

CLAIMS:

1. A method for probabilistically assigning a tissue of origin to a nucleic acid in a cell-free fluid sample obtained from a human subject, comprising:

- (a) generating a hydroxymethylation profile of the nucleic acid;
- (b) comparing the hydroxymethylation profile of the nucleic acid with each of a plurality of reference hydroxymethylation profiles in a reference data set, each reference hydroxymethylation profile corresponding to a reference locus contained within a genomic region associated with a tissue-specific gene;
- (c) identifying at least one reference locus having a reference hydroxymethylation profile that is substantially similar to the detected hydroxymethylation profile in (a); and
- (d) assigning at least one tissue of origin to the nucleic acid based on the at least one reference locus identified in (c) and the corresponding tissue-specific gene.

2. The method of claim 1, wherein the genomic region comprises a differentially hydroxymethylated genomic region that is functionally associated with the tissue-specific gene.

3. The method of claim 2, further comprising, between (c) and (d), (c') determining from the substantial similarity a probability that the nucleic acid has a tissue of origin corresponding to the at least one reference locus.

4. The method of claim 3, wherein the substantial similarity is detected from a hydroxymethylation difference data set that comprises differences identified between the generated hydroxymethylation profile of the nucleic acid and each of the plurality of reference hydroxymethylation profiles.

5. The method of any one of claims 1-4, wherein each reference hydroxymethylation profile in the reference data set is contained within a hydroxymethylation vector that also identifies at least the following: the tissue-specific gene associated with the reference locus; and the tissue with which the gene and reference locus are associated.

6. The method of claim 5, wherein the hydroxymethylation profile at each reference locus includes at least one of:

- hydroxymethylation density within the reference locus;
- total 5-hydroxymethylcytosine residues within the reference locus;
- location of the 5-hydroxymethylcytosine residues within the reference locus;
- identification of a hydroxymethylated site as hemi-hydroxymethylated or fully hydroxymethylated; and
- relative positions of 5-hydroxymethylcytosine residues within the reference locus.

7. The method of any one of claims 1-6, wherein the at least one reference locus is contained within a gene body or a component thereof.

8. The method of any one of claims 1-6, wherein the at least one reference locus is contained within a genomic annotation feature outside of the gene body.

9. The method of claim 8, wherein the at least one reference locus is contained within a promoter, an enhancer, a transcription initiation site, a transcription stop site, a DNA binding site, or a combination thereof.

10. The method of any one of claims 1-9, further including determining at least one of: nucleic acid length; nucleic acid fragment distribution; methylation profile; and nucleosome positioning.

11. The method of any one of claims 1-10, wherein the plurality of reference hydroxymethylation profiles in the reference data set comprise a hydroxymethylation profile of at least one reference locus associated with at least one gene originating from a human tissue type comprising: adipose; adrenal gland; bladder; bone marrow; brain; breast; colon; cerebral cortex; cervical; uterine; digestive; endometrial; epididymal; esophageal; Fallopian tube; gall bladder; gastrointestinal; heart muscle; hypothalamus; kidney; liver; lung; lymph nodes; ovary;

pancreas; parathyroid gland; placenta; prostate; salivary; seminal vesicle; skeletal muscle; smooth muscle; skin; spleen; stomach; testis; thyroid gland; tonsil; or a combinations thereof.

12. The method of any one of claims 1-10, wherein the plurality of reference hydroxymethylation profiles in the reference data set comprise a hydroxymethylation profile of at least one reference locus associated with at least one gene originating from a human tissue type comprising: bladder; bone marrow; brain; breast; sigmoid colon; transverse colon; gastrointestinal; heart; hypothalamus; kidney; liver; lung; lymph node; ovary; pancreas; placenta; prostate; skin; smooth muscle; testis; or a combination thereof.

13. The method of claim 12, wherein the reference data set comprises two or more reference data sets selected from Set 3A, Set 3B, Set 3C, Set 3D, Set 3E, Set 3F, Set 3G, Set 3H, Set 3I, Set 3J, Set 3K, Set 3L, Set 3M, Set 3N, Set 3O, Set 3P, Set 3Q, Set 3R, and Set 3S.

14. The method of any one of claims 1-13, wherein the reference data set comprises hydroxymethylation vectors for at least five tissue types.

15. The method of any one of claims 1-14, wherein the reference data set comprises hydroxymethylation vectors for at least 5 genes per tissue type.

16. The method of claim 1, wherein each reference locus is contained within a differentially represented gene comprising AARD, ADARB1, AKR1B10, ANAPC7, APCDD1L-AS1, APOA1BP, CALHM2, CASC3, CLEC2L, COL4A5, CRYM-AS1, EPHA3, FAHD2B, FKBP9L, FOPNL, GNG11, GSN, GSTTP2, GTSF1, IAH1, KCNMB1, KIAA1644, LAMC1, LINC00310, LOC100506394, LOC100507066, LOC493754, MAP1B, MGC27382, MIR5695, NENF, NT5DC3, P2RX1, PCP4, PGM5, PLCD4, PTGFR, RBFOX3, RPL30, SCARA3, SLIT3, SNX29P1, SPATA4, ST8SIA1, TBX4, TXNRD1, VCL, VPS72, WFDC3, ZNF791, ADAMTS20, AFF2, ANKRD18B, ANKRD18DP, ANKRD20A5P, ANKRD20A8P, ANKRD26P1, ANKRD30BP2, ANKRD34B, ANKRD34C, ATP6V0B, AVPR1A, BLOC1S3, BOLL, BRIP1, C5orf63, CA1, CALB1, CALCR, CCDC39, CCDC96, CDCA5, CDH12, CDH9, CEACAM8, CENPE, CENPK, CFL1, CHAT, COMMD5, COMMD8, CRISP1, CRISP2,

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 TCERG1L, TEK4P2, THEG, TMEM130, TPO, UPK3B, WASH3P, WRAP53, ZNF280B, or
 ZNF793.

17. The method of claim 1, wherein each reference locus is contained within a
 differentially represented, differentially expressed gene comprising AARD, ADARB1,
 AKR1B10, CRYM-AS1, EPHA3, GTSF1, KCNMB1, MAP1B, NT5DC3, P2RX1, PCP4,

PGM5, PLCD4, PTGFR, RBFOX3, SCARA3, SLIT3, SNX29P1, ST8SIA1, TBX4, TXNRD1, VCL, WFDC3, ABCA13, AZU1, CA1, CEACAM8, CLEC6A, DAZL, DRGX, DYT1, ELANE, FCAR, GFI1, GYPA, HK3, IL18RAP, LINC00333, LINC00550, LINC00558, LIPN, LOC100129620, LOC442028, LPO, MEFV, MMP8, MMP9, MPO, MS4A3, MYB, MYO1F, NCOR1P1, NME8, OR8U8, OSCAR, PARPBP, PAX3, PDCL2, PRDM13, PROK2, RGS18, RGS21, RRM2, RXFP2, SERPINB10, SLC22A16, SPATA16, SPI1, SPTA1, TARM1, TMPRSS15, TRIM58, VSTM1, XKR3, ASPHD1, BRSK1, CCDC177, CNTN2, HAPLN2, KCNJ10, KIF1A, LGI3, NCAN, NR2E1, RHBDL3, TMEM151A, TMEM235, TMEM59L, ZNF488, FGL2, SCNN1B, ADPRHL1, ASB18, ATP1A3, CDH13, CORO6, FSD2, GALNT16, GJA3, MYOM2, PCDHGA1, PCDHGA10, PCDHGA11, PCDHGA12, PCDHGA2, PCDHGA3, PCDHGA4, PCDHGA5, PCDHGA6, PCDHGA7, PCDHGA8, PCDHGA9, PCDHGB1, PCDHGB2, PCDHGB3, PCDHGB5, PCDHGB6, PCDHGB7, PXDNL, RPL3L, SGCG, TNNT1, ASTN1, DGK1, BBOX1, BCRP3, CA12, COL4A3, CXCL14, CYS1, EVC, FIGNL2, GALNT14, GLIS2, HAVCR1, LOC100130238, PAQR5, PAX2, PAX8, PLA2G15, SLC22A2, SLC9A3, SULT1C2, TSPAN33, ABCC2, ABCG5, ABCG8, AHSG, AKR1C4, AMDHD1, APOH, ASGR1, ASGR2, C3P1, C8A, C8B, C9, CA5A, CFHR4, CPN2, CREB3L3, CYP2B6, CYP2C9, CYP2E1, CYP3A4, DHODH, F12, F2, F7, GC, HAL, HPD, HPX, INHBC, ITIH1, ITIH2, ITIH3, KNG1, LBP, PGLYRP2, PLG, PROC, PRODH2, SERPINA6, SERPINC1, SLC13A5, SLC22A1, SLC25A47, SLC27A5, SULT2A1, TFR2, TMPRSS6, UROC1, ANXA3, BMP5, CYP4Z2P, DRAM1, FMO2, GNA15, IDO1, KCNS3, LIMCH1, MBIP, PAPSS2, PCDH17, RSPH4A, RTKN2, TRPC6, ACAP1, AKNA, ARHGAP9, BCL11B, BIRC3, CARD11, CD180, CD37, CD3E, CD3G, CD40, CETP, CIITA, CLEC2D, CNR2, CXCR5, DOCK10, ETS1, GPR132, GPR18, ICAM2, ICOS, ITGB7, ITK, KIAA1551, KLHL6, LCK, LINC00426, LY86, MDS2, MEOX2, MX2, NAPSBB, PATL2, PCED1B-AS1, PIK3CD, PLVAP, POU2F2, SCIMP, SCML4, SLFN12L, SMAP2, SP110, SPIB, TLR10, TMC8, TMEM156, TNFAIP8, TNFRSF9, TNFSF11, TRAF1, TRIM22, UCP2, ZC3H12D, ABCA10, ACSS3, ADAMTS5, AQP11, C7, CDH3, CDON, CLDN11, COL14A1, COLEC11, ESR2, FAM198B, FZD3, GALNT10, GLI2, GSTM5, HS3ST1, LEMD1-AS1, LHX9, LRRC17, MCHR1, MRC2, NTF3, OMD, PDGFRA, PGR, PKNOX2, PTCH2, RWDD4, SCD5, SERPINE2, SIMC1, SLC25A17, SNCAIP, SULF2, TENM4, TSPAN5, TTC8, UBXLN8, ALDH1L2, ANKRD1, ASNS, B3GALNT2, BCAT1, CASP9, CCDC110, CELA2B, CELA3B, CFTR, CHMP4C,

CLDN1, CNIH3, COCH, CUZD1, DEFB1, EGF, EIF4EBP1, ERP27, FAM24B-CUZD1, FBXW12, GUCA1C, KCTD16, KIAA1324, LINC00339, LNX2, MKNK1, NAA16, NPHS1, PAIP2B, PM20D1, PRSS3, SCGN, SEL1L, SERPINI2, SH3YL1, SLC33A1, SLC4A4, TC2N, TDH, TMEM51-AS1, TRHDE, UMOD, ADAM12, ATG9B, ATP6V1C2, BCAR4, BMP1, BPGM, CSF3R, CYP11A1, CYP19A1, DACT2, DEPDC1B, DLX5, EBI3, GCM1, GPR78, GSTA3, IGF2BP3, IGSF5, ISM2, KISS1, KRT23, LIN28B, MMP11, PGF, PSG11, PSG2, PSG3, PSG6, PSG7, PSG8, SPTLC3, TPRXL, ZFAT, ZNF554, ABCC4, ACPP, ALOX15B, ANO7, AP1B1P1, ARG2, BEND4, C6orf132, C6orf52, CANT1, CASZ1, CBFA2T2, CHRM1, CHRNA2, COL26A1, EVX1, EYA2, FAM135A, HMGN2P46, KLK2, KLKP1, MME, MPPED2, MUC12, NANS, NCAPD3, NEFH, NIPAL3, OACYLP, OR51E2, PAK1IP1, PDE9A, PI15, PMEPA1, POTEF, RDH11, SCNN1G, SIM2, SLC14A1, SLC22A3, SLC2A12, SLC30A4, SLC35F2, SLC37A1, SLC39A6, SPDEF, STEAP2, THSD4, TMEM79, TPM3P9, TXNDC16, URB1, VIPR1, ZNF350, ZNF532, ZNF613, ZNF649, ZNF761, ZNF827, GADL1, GIPC3, PTGES3L, WSCD2, CCDC27, DMRT1, DNAJC5G, FBXO24, IGLL1, MOV10L1, SEPT14, THEG, or TTC16.

18. An improved method for analyzing a cell-free DNA sample obtained from human plasma in which cell-free DNA fragments in the sample are isolated, amplified, and sequenced, wherein the improvement comprises identifying contamination of the sample with genomic material originating from peripheral blood mononuclear cells (PBMCs) by:

(a) generating a hydroxymethylation profile of DNA fragments in the cell-free sample; and

(b) comparing the hydroxymethylation profile generated in (a) with each of a plurality of reference hydroxymethylation profiles in a reference data set, each reference hydroxymethylation profile associated with a reference locus corresponding to a tissue-specific gene, wherein the reference hydroxymethylation profiles include at least one PBMC hydroxymethylation profile; and

(c) identifying, from the comparison, the presence of genomic material originating from PBMCs.

19. The improved method of claim 18, further including estimating the level of PBMC genomic contamination from (b) and (c).

20. The improved method of claim 18 or claim 19, wherein the reference data set comprises a vector of a plurality of reference hydroxymethylation profiles each corresponding to a gene locus associated with a PBMC sub-type.

21. The improved method of any one of claims 18-20, further including offsetting PBMC contamination in the cell-free sample the vector to calibrate and normalize at least one of mutation load, fragment count, variant allele frequency, and minor allele frequency.

22. A method for determining whether a human subject is predisposed to develop an abnormal condition of a tissue or organ, the method comprising:

(a) generating a hydroxymethylation profile at one or more loci of DNA fragments in a cell-free fluid sample obtained from the subject;

(b) comparing the detected hydroxymethylation profile with a plurality of reference hydroxymethylation profiles in a reference data set each associated with (i) a reference locus on a tissue-specific gene and (ii) a condition of the tissue indicating a predisposition to develop an abnormal condition of the specific tissue or organ; and

(c) identifying a predisposition to develop the abnormal condition of the tissue from the comparison in (b).

23. A method for differentiating nucleic acids associated with different tissues of origin in a sample of cell-free DNA obtained from a human subject, the method comprising:

(a) generating hydroxymethylation profiles of each of a plurality of nucleic acids in the cell-free DNA sample;

(b) comparing each hydroxymethylation profile with a plurality of reference hydroxymethylation profiles in a reference data set each associated with a specific reference locus on a tissue-specific gene; and

(c) differentiating nucleic acids originating from different tissues based on the comparison in (b).

24. The method of claim 23, wherein the reference data set comprises two or more reference data sets selected from Set 3A, Set 3B, Set 3C, Set 3D, Set 3E, Set 3F, Set 3G, Set 3H, Set 3I, Set 3J, Set 3K, Set 3L, Set 3M, Set 3N, Set 3O, Set 3P, Set 3Q, Set 3R, and Set 3S.