with lung, colon, liver, ovarian, pancreatic, prostate, rectal, and breast cell proliferative disorder detection and disease progression.

[0005a] In an aspect, the present disclosure provides a system comprising one or more computer processors and a computer-readable memory, the computer-readable memory comprising machine-executable code that, upon execution by the one or more computer processors, implements a method for determining a methylation profile of a cell-free deoxyribonucleic acid (cfDNA) sample from a subject, the method comprising: a) providing conditions for converting unmethylated cytosines to uracils in nucleic acid molecules of the cfDNA sample to produce a plurality of converted nucleic acid molecules; b) contacting the plurality of converted nucleic acids with nucleic acid probes complementary to a pre-identified methylation signature panel characteristic of at least two cell proliferative disorders, wherein the methylation signature panel comprises one or more genomic regions selected from the group consisting of genomic regions in **Tables 1-17** to enrich for sequences corresponding to the pre-identified methylation signature panel; c) determining nucleic acid sequences of the plurality of converted nucleic acid molecules; and aligning the nucleic acid sequences of the plurality of converted nucleic acid molecules to a reference nucleic acid sequence, thereby determining the methylation profile of the subject.

[0005b] In an aspect, the present disclosure provides system comprising one or more computer processors and a computer-readable memory, the computer-readable memory comprising machine-executable code that, upon execution by the one or more computer processors, implements a method for detecting a cell proliferative disorder in a subject, the method comprising: a) obtaining methylation sequencing information for a preselected panel of genomic regions associated with the presence of at least two different cell proliferative disorder tissue types from a nucleic acid sample from the subject, b) applying the sequence information from the subject to a classification model trained on a preselected panel of genomic regions associated with the presence of the at least two cell proliferative disorder types, to identify the presence of a cell proliferative disorder, and if a cell proliferative disorder is detected, and c) applying sequence information from the subject to a classification model trained on a preselected panel of genomic regions associated with associated with the presence of cell proliferative disorders in different tissue types to determine tissue of origin of the cell proliferative disorder in the subject.

[0005c] In an aspect, the present disclosure provides a system comprising one or more computer processors and a computer-readable memory, the computer-readable memory comprising machine-executable code that, upon execution by the one or more computer processors, implements a method for detecting a cell proliferative disorder in a subject, the method comprising: a) obtaining methylation sequencing information disorders from a nucleic acid

sample from the subject for a preselected panel of genomic regions associated with at least two different cell proliferative disorders, b) calculating a methylation profile of cfDNA in the sample corresponding to the preselected panel of predetermined methylated genomic regions associated with the at least two types of cell proliferative disorders, and c) applying a machine learning classifier trained on a panel of predetermined methylated genomic regions associated with two or more types of cell proliferative disorder, and having pre-selected sensitivity and specificity for the different types of cell proliferative disorder to be detected using the panel.

[0005d] In an aspect, the present disclosure provides a system comprising one or more computer processors and a computer-readable memory, the computer-readable memory comprising machine-executable code that, upon execution by the one or more computer processors, implements a method for detecting a presence or an absence of a cell proliferative disorder in a subject, the method comprising: a) providing conditions for converting unmethylated cytosines to uracils in nucleic acid molecules of a biological sample obtained or derived from the subject to produce a plurality of converted nucleic acid molecules; b) contacting the plurality of converted nucleic acids with nucleic acid probes complementary to a pre-identified methylation signature panel of at least two differentially methylated regions selected from the group consisting of **Tables 1-17** to enrich for sequences corresponding to the signature panel; c) determining nucleic acid sequences of the converted nucleic acid molecules; d) aligning the nucleic acid sequences of the plurality of converted nucleic acid molecules to a reference nucleic acid sequence, thereby determining a methylation profile of the subject; and e) applying a trained machine learning classifier to the methylation profile, wherein the trained machine learning classifier is trained to be capable of distinguishing between healthy subjects and subjects with a cell proliferative disorder to provide an output value associated with presence of a cell proliferative disorder, thereby detecting the presence or the absence of the cell proliferative disorder in the subject.

[0005e] In an aspect, the present disclosure provides a system comprising one or more computer processors and a computer-readable memory, the computer-readable memory comprising machine-executable code that, upon execution by the one or more computer processors, implements a method for detecting a cell proliferative disorder in a subject, the method comprising: a) providing conditions for converting unmethylated cytosines to uracils in nucleic acid molecules of a cfDNA sample to produce a plurality of converted nucleic acids; b) amplifying converted nucleic acids with polymerase chain reaction; c) probing the converted nucleic acids with nucleic acid probes complementary to a pre-identified methylation signature panel of at least two differentially methylated regions selected from the group consisting of **Tables 1-17** to enrich for sequences corresponding to the signature panel; d) determining the

nucleic acid sequence of the converted nucleic acid molecules at a depth of greater than 5000x, and e) aligning the nucleic acid sequence of the converted nucleic acid molecules to a reference nucleic acid sequence for the pre-identified panel of CpG loci, to determine the methylation profile of the subject, and f) analyzing the methylation profile using a machine learning model trained to be capable of distinguishing between healthy subjects and subjects with a cell proliferative disorder to provide an output value associated with presence of a cell proliferative disorder, thereby indicating the presence of a cell proliferative disorder in the subject.

[0005f] In an aspect, the present disclosure provides a methylation signature panel characteristic of at least two cell proliferative disorders comprising: one or more genomic regions selected from the group consisting of genomic regions in **Table 1**, wherein the one or more genomic regions are more methylated in a biological sample from a subject having a cell proliferative disorder or subtype thereof, and are less methylated in a biological sample from a subject not having the cell proliferative disorder or subtype thereof.

[0006] [0005g] In an aspect, the present disclosure provides a system comprising one or more computer processors and a computer-readable memory, the computer-readable memory comprising machine-executable code that, upon execution by the one or more computer processors, implements a method for monitoring minimal residual disease in a subject previously treated for disease, the method comprising: determining a methylation profile as described herein as a baseline methylation state and repeating an analysis to determine the methylation profile at one or more predetermined time points wherein a change from baseline indicates a change in the minimal residual disease status at baseline in the subject.In an aspect, the present disclosure provides a methylation signature panel characteristic of at least two cell proliferative disorders comprising: six or more methylated genomic regions selected from the group consisting of **Table 1**, wherein the one or more regions are more methylated in a biological sample from an subject having a cell proliferative disorder or cell proliferative disorder subtype and are less methylated in normal tissues and normal blood cells in an subject not having a cell proliferative disorder.

[0007] In some embodiments, the biological sample comprises a nucleic acid, DNA, RNA, or cell-free nucleic acid (cfDNA or cfRNA).

[0008] In some embodiments, the genomic region is a non-coding region, a coding region, or a non-transcribed or regulator region.

[0009] In some embodiments, the signature panel comprises increased methylation in 6 or more, or 12 or more genomic regions in **Table 1**.

[0010] In some embodiments, the signature panel comprises increased methylation in six or more methylated genomic regions in **Table 1** that are associated with a type of cancer.

[0011] In some embodiments, 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, and combinations thereof.

[0012] In some embodiments, the cell proliferative disorder is selected from colorectal, prostate, lung, breast, pancreatic, ovarian, uterine, liver, esophagus, stomach, or thyroid cell proliferation.

[0013] In some embodiments, the cell proliferative disorder is selected from colon adenocarcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, ovarian serious cystadenocarcinoma, pancreatic adenocarcinoma, prostate adenocarcinoma, and rectum adenocarcinoma.

[0014] In some embodiments, the cell proliferative disorder is selected from stage 1 cancer, stage 2 cancer, stage 3 cancer, or stage 4 cancer.

[0015] In some embodiments, the signature panel comprises three or more methylated genomic regions in **Table 1**, four or more methylated genomic regions in **Table 1**, five or more methylated genomic regions in **Table 1,** six or more methylated genomic regions in **Table 1**, seven or more methylated genomic regions in **Table 1**, eight or more methylated genomic regions in **Table 1**, nine or more methylated genomic regions in **Table 1**, ten or more methylated genomic regions in **Table 1**, eleven or more methylated genomic regions in **Table 1**, twelve or more methylated genomic regions in **Table 1**, or thirteen or more methylated genomic regions in **Table 1**.