a) contacting a sample from a human subject with three capture reagents, wherein each of the three capture reagents has affinity for a protein selected from PH, FUT5, and CRLF1; and
- b) measuring the level of each protein with the three capture reagents.

[0058] 38. A method comprising:

- a) contacting a sample from a human subject with three capture reagents, wherein each of the three capture reagents has affinity for a protein selected from FUT5, CRLF1, and PSP-94; and
- b) measuring the level of each protein with the three capture reagents.

[0059] 39. A method comprising:

- a) measuring the level of PSP-94, PH, and FUT5 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of PSP-94, PH, and FUT5.

[0060] 40. A method comprising:

- a) measuring the level of PSP-94, PH, and CRLF1 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of PSP-94, PH, and CRLF1.

[0061] 41. A method comprising:

- a) measuring the level of PH, FUT5, and CRLF1 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of PH, FUT5, and CRLF1.

[0062] 42. A method comprising:

- a) measuring the level of FUT5; CRLF1, and PSP-94 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of FUT5; CRLF1, and PSP-94.

[0063] 43. The method of any one of examples 23-42, further comprising measuring the level of MMP-12 protein.

[0064] 44. The method of any one of examples 23-43, further comprising measuring the level of SP-D protein.

[0065] 45. The method of any one of examples 23-44, further comprising measuring the level of HE4 protein.

[0066] 46. A method comprising:

a) measuring the level of at least three, four, five, six, or seven proteins selected from the group consisting of MMP-12, SP-D, HE4, PSP-94, PH, FUT5 and CRLF1 in a sample from a human subject; and

b) identifying the human subject as being at risk for developing lung cancer based on the level of the at least three, four, five, six, or seven proteins.

[0067] 47. The method of example 46, wherein the method comprises measuring MMP-12, SP-D and HE4; MMP-12, SP-D and PSP-94; MMP-12, SP-D and PH; MMP-12, SP-D and FUT5; MMP-12, SP-D and CRLF1; MMP-12, HE4 and PSP-94; MMP-12, HE4 and PH; MMP-12, HE4 and FUT5; MP-12, HE4 and CRLF1; MMP-12, PSP-94 and PH; MMP-12, PSP-94 and FUT5; MMP-12, PSP-94 and CRLF1; MMP-12, PH and FUT5; MMP-12, PH and CRLF1; MMP-12, FUT5 and CRLF1; SP-D, HE4 and PSP-94; SP-D, HE4 and PH; SP-D, HE4 and FUT5; SP-D, HE4 and CRLF1; SP-D, PSP-94 and PH; SP-D, PSP-94 and FUT5; SP-D, PSP-94 and CRLF1; SP-D, PH and FUT5; SP-D, PH and CRLF1; SP-D, FUT5 and CRLF1; HE4, PSP-94 and PH; HE4, PSP-94 and FUT5; HE4, PSP-94 and CRLF1; HE4, PH and FUT5; HE4, PH and CRLF1; HE4, FUT5 and CRLF1; PSP-94, PH and FUT5; PSP-94, PH and CRLF1; PSP-94, FUT5 and CRLF1; or PH, FUT5, and CRLF1.

[0068] 48. The method of example 46 or 47, further comprising measuring one or more of PSP-94, PH, FUT5, and CRLF1.

[0069] 49. A method comprising:

a) contacting a sample from a human subject with a set of capture reagents, wherein each capture reagent has affinity for a different protein of the set of proteins comprising at least three, four, five, six, or seven proteins selected from the group consisting of MMP-12, SP-D, HE4, PSP-94, PH, FUT5 and CRLF1 in a sample from a human subject; and

b) measuring the level of each protein of the set of proteins with the set of capture reagents.

[0070] 50. The method of example 49, wherein the method comprises measuring MMP-12, SP-D and HE4; MMP-12, SP-D and PSP-94; MMP-12, SP-D and PH; MMP-12, SP-D and FUT5; MMP-12, SP-D and CRLF1; MMP-12, HE4 and PSP-94; MMP-12, HE4 and PH; MMP-12, HE4 and FUT5; MP-12, HE4 and CRLF1; MMP-12, PSP-94 and PH; MMP-12, PSP-94 and FUT5; MMP-12, PSP-94 and CRLF1; MMP-12, PH and FUT5; MMP-12, PH and CRLF1; MMP-12, FUT5 and CRLF1; SP-D, HE4 and PSP-94; SP-D, HE4 and PH; SP-D, HE4

and FUT5; SP-D, HE4 and CRLF1; SP-D, PSP-94 and PH; SP-D, PSP-94 and FUT5; SP-D, PSP-94 and CRLF1; SP-D, PH and FUT5; SP-D, PH and CRLF1; SP-D, FUT5 and CRLF1; HE4, PSP-94 and PH; HE4, PSP-94 and FUT5; HE4, PSP-94 and CRLF1; HE4, PH and FUT5; HE4, PH and CRLF1; HE4, FUT5 and CRLF1; PSP-94, PH and FUT5; PSP-94, PH and CRLF1; PSP-94, FUT5 and CRLF1; or PH, FUT5, and CRLF1.

[0071] 51. The method of example 49 or 50, further comprising measuring one or more of PSP-94, PH, FUT5 and CRLF1.

[0072] 52. A method comprising:

- a) measuring the level of MMP-12 protein, and the level of at least one, two, three, four, five, or six proteins selected from the group consisting of SP-D, HE4, PSP-94, PH, FUT5 and CRLF1 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of MMP-12 and the level of the at least one, two, three, four, five, or six, proteins.

[0073] 53. A method comprising:

- a) measuring the level of SP-D protein, and the level of at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, HE4, PSP-94, PH, FUT5 and CRLF1 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of SP-D and the level of the at least one, two, three, four, five, six, seven, eight, or nine proteins.

[0074] 54. A method comprising:

- a) measuring the level of HE4 protein, and the level of at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, SP-D, PSP-94, PH, FUT5 and CRLF1 in a sample from a human subject; and
- b) identifying the human subject as being at risk for developing lung cancer based on the level of HE4 and the level of the at least one, two, three, four, five, six, seven, eight, or nine proteins.

[0075] 55. A method comprising:

- a) contacting a sample from a human subject with a set of capture reagents, wherein each capture reagent has affinity for a different protein of the set of proteins comprising MMP-12 protein, and at least one, two, three, four, five, or six proteins selected from the group consisting of SP-D, HE4, PSP-94, PH, FUT5 and CRLF1; and
- b) measuring the level of each protein of the set of proteins with the set of capture reagents.

[0076] 56. A method comprising:

- a) contacting a sample from a human subject with a set of capture reagents, wherein each capture reagent has affinity for a different protein of the set of proteins comprising SP-D protein, and at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, HE4, PSP-94, PH, FUT5 and CRLF1; and
- b) measuring the level of each protein of the set of proteins with the set of capture reagents.

[0077] 57. A method comprising:

- a) contacting a sample from a human subject with a set of capture reagents, wherein each capture reagent has affinity for a different protein of the set of proteins comprising HE4 protein, and at least one, two, three, four, five, or six proteins selected from the group consisting of MMP-12, SP-D, PSP-94, PH, FUT5 and CRLF1; and
- b) measuring the level of each protein of the set of proteins with the set of capture reagents.

[0078] 58. The method of any one of examples 5-28, 36-38, 49-51, and 55-57, wherein the set of capture reagents is selected from aptamers, antibodies and a combination of aptamers and antibodies.

[0079] 59. The method of any one of the preceding examples, wherein the measuring is performed using mass spectrometry, an aptamer based assay and/or an antibody based assay.

[0080] 60. The method of example 58 or claim 59, wherein the level of each biomarker protein measured is determined from a relative florescence unit (RFU) or a protein concentration.

[0081] 61. The method of any one of the preceding examples, wherein the sample is selected from blood, plasma, serum or urine.

[0082] 62. The method of any one of the preceding examples, wherein the protein levels are used to identify a human subject as being at risk for developing lung cancer.

[0083] 63. The method of example 62, wherein the risk for developing lung cancer is within a 5 year period.

[0084] 64. The method of example 62 or example 63, wherein the risk for developing lung cancer is within a period of 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, or 10 years.

[0085] 65. The method of any one of the preceding examples, wherein the human subject is a current smoker or a former smoker.

[0086] 66. The method of any one of the preceding examples, wherein the subject has lung cancer.

[0087] 67. The method of any one of the preceding examples, wherein the method provides an area under the curve (AUC) of 0.62, 0.67, 0.68, 0.68, 0.70, 0.71, 0.72, 0.73, 0.74, 0.75, 0.76, or above.

- [0088]** 68. The method of any one of the preceding examples, wherein the method provides an area under the curve (AUC) from about 0.6 to about 0.8, from about 0.61 to about 0.78, from about 0.62 to about 0.76, from about 0.62 to about 0.68, from about 0.67 to about 0.72, from about 0.69 to about 0.74, from about 0.71 to about 0.74, from about 0.73 to about 0.76, or from about 0.74 to about 0.76.
- [0089]** 69. The method of any one of the preceding examples, wherein predicting the risk for developing lung cancer is based on input of the levels of the measured proteins in a statistical model.
- [0090]** 70. The method of example 69, wherein the predicting comprises analyzing the levels of the measured proteins using an Accelerated Failure Time (AFT) Weibull survival model.
- [0091]** 71. The method of any one of the preceding examples, further comprising performing a diagnostic screening.
- [0092]** 72. The method of example 71, wherein the diagnostic screening is selected from low dose computed tomography (LDCT), chest radiography, and sputum cytology.
- [0093]** 73. The method of any one of the preceding examples, wherein the method comprises predicting the risk for developing lung cancer for the purpose of determining a medical insurance premium or life insurance premium.
- [0094]** 74. The method of example 73, wherein the method further comprises determining coverage or premium for medical insurance or life insurance.
- [0095]** 75. The method of any one of examples 1-72, wherein the method further comprises using information resulting from the method to predict and/or manage the utilization of medical resources.
- [0096]** 76. The method of any one of examples 1-72, wherein the method further comprises using information resulting from the method to enable a decision to acquire or purchase a medical practice, hospital, or company.
- [0097]** 77. A kit comprising N protein capture reagents, wherein N is at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, or at least 7, and wherein at least one of the N protein capture reagents specifically binds to a protein selected from PSP-94, MMP-12, SP-D, HE4, PH, FUT5 and CRLF1.
- [0098]** 78. The kit of example 77, wherein N is at least two and at least one to the two N protein capture reagents specifically binds to the protein selected from PSP-94, MMP-12, SP-D, HE4, PH, FUT5 and CRLF1.
- [0099]** 79. The kit of example 77 or 78, wherein N is 2 to 7, or N is 3 to 7, or N is 4 to 7, or N is 5 to 7, or N is 6 to 7.

[00100] 80. The kit of any one of examples 77-79, wherein N is 2, N is 3, N is 4, N is 5, N is 6, or N is 7.

[00101] 81. The kit of any one of examples 77-80, wherein each of the N protein capture reagents specifically binds to a different biomarker protein.

[00102] 82. The kit of any one of examples 77-81, wherein each of the N protein capture reagents specifically binds to a protein selected from PSP-94, MMP-12, SP-D, HE4, PH, FUT5 and CRLF1.

[00103] 83. The kit of any one of examples 77-81, wherein two of the N protein capture reagents specifically bind PSP-94 and MMP-12; or two of the N protein capture reagents specifically bind PSP-94 and SP-D; or two of the N protein capture reagents specifically bind PSP-94 and HE4; or two of the N protein capture reagents specifically bind PSP-94 and PH; or two of the N protein capture reagents specifically bind PSP-94 and FUT5; or two of the N protein capture reagents specifically bind PSP-94 and CRLF1.

[00104] 84. The kit of any one of examples 77-81, wherein three of the N protein capture reagents specifically bind PSP-94, MMP-12 and SP-D; or three of the N protein capture reagents specifically bind PSP-94, MMP-12 and HE4; or three of the N protein capture reagents specifically bind PSP-94, MMP-12 and PH; or three of the N protein capture reagents specifically bind PSP-94, MMP-12 and FUT5; or three of the N protein capture reagents specifically bind PSP-94, MMP-12 and CRLF1; or three of the N protein capture reagents specifically bind PSP-94, SP-D and HE4; or three of the N protein capture reagents specifically bind PSP-94, SP-D and PH; or three of the N protein capture reagents specifically bind PSP-94, SP-D and FUT5; or three of the N protein capture reagents specifically bind PSP-94, SP-D and CRLF1; or three of the N protein capture reagents specifically bind PSP-94, HE4 and PH; PSP-94, HE4 and FUT5; or three of the N protein capture reagents specifically bind PSP-94, HE4 and CRLF1; or three of the N protein capture reagents specifically bind PSP-94, PH and FUT5; or three of the N protein capture reagents specifically bind PSP-94, PH and CRLF1; or three of the N protein capture reagents specifically bind PSP-94, FUT5 and CRLF1.

[00105] 85. The kit of any one of examples 77-81, wherein two of the N protein capture reagents specifically bind PH and MMP-12; or two of the N protein capture reagents specifically bind PH and SP-D; or two of the N protein capture reagents specifically bind PH and HE4; or two of the N protein capture reagents specifically bind PH and PSP-94; PH and FUT5; or two of the N protein capture reagents specifically bind PH and CRLF1.

[00106] 86. The kit of any one of examples 77-81, wherein three of the N protein capture reagents specifically bind PH, MMP-12 and SP-D; or three of the N protein capture reagents specifically bind PH, MMP-12 and HE4; or three of the N protein capture reagents specifically

bind PH, MMP-12 and PSP-94; or three of the N protein capture reagents specifically bind PH, MMP-12 and FUT5; or three of the N protein capture reagents specifically bind PH, MMP-12 and CRLF1; or three of the N protein capture reagents specifically bind PH, SP-D and HE4; or three of the N protein capture reagents specifically bind PH, SP-D and PSP-94; or three of the N protein capture reagents specifically bind PH, SP-D and FUT5; or three of the N protein capture reagents specifically bind PH, SP-D and CRLF1; or three of the N protein capture reagents specifically bind PH, HE4 and PSP-94; or three of the N protein capture reagents specifically bind PH, HE4 and FUT5; or three of the N protein capture reagents specifically bind PH, HE4 and CRLF1; or three of the N protein capture reagents specifically bind PH, PSP-94 and FUT5; PH, PSP-94 and CRLF1; or three of the N protein capture reagents specifically bind PH, FUT5 and CRLF1.

[00107] 87. The kit of any one of examples 77-81, wherein two of the N protein capture reagents specifically bind FUT5 and MMP-12; or two of the N protein capture reagents specifically bind FUT5 and SP-D; or two of the N protein capture reagents specifically bind FUT5 and HE4; or two of the N protein capture reagents specifically bind FUT5 and PSP-94; or two of the N protein capture reagents specifically bind FUT5 and PH; or two of the N protein capture reagents specifically bind FUT5 and CRLF1.

[00108] 88. The kit of any one of examples 77-81, wherein three of the N protein capture reagents specifically bind FUT5, MMP-12 and SP-D; or three of the N protein capture reagents specifically bind FUT5, MMP-12 and HE4; or three of the N protein capture reagents specifically bind FUT5, MMP-12 and PSP-94; or three of the N protein capture reagents specifically bind FUT5, MMP-12 and PH; or three of the N protein capture reagents specifically bind FUT5, MMP-12 and CRLF1; or three of the N protein capture reagents specifically bind FUT5, SP-D and HE4; or three of the N protein capture reagents specifically bind FUT5, SP-D and PSP-94; or three of the N protein capture reagents specifically bind FUT5, SP-D and PH; or three of the N protein capture reagents specifically bind FUT5, SP-D and CRLF1; or three of the N protein capture reagents specifically bind FUT5, HE4 and PSP-94; or three of the N protein capture reagents specifically bind FUT5, HE4 and PH; or three of the N protein capture reagents specifically bind FUT5, HE4 and CRLF1; or three of the N protein capture reagents specifically bind FUT5, PSP-94 and PH; or three of the N protein capture reagents specifically bind FUT5, PSP-94 and CRLF1; or three of the N protein capture reagents specifically bind FUT5, PH and CRLF1.

[00109] 89. The kit of any one of examples 77-81, wherein two of the N protein capture reagents specifically bind CRLF1 and MMP-12; or two of the N protein capture reagents specifically bind CRLF1 and SP-D; or two of the N protein capture reagents specifically bind

CRLF1 and HE4; or CRLF1 and PSP-94; or two of the N protein capture reagents specifically bind CRLF1 and PH; or two of the N protein capture reagents specifically bind CRLF1 and FUT5.

[00110] 90. The kit of any one of examples 77-81, wherein three of the N protein capture reagents specifically bind CRLF1, MMP-12 and SP-D; or three of the N protein capture reagents specifically bind CRLF1, MMP-12 and HE4; or three of the N protein capture reagents specifically bind CRLF1, MMP-12 and PSP-94; or three of the N protein capture reagents specifically bind CRLF1, MMP-12 and PH; or three of the N protein capture reagents specifically bind CRLF1, MMP-12 and FUT5; or three of the N protein capture reagents specifically bind CRLF1, SP-D and HE4; or three of the N protein capture reagents specifically bind CRLF1, SP-D and PSP-94; or three of the N protein capture reagents specifically bind CRLF1, SP-D and PH; or three of the N protein capture reagents specifically bind CRLF1, SP-D and FUT5; or three of the N protein capture reagents specifically bind CRLF1, HE4 and PSP-94; or three of the N protein capture reagents specifically bind CRLF1, HE4 and PH; or three of the N protein capture reagents specifically bind CRLF1, HE4 and FUT5; or three of the N protein capture reagents specifically bind CRLF1, PSP-94 and PH; or three of the N protein capture reagents specifically bind CRLF1, PSP-94 and FUT5; or three of the N protein capture reagents specifically bind CRLF1, PH and FUT5.

[00111] 91. A kit comprising N protein capture reagents, wherein the kit comprises protein capture reagents for carrying out the methods any one of claims 1-76.

[00112] 92. The kit of any one of examples 77-91, wherein each of the N biomarker protein capture reagents is an antibody or an aptamer.

[00113] 93. The kit of example 92, wherein each biomarker protein capture reagent is an aptamer.

[00114] 94. The kit of any one of examples 77-93, for use in detecting the N biomarker proteins in a sample from a subject.

[00115] 95. The kit of example 94, for use in predicting risk of a subject for developing lung cancer.

[00116] 96. The kit of example 95, wherein the subject has lung cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[00117] **Figure 1** shows the effect of smoking, and smoking cessation on lifetime risk for lung cancer in men and women since 1995. Image from Bruder et al. "Estimating lifetime and 10-year risk of lung cancer." *Prev Med Rep* 2018;11:125-30.