a) obtaining a biological sample containing a nucleic acid;
b) ligating oligonucleotide adapters to the nucleic acids in the biological sample wherein the adapters comprise 5hmC, 5gmC, 5caC, 5cxmC, or a combination thereof and no cytosine nucleotides;
c) subjecting the ligated nucleic acids to conversion conditions necessary to convert unmethylated and methylated cytosines in the nucleic acids to uracil;
d) sequencing the nucleic acids to obtain a nucleic acid sequence of the nucleic acids, to provide hydroxymethylation state data in the nucleic acids; and
e) training a machine learning model to generate a classifier using the hydroxymethylation state data.

[0133] In some embodiments, the adapters comprise 5hmC, 5gmC, 5caC, 5cxmC, or a combination thereof and no cytosine nucleotides in flow cell binding regions or primer binding sites in the adapters.

[0134] In some embodiments, the method comprises subjecting the ligated nucleic acids to glucosylation by β-GT/UDP-glucose to convert hydroxymethylated C's to 5gmC, before subjecting to conversion conditions necessary to convert unmethylated and methylated cytosines in the nucleic acid to uracil.

[0135] In another aspect, the present disclosure provides a method for detecting a cell proliferative disorder in a subject, the method comprising:

a) obtaining a biological sample containing a nucleic acid;
b) ligating oligonucleotide adapters to the nucleic acids in the biological sample wherein the adapters comprise 5hmC, 5gmC, 5caC, 5cxmC, or a combination thereof and no cytosine nucleotides;
c) subjecting the ligated nucleic acids to conversion conditions necessary to convert unmethylated and methylated cytosines in the nucleic acids to uracil;
d) sequencing the nucleic acids to obtain a nucleic acid sequence of the nucleic acids, to provide hydroxymethylation state data in the nucleic acids; and

f) processing the hydroxymethylation state data 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.

[0135a] In another aspect, the present disclosure provides a method for detecting a cell proliferative disorder in a subject, the method comprising:

a) ligating oligonucleotide adapters to at least a portion of nucleic acids in a biological sample containing nucleic acids obtained from the subject, wherein the

b) oligonucleotide adapters comprise 5hmC nucleotides, 5gmC nucleotides, 5caC nucleotides, 5cxmC nucleotides, or a combination thereof, thereby generating ligated nucleic acids;

c) subjecting at least a portion of the ligated nucleic acids to a conversion condition that converts unmethylated and methylated cytosine nucleotides in the ligated nucleic acids into uracil nucleotides, thereby generating converted nucleic acids;

d) sequencing at least a portion of the converted nucleic acids to obtain a nucleic acid sequence of the converted nucleic acids to provide hydroxymethylation state data of the nucleic acids; and

e) processing the hydroxymethylation state data using a machine learning model trained to be capable of distinguishing between healthy subjects and subjects with the cell proliferative disorder to provide an output value associated with a presence or a susceptibility of the cell proliferative disorder, thereby indicating the presence or the susceptibility of the cell proliferative disorder in the subject.

[0136] In some embodiments, the adapters comprise 5hmC, 5gmC, 5caC, 5cxmC, or a combination thereof and no cytosine nucleotides in flow cell binding regions or primer binding sites in the adapters.