detecting a first number of methylated or unmethylated DNA fragments in a cell-free mixture of the blood sample at one or more differentially-methylated regions based on signals obtained from an assay, the cell-free mixture including cell-free DNA from a plurality of cell lineages, and each of the one or more differentially-methylated regions specific to a particular hematological cell lineage by being hypomethylated or hypermethylated relative to other cell lineages, wherein the particular hematological cell lineage is nucleated red blood cells; ~~detecting a first number of methylated or unmethylated DNA fragments in the cell-free mixture at the one or more differentially-methylated regions based on signals obtained from the assay;~~ determining a methylation level using the first number; and comparing the methylation level to one or more cutoff values as part of determining a classification of a hematological disorder of red blood cells in the mammal.

[0004b] In another aspect, the present invention provides a method of measuring an amount of cells of a particular cell lineage in a biological sample, the method comprising: obtaining a cell-free mixture of the biological sample, the cell-free mixture including cell-free DNA from a plurality of cell lineages; performing an assay by contacting DNA fragments in the cell-free mixture with reagents hybridizing to a plurality of sites in one or more differentially-methylated regions, each of the one or more differentially-methylated regions specific to the particular cell lineage by being hypomethylated or hypermethylated relative to other cell lineages; detecting a first number of methylated or unmethylated DNA fragments in the cell-free mixture at the plurality of sites in the one or more differentially-methylated regions based on signals obtained from the assay; determining a first methylation level using the first number; obtaining one or more calibration data points, wherein each calibration data point specifies (1) an amount of cells of the particular cell lineage and (2) a calibration methylation level, and wherein the one or more calibration data points are determined from a plurality of calibration samples; comparing the first methylation level to a calibration methylation level of at least one calibration data point; and estimating the amount of cells of the particular cell lineage in the biological sample based on the comparing.

[0004c] In yet another aspect, the present invention provides for a computer product comprising a computer readable medium storing a plurality of instructions for controlling a system to perform a method of the present disclosure.

[0004d] In yet another aspect, the present invention provides for a system comprising: the computer product of the present disclosure; and one or more processors for executing instructions stored on the computer readable medium.

[0004e] In yet another aspect, the present invention provides for a system configured to perform a method of the present disclosure.

[0004f] In yet another aspect, the present invention provides for a computer product comprising a computer readable medium storing a plurality of instructions for controlling a

WHAT IS CLAIMED IS:

1. An *in-vitro* method of analyzing a blood sample of a mammal, the method comprising:

detecting a first number of methylated or unmethylated DNA fragments in a cell-free mixture of the blood sample at one or more differentially-methylated regions based on signals obtained from an assay, the cell-free mixture including cell-free DNA from a plurality of cell lineages, and each of the one or more differentially-methylated regions specific to a particular hematological cell lineage by being hypomethylated or hypermethylated relative to other cell lineages, wherein the particular hematological cell lineage is nucleated red blood cells;

~~detecting a first number of methylated or unmethylated DNA fragments in the cell-free mixture at the one or more differentially-methylated regions based on signals obtained from the assay;~~

determining a methylation level using the first number; and

comparing the methylation level to one or more cutoff values as part of determining a classification of a hematological disorder of red blood cells in the mammal.

2. The method of claim 1, further comprising:

determining a total number of DNA fragments in the cell-free mixture at the one or more differentially-methylated regions; and

determining the methylation level using the first number and the total number.

3. The method of claim 1, further comprising:

determining a volume of the cell-free mixture, wherein the methylation level is determining the first number and the volume of the cell-free mixture.

4. The method of claim 1, wherein obtaining the cell-free mixture includes:

separating the cell-free mixture from the blood sample, the cell-free mixture comprising plasma or serum.

5. The method of claim 1, further comprising identifying one of the one or more differentially-methylated regions by:

obtaining methylation indexes of a plurality of sites in a genome for each of the plurality of cell lineages, including the particular hematological cell lineage and the other cell lineages;

at each site of the plurality of sites, comparing the methylation indexes of the plurality of cell lineages;

identifying one or more sites of the plurality of sites that have a methylation index in the particular hematological cell lineage that is below/above a first methylation threshold and methylation indexes in each of the other cell lineages that are above/below a second methylation threshold; and

identifying the one of the one or more differentially-methylated regions that contains the one or more sites.

6. The method of claim 1, further comprising determining the one or more cutoff values, including:

obtaining a plurality of samples, each sample known to have a particular classification of the hematological disorder, the plurality of samples having at least two classifications of the hematological disorder;

determining a methylation level of the one or more differentially-methylated regions for each of the plurality of samples;

identifying a first set of samples that have a first classification of the hematological disorder;

identifying a second set of samples that have a second classification of the hematological disorder, the first set of samples collectively having a statistically higher methylation level than the second set of samples; and

determining a cutoff value that discriminates between the first set of samples and the second set of samples within a specified specificity and sensitivity.

7. The method of claim 1, wherein determining the classification of the hematological disorder includes identifying a particular type of the hematological disorder.

8. The method of claim 1, further comprising:

determining that the hematological disorder exists based on comparing the methylation level to one or more cutoff values; and

determining that a bone marrow biopsy is to be performed in response to determining that the hematological disorder exists.

9. The method of claim 1, wherein the assay is a PCR assay or a sequencing assay.

10. The method of claim 1, wherein the one or more differentially-methylated regions comprise CpG sites.

11. The method of claim 10, wherein a first region of the one or more differentially-methylated regions comprises a plurality of CpG sites that are within 100 bp of each other, and wherein the plurality of CpG sites are all hypomethylated or hypermethylated.

12. The method of claim 11, wherein the plurality of CpG sites span 100 bp or less on a reference genome corresponding to the mammal.

13. The method of claim 1, further comprising:

measuring a hemoglobin level of the blood sample;

comparing the hemoglobin level to a hemoglobin threshold; and

determining the classification of the hematological disorder further based on the comparing of the hemoglobin level to the hemoglobin threshold.

14. The method of claim 1, wherein one of the one or more differentially-methylated regions is in the FECH gene.

15. The method of claim 1, wherein one of the one or more differentially-methylated regions is in chromosome 12 at genomic coordinates 48227688 – 48227701 in human reference genome hg19.

16. The method of claim 1, wherein one of the one or more differentially-methylated regions is in chromosome 12 at genomic coordinates 48228144 – 48228154 in human reference genome hg19.

17. The method of claim 1, wherein the hematological disorder is anemia.

18. The method of claim 17, wherein the classification of the hematological disorder corresponds to increased erythropoietic activity, intermediate erythropoietic activity, or reduced erythropoietic activity.

19. The method of claim 18, wherein the classification of the hematological disorder is increased erythropoietic activity from β-thalassemia.

20. The method of claim 18, wherein the classification of the hematological disorder is intermediate erythropoietic activity from iron deficient anemia.

21. The method of claim 18, wherein the classification of the hematological disorder is reduced erythropoietic activity from aplastic anemia or chronic renal failure.

22. The method of claim 1, wherein the one or more differentially-methylated regions are hypomethylated.

23. The method of claim 1, wherein the cell-free mixture is plasma.

24. The method of claim 1, wherein each of the one or more differentially-methylated regions specific to the particular hematological cell lineage are hypomethylated or hypermethylated relative to the other cell lineages by having a difference of at least 60% in a methylation density.

25. A method of measuring an amount of cells of a particular cell lineage in a biological sample, the method comprising:

obtaining a cell-free mixture of the biological sample, the cell-free mixture including cell-free DNA from a plurality of cell lineages;

performing an assay by contacting DNA fragments in the cell-free mixture with reagents hybridizing to a plurality of sites in one or more differentially-methylated regions, each of the one or more differentially-methylated regions specific to the particular cell lineage by being hypomethylated or hypermethylated relative to other cell lineages;

detecting a first number of methylated or unmethylated DNA fragments in the cell-free mixture at the plurality of sites in the one or more differentially-methylated regions based on signals obtained from the assay;

determining a first methylation level using the first number;

obtaining one or more calibration data points, wherein each calibration data point specifies (1) the amount of cells of the particular cell lineage and (2) a calibration methylation level, and wherein the one or more calibration data points are determined from a plurality of calibration samples;

comparing the first methylation level to a calibration methylation level of at least one calibration data point; and

estimating the amount of cells of the particular cell lineage in the biological sample based on the comparing.

26. The method of claim 25, wherein the particular cell lineage is a particular hematological cell lineage.

27. The method of claim 26, wherein the particular hematological cell lineage is nucleated red blood cells.

28. The method of claim 25, wherein the one or more calibration data points are a plurality of calibration data points, and wherein the calibration data points form a calibration curve.

29. A computer product comprising a computer readable medium storing a plurality of instructions for controlling a system to perform the method of any one of claims 1-28.

30. A system comprising:

the computer product of claim 29; and

one or more processors for executing instructions stored on the computer readable medium.

31. A system configured to perform the method of any one of claims 1-28.

32. A computer product comprising a computer readable medium storing a plurality of instructions for controlling a system to analyze a blood sample of a mammal by performing:

detecting a first number of methylated or unmethylated DNA fragments in a cell-free mixture of the blood sample at one or more differentially-methylated regions based on signals obtained from an assay, each of the one or more differentially-methylated regions specific to a particular hematological cell lineage by being hypomethylated or hypermethylated relative to other cell lineages, wherein the particular hematological cell lineage is nucleated red blood cells;

determining a methylation level using the first number; and

comparing the methylation level to one or more cutoff values as part of determining a classification of a hematological disorder in the mammal.

33. A computer product comprising a computer readable medium storing a plurality of instructions for controlling a system to measure an amount of cells of a particular cell lineage in a biological sample by performing:

detecting a first number of methylated or unmethylated DNA fragments in a cell-free mixture of the biological sample at a plurality of sites in one or more differentially-methylated regions based on signals obtained from an assay, each of the one or more differentially-methylated regions specific to the particular cell lineage by being hypomethylated or hypermethylated relative to other cell lineages;

determining a first methylation level using the first number;

obtaining one or more calibration data points, wherein each calibration data point specifies (1) an amount of cells of the particular cell lineage and (2) a calibration methylation level, and wherein the one or more calibration data points are determined from a plurality of calibration samples;

comparing the first methylation level to a calibration methylation level of at least one calibration data point; and

estimating the amount of cells of the particular cell lineage in the biological sample based on the comparing.