CLAIMS

1. A tiered, multipart method for detecting one or more early stage cancers in a subject, comprising:

performing an analysis of sequence information of the subject that has been obtained from a biological sample of the subject to identify whether the subject is not at risk of having one or more of the early stage cancers; and then if the patient has not been identified as not at risk:

analyzing sequence information of the subject not identified as not at risk by performing a second analysis to detect the presence of at least one specific cancer in the subject.

2. The method of claim 1, wherein the one or more of the early stage cancers is fifteen or more different cancers, optionally wherein the one or more of the early stage or preclinical phase cancers is a set of acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, soft tissue sarcoma, lymphoma, anal cancer, gastrointestinal cancer, brain cancer, skin cancer, bile duct cancer, bladder cancer, bone cancer, breast cancer, lung cancer, cardiac cancer, central nervous system cancer, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative neoplasms, colorectal cancer, uterine cancer, esophageal cancer, head and neck cancer, eye cancer, fallopian tube cancer, gallbladder cancer, gastric cancer, germ cell tumor, gestational trophoblastic cancer, hairy cell leukemia, liver cancer, Hodgkin lymphoma, intraocular melanoma, pancreatic cancer, kidney cancer, leukemia, mesothelioma, metastatic cancer, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma neoplasms, myelodysplastic neoplasms, ovarian cancer, parathyroid cancer, penile cancer, pheochromocytoma, pituitary cancer, plasma cell neoplasm, primary peritoneal cancer, prostate cancer, rectal cancer, retinoblastoma, sarcoma, small intestine cancer, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, vaginal cancer, and vulvar cancer.

3. The method of claim 1 or 2, wherein the early stage cancer is a preclinical phase cancer, optionally wherein the preclinical phase cancer is stage I or stage II cancer.

4. The method of any one of claims 1-3, wherein the sequence information comprises methylation sequence information, optionally wherein the methylation sequence

information comprises methylation statuses for a plurality of genomic sites, optionally wherein the plurality of genomic sites comprise a plurality of CpG sites.

5. The method of any one of claims 1-4, wherein performing an analysis of sequence information of the subject comprises applying a trained machine learning model.

6. The method of claim 5, wherein performing an analysis of sequence information of the subject further comprises:

computing, for one or more instances of an analyte in a window of a plurality of windows on a target region of the analyte, a metric specific for the window and the target region; and

analyzing, using the trained machine learning model, at least the metric specific for the window and the target region.

7. The method of any one of claims 1-6, wherein the sequence information is obtained from an assay, wherein the assay comprises performing one or more of:

a. sequencing of nucleic acids in the sample;

b. hybrid capture;

c. methylation-specific PCR;

d. an assay that generates methylation information; and

e. sequencing a clone library generated from a template immortalized library.

8. The method of claim 7, wherein performing the assay that generates sequence information comprises:

obtaining bisulfite converted cell free DNA (cfDNA);

selectively amplifying target regions of the bisulfite converted cfDNA; and

sequencing amplicons comprising the amplified target regions to generate the sequence information.

9. The method of claim 8, wherein the target regions of the bisulfite converted cfDNA comprise previously identified regions that are differentially methylated in cancer.

10. The method of claim 8, wherein the target regions of the bisulfite converted cfDNA comprise one or more CpG islands or portions of one or more CpG islands shown in Tables 1-4.

11. The method of claim 8, wherein the target regions of the bisulfite converted cfDNA comprise:

at most 10%, at most 20%, at most 30%, at most 40%, at most 50%, at most 55%, at most 60%, at most 65%, at most 70%, at most 75%, at most 80%, at most 85%, or at most 90% of CpG islands or portions of CpG islands shown in any one of Tables 1-4, or

at most 100, at most 150, at most 200, at most 300, at most 400, at most 500, at most 600, at most 700, at most 800, at most 900, at most 1000, at most 1500, at most 2000, at most 2500, at most 3000, at most 3500, or at most 4000 CpG islands or portions of CpG islands selected from Tables 1-4.

12. The method of any one of claims 1-11, wherein analyzing sequence information of the subject not identified as not at risk comprises analyzing sequence information generated from target regions comprising one or more CpG islands or a portion of one or more CpG islands shown in Tables 1-4.

13. The method of claim 12, wherein the target regions comprise:

at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% of CpG islands or portions of CpG islands shown in any one of Tables 1-4, or

at least 100, at least 150, at least 200, at least 300, at least 400, at least 500, at least 600, at least 700, at least 800, at least 900, at least 1000, at least 1500, at least 2000, at least 2500, at least 3000, at least 3500, at least 4000, at least 4500, at least 5000, at least 5500, or at least 6000 CpG islands or portions of CpG islands selected from Tables 1-4.

14. The method of any one of claims 1-13, wherein performing the second analysis comprises analyzing methylation statuses of more CpG islands in comparison to a quantity of CpG islands analyzed when performing the analysis of sequence information of the subject, optionally wherein performing the second analysis comprises analyzing methylation statuses of at least 5 times more CpG islands in comparison to a quantity of CpG islands analyzed when performing the analysis of sequence information of the subject.

15. The method of claim 14, wherein performing the second analysis comprises analyzing methylation statuses of at least 500 CpG islands, and wherein performing the analysis of sequence information of the subject comprises analyzing methylation statuses of at least 100 CpG islands.

16. The method of any one of claims 1-15, wherein the biological sample is obtained from the subject while the subject is asymptomatic, optionally wherein the biological sample comprises any one of:
a blood sample,
a stool sample,
a urine sample,
a mucous sample,
a saliva sample.

17. The method of any one of claims 1-16, wherein the second analysis comprises whole genome sequencing, optionally whole genome bisulfite sequencing.

18. The method of any one of claims 1-17, further comprising determining a tissue of origin of the at least one specific cancer in the subject using the sequence information of the subject.

19. The method of any one of claims 1-18, further comprising:
performing an analysis of additional sequence information of the subject that has been obtained from an additional biological sample of the subject obtained subsequent to a timepoint that the biological sample was obtained;
determining one or more changes between the additional sequence information of the subject and the sequence information; and
determining a progression of the at least one specific cancer in the subject based on the determined one or more changes.

20. A kit comprising:
a. equipment to draw a sample from a subject;
b. a set of detection reagents that, when combined with the sample, allows detection of biomarkers in the sample; and

c. instructions for accessing computer program instructions stored on a computer storage medium that, when processed by a processor of a computer system, cause the processor to:

perform an analysis of sequence information to identify whether the subject is not at risk of having one or more early stage cancers; and then if the patient has not been identified as not at risk:

analyze sequence information of the subject not identified as not at risk derived from second analysis to detect the presence of the one or more early stage cancers in the subject.