CLAIMS:

1. A method for identifying, in a sample, one or more parent nucleic acid molecules containing a target nucleotide sequence differing from nucleotide sequences in other parent nucleic acid molecules in the sample by one or more methylated or hydroxymethylated residues, said method comprising:

providing a sample containing one or more parent nucleic acid molecules potentially containing the target nucleotide sequence differing from the nucleotide sequences in other parent nucleic acid molecules by one or more methylated or hydroxymethylated residues;

subjecting the nucleic acid molecules in the sample to a treatment with one or more DNA repair enzymes under conditions suitable to convert 5-methylated and 5-hydroxymethylated cytosine residues to 5-carboxycytosine residues, followed by treatment with one or more DNA deamination enzymes under conditions suitable to convert unmethylated cytosine but not 5-carboxycytosine residues into dexoyuracil (dU) residues to produce a treated sample;

providing one or more enzymes capable of digesting deoxyuracil (dU)-containing nucleic acid molecules present in the sample;

providing one or more primary oligonucleotide primer sets, each primary oligonucleotide primer set comprising (a) a first primary oligonucleotide primer that comprises a nucleotide sequence that is complementary to a sequence in the parent nucleic acid molecule adjacent to the DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence containing the one or more converted methylated or hydroxymethylated residue and (b) a second primary oligonucleotide primer that comprises a nucleotide sequence that is complementary to a portion of an extension product formed from the first primary oligonucleotide primer, wherein the first or second primary oligonucleotide primer further comprises a 5’ primer-specific portion;

blending the treated sample, the one or more first primary oligonucleotide primers of the primer sets, a deoxynucleotide mix, and a DNA polymerase to form one or more polymerase extension reaction mixtures;

subjecting the one or more polymerase extension reaction mixtures to conditions suitable for carrying out one or more polymerase extension reaction cycles comprising a denaturation treatment, a hybridization treatment, and an extension treatment, thereby forming primary extension products comprising the complement of the DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence;

blending the one or more polymerase extension reaction mixtures comprising the primary extension products, the one or more second primary oligonucleotide primers of the one or more primary oligonucleotide primer sets, the one or more enzymes capable of digesting deoxyuracil (dU)-containing nucleic acid molecules

in the reaction mixture, a deoxynucleotide mix, and a DNA polymerase to form one or more first polymerase chain reaction mixtures;

subjecting the one or more first polymerase chain reaction mixtures to conditions suitable for digesting deoxyuracil (dU)-containing nucleic acid molecules present in the first polymerase chain reaction mixtures and for carrying out one or more first polymerase chain reaction cycles comprising a denaturation treatment, a hybridization treatment, and an extension treatment, thereby forming first polymerase chain reaction products comprising the DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence or a complement thereof;

providing one or more secondary oligonucleotide primer sets, each secondary oligonucleotide primer set comprising (a) a first secondary oligonucleotide primer having a 3’ portion that is complementary to a portion of a first polymerase chain reaction product formed from the first primary oligonucleotide primer and (b) a second secondary oligonucleotide primer having a 3’ portion that comprises a nucleotide sequence that is complementary to a portion of a first polymerase chain reaction product formed from the first secondary oligonucleotide primer;

blending the first polymerase chain reaction products, the one or more secondary oligonucleotide primer sets, the one or more enzymes capable of digesting deoxyuracil (dU)-containing nucleic acid molecules, a deoxynucleotide mix including dUTP, and a DNA polymerase to form one or more second polymerase chain reaction mixtures;

subjecting the one or more second polymerase chain reaction mixtures to conditions suitable for digesting deoxyuracil (dU)-containing nucleic acid molecules present in the second polymerase chain reaction mixtures and for carrying out two or more polymerase chain reaction cycles comprising a denaturation treatment, a hybridization treatment, and an extension treatment thereby forming second polymerase chain reaction products; and

detecting and distinguishing the second polymerase chain reactions products in the one or more second polymerase chain reaction mixtures to identify the presence of one or more parent nucleic acid molecules containing target nucleotide sequences differing from nucleotide sequences in other parent nucleic acid molecules in the sample by one or more methylated or hydroxymethylated residues.

2. A method for identifying, in a sample, one or more parent nucleic acid molecules containing a target nucleotide sequence differing from nucleotide sequences in other parent nucleic acid molecules in the sample by one or more methylated or hydroxymethylated residues, said method comprising:

providing a sample containing one or more parent nucleic acid molecules potentially containing the target nucleotide sequence differing from the nucleotide sequences in other parent nucleic acid molecules by one or more methylated or hydroxymethylated residues;

subjecting the nucleic acid molecules in the sample to a treatment with one or more DNA repair enzymes under conditions suitable to convert 5-methylated and 5-hydroxymethylated cytosine residues to 5-carboxycytosine residues, followed by treatment with one or more DNA deamination enzymes under conditions suitable to convert unmethylated cytosine but not 5-carboxycytosine residues into dexoyuracil residues to produce a treated sample;

providing one or more enzymes capable of digesting deoxyuracil (dU)-containing nucleic acid molecules;

providing one or more primary oligonucleotide primer sets, each primary oligonucleotide primer set comprising (a) a first primary oligonucleotide primer that comprises a nucleotide sequence that is complementary to a sequence in the parent nucleic acid molecule adjacent to the DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence containing the one or more converted methylated or hydroxymethylated residue and (b) a second primary oligonucleotide primer that comprises a nucleotide sequence that is complementary to a portion of an extension product formed from the first primary oligonucleotide primer, wherein the first or second primary oligonucleotide primer further comprises a 5’ primer-specific portion;

blending the treated sample, the one or more first primary oligonucleotide primers of the primer sets, a deoxynucleotide mix, and a DNA polymerase to form one or more polymerase extension reaction mixtures;

subjecting the one or more polymerase extension reaction mixtures to conditions suitable for carrying out one or more polymerase extension reaction cycles comprising a denaturation treatment, a hybridization treatment, and an extension treatment, thereby forming primary extension products comprising the complement of the DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence;

blending the one or more polymerase extension reaction mixtures comprising the primary extension products, the one or more second primary oligonucleotide primers of the primer sets, the one or more enzymes capable of digesting deoxyuracil (dU)-containing nucleic acid molecules, a deoxynucleotide mix including dUTP, and a DNA polymerase to form one or more first polymerase chain reaction mixtures;

subjecting the one or more first polymerase chain reaction mixtures to conditions suitable for digesting deoxyuracil (dU)-containing nucleic acid molecules present in the first polymerase chain reaction mixtures and for carrying out one or more

first polymerase chain reaction cycles comprising a denaturation treatment, a hybridization treatment, and an extension treatment, thereby forming first polymerase chain reaction products comprising the DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence or a complement thereof;

providing one or more oligonucleotide probe sets, each probe set comprising (a) a first oligonucleotide probe having a 5' primer-specific portion and a 3' DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence-specific or complement sequence-specific portion, and (b) a second oligonucleotide probe having a 5' DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence-specific or complement sequence-specific portion and a 3' primer-specific portion, and wherein the first and second oligonucleotide probes of a probe set are configured to hybridize, in a base specific manner, on a complementary nucleotide sequence of a first polymerase chain reaction product;

blending the first polymerase chain reaction products with a ligase and the one or more oligonucleotide probe sets to form one or more ligation reaction mixtures;

subjecting the one or more ligation reaction mixtures to one or more ligation reaction cycles whereby the first and second oligonucleotide probes of the one or more oligonucleotide probe sets are ligated together, when hybridized to their complementary sequences, to form ligated product sequences in the ligation reaction mixture wherein each ligated product sequence comprises the 5' primer-specific portion, the DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence-specific or complement sequence-specific portion, and the 3' primer-specific portion;

providing one or more secondary oligonucleotide primer sets, each secondary oligonucleotide primer set comprising (a) a first secondary oligonucleotide primer comprising the same nucleotide sequence as the 5' primer-specific portion of the ligated product sequence and (b) a second secondary oligonucleotide primer comprising a nucleotide sequence that is complementary to the 3' primer-specific portion of the ligated product sequence;

blending the ligated product sequences, the one or more secondary oligonucleotide primer sets, the one or more enzymes capable of digesting deoxyuracil (dU)-containing nucleic acid molecules, a deoxynucleotide mix including dUTP, and a DNA polymerase to form one or more second polymerase chain reaction mixtures;

subjecting the one or more second polymerase chain reaction mixtures to conditions suitable for digesting deoxyuracil (dU)-containing nucleic acid molecules present in the second polymerase chain reaction mixtures and for carrying out one or more polymerase chain reaction cycles comprising a denaturation treatment, a hybridization treatment, and an extension treatment thereby forming second polymerase chain reaction products; and

detecting and distinguishing the second polymerase chain reaction products in the one or more second polymerase chain reaction mixtures to identify the presence of one or more parent nucleic acid molecules containing target nucleotide sequences differing from nucleotide sequences in other parent nucleic acid molecules in the sample by one or more methylated or hydroxymethylated residues.

3. A method for identifying, in a sample, one or more parent nucleic acid molecules containing a target nucleotide sequence differing from nucleotide sequences in other parent nucleic acid molecules in the sample by one or more methylated or hydroxymethylated residues, said method comprising:

providing a sample containing one or more parent nucleic acid molecules potentially containing the target nucleotide sequence differing from the nucleotide sequences in other parent nucleic acid molecules by one or more methylated or hydroxymethylated residues;

subjecting the nucleic acid molecules in the sample to a treatment with one or more DNA repair enzymes under conditions suitable to convert 5-methylated and 5-hydroxymethylated cytosine residues to 5-carboxycytosine residues, followed by treatment with one or more DNA deamination enzymes under conditions suitable to convert unmethylated cytosine but not 5-carboxycytosine residues into dexoyuracil (dU) residues to produce a treated sample;

providing one or more enzymes capable of digesting deoxyuracil (dU)-containing nucleic acid molecules;

providing one or more first primary oligonucleotide primer(s) that comprises a nucleotide sequence that is complementary to a sequence in the parent nucleic acid molecule adjacent to the the DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence containing the one or more methylated or hydroxymethylated residue;

blending the treated sample, the one or more first primary oligonucleotide primers, a deoxynucleotide mix, and a DNA polymerase to form one or more polymerase extension reaction mixtures;

subjecting the one or more polymerase extension reaction mixtures to conditions suitable for carrying out one or more polymerase extension reaction cycles comprising a denaturation treatment, a hybridization treatment, and an extension treatment, thereby forming primary extension products comprising the complement of the DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence;

providing one or more secondary oligonucleotide primer sets, each secondary oligonucleotide primer set comprising (a) a first secondary oligonucleotide primer having a 5’ primer-specific portion and a 3’ portion that is complementary to a

portion of the polymerase extension product formed from the first primary oligonucleotide primer and (b) a second secondary oligonucleotide primer having a 5′ primer-specific portion and a 3′ portion that comprises a nucleotide sequence that is complementary to a portion of an extension product formed from the first secondary oligonucleotide primer;

blending the one or more polymerase extension reaction mixtures comprising the primary extension products, the one or more secondary oligonucleotide primer sets, the one or more enzymes capable of digesting deoxyuracil (dU)-containing nucleic acid molecules, a deoxynucleotide mix, and a DNA polymerase to form one or more first polymerase chain reaction mixtures;

subjecting the one or more first polymerase chain reaction mixtures to conditions suitable for digesting deoxyuracil (dU)-containing nucleic acid molecules present in the first polymerase chain reaction mixtures, and conditions suitable for carrying out two or more polymerase chain reaction cycles comprising a denaturation treatment, a hybridization treatment, and an extension treatment, thereby forming first polymerase chain reaction products comprising a 5′ primer-specific portion of the first secondary oligonucleotide primer, a DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence-specific or complement sequence-specific portion, and a complement of the 5′ primer-specific portion of the second secondary oligonucleotide primer;

providing one or more tertiary oligonucleotide primer sets, each tertiary oligonucleotide primer set comprising (a) a first tertiary oligonucleotide primer comprising the same nucleotide sequence as the 5′ primer-specific portion of the first polymerase chain reaction products and (b) a second tertiary oligonucleotide primer comprising a nucleotide sequence that is complementary to the 3′ primer-specific portion of the first polymerase chain reactions product sequence;

blending the first polymerase chain reaction products, the one or more tertiary oligonucleotide primer sets, the one or more enzymes capable of digesting deoxyuracil (dU) containing nucleic acid molecules, a deoxynucleotide mix including dUTP, and a DNA polymerase to form one or more second polymerase chain reaction mixtures;

subjecting the one or more second polymerase chain reaction mixtures to conditions suitable for digesting deoxyuracil (dU)-containing nucleic acid molecules present in the second polymerase chain reaction mixtures and for carrying out one or more polymerase chain reaction cycles comprising a denaturation treatment, a hybridization treatment, and an extension treatment thereby forming second polymerase chain reaction products; and

detecting and distinguishing the second polymerase chain reaction products in the one or more second polymerase chain reaction mixtures to identify the presence of one or more parent nucleic acid molecules containing target nucleotide sequences differing from nucleotide sequences in other parent nucleic acid molecules in the sample by one or more methylated or hydroxymethylated residues.

4. A method for identifying, in a sample, one or more parent nucleic acid molecules containing a target nucleotide sequence differing from nucleotide sequences in other parent nucleic acid molecules in the sample by one or more methylated or hydroxymethylated residues, said method comprising:

providing a sample containing one or more parent nucleic acid molecules potentially containing the target nucleotide sequence differing from the nucleotide sequences in other parent nucleic acid molecules by one or more methylated or hydroxymethylated residues;

subjecting the nucleic acid molecules in the sample to a treatment with one or more DNA repair enzymes under conditions suitable to convert 5-methylated and 5-hydroxymethylated cytosine residues to 5-carboxycytosine residues, followed by treatment with one or more DNA deamination enzymes under conditions suitable to convert unmethylated cytosine but not 5-carboxycytosine residues into dexoyuracil (dU) residues to produce a treated sample;

providing one or more enzymes capable of digesting deoxyuracil (dU)-containing nucleic acid molecules present in the sample;

providing one or more primary oligonucleotide primer sets, each primary oligonucleotide primer set comprising (a) a first primary oligonucleotide primer having a 5’ primer-specific portion and a 3’ portion that comprises a nucleotide sequence that is complementary to a sequence in the parent nucleic acid molecule adjacent to the DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence containing the one or more converted methylated or hydroxymethylated residue and (b) a second primary oligonucleotide primer having a 5’ primer-specific portion and a 3’ portion that comprises a nucleotide sequence that is complementary to a portion of an extension product formed from the first primary oligonucleotide primer;

blending the treated sample, the one or more first primary oligonucleotide primers of the one or more primary oligonucleotide primer sets, a deoxynucleotide mix, and a DNA polymerase to form one or more polymerase extension reaction mixtures;

subjecting the one or more polymerase extension reaction mixtures to conditions suitable for carrying out one or more polymerase extension reaction cycles comprising a denaturation treatment, a hybridization treatment, and an extension

treatment, thereby forming primary extension products comprising the complement of the DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence;

blending the one or more polymerase extension reaction mixtures comprising the primary extension products, the one or more second primary oligonucleotide primers of the one or more primary oligonucleotide primer sets, the one or more enzymes capable of digesting deoxyuracil (dU)-containing nucleic acid molecules in the reaction mixture, a deoxynucleotide mix, and a DNA polymerase to form one or more first polymerase chain reaction mixtures;

subjecting the one or more first polymerase chain reaction mixtures to conditions suitable for digesting deoxyuracil (dU)-containing nucleic acid molecules present in the polymerase chain reaction mixtures and for carrying out one or more first polymerase chain reaction cycles comprising a denaturation treatment, a hybridization treatment, and an extension treatment, thereby forming first polymerase chain reactions products comprising the DNA repair enzyme and DNA deaminase enzyme-treated target nucleotide sequence or a complement thereof;

providing one or more secondary oligonucleotide primer sets, each secondary oligonucleotide primer set comprising (a) a first secondary oligonucleotide primer comprising the same nucleotide sequence as the 5’ primer-specific portion of the first polymerase chain reaction products or their complements and (b) a second secondary oligonucleotide primer comprising a nucleotide sequence that is complementary to the 3’ primer-specific portion of the first polymerase chain reaction products or their complements;

blending the first polymerase chain reaction products, the one or more secondary oligonucleotide primer sets, the one or more enzymes capable of digesting deoxyuracil (dU)-containing nucleic acid molecules, a deoxynucleotide mix including dUTP, and a DNA polymerase to form one or more second polymerase chain reaction mixtures;

subjecting the one or more second polymerase chain reaction mixtures to conditions suitable for digesting deoxyuracil (dU)-containing nucleic acid molecules present in the second polymerase chain reaction mixtures and for carrying out one or more polymerase chain reaction cycles comprising a denaturation treatment, a hybridization treatment, and an extension treatment thereby forming second polymerase chain reaction products; and

detecting and distinguishing the second polymerase chain reaction products in the one or more second polymerase chain reaction mixtures to identify the presence of one or more parent nucleic acid molecules containing target nucleotide sequences differing from nucleotide sequences in other parent nucleic acid molecules in the sample by one or more methylated or hydroxymethylated residues.

5. The method of any one of claims 1 to 4:

I. further comprising:

a) providing one or more blocking oligonucleotide primers comprising one or more mismatched bases at the 3’ end or one or more nucleotide analogs and a blocking group at the 3’ end, such that the 3’ end of said blocking oligonucleotide primer is unsuitable for polymerase extension when hybridized in a base-specific manner to wild-type nucleic acid sequence or complement sequence thereof, wherein said blocking oligonucleotide primer comprises a portion having a nucleotide sequence that is the same as a nucleotide sequence portion in the wild-type nucleic acid sequence or complement sequence thereof to which the blocking oligonucleotide primer hybridizes but has one or more nucleotide sequence mismatches to a corresponding nucleotide sequence portion in the target nucleic acid sequence or DNA repair enzyme and DNA deaminase enzyme-treated methylated or hydroxymethylated nucleic acid sequence or complement sequence thereof and

blending the one or more blocking oligonucleotide primers with the sample or products subsequently produced from the sample prior to a polymerase extension reaction, polymerase chain reaction, or ligation reaction, whereby during the hybridization step said one or more blocking oligonucleotide primers preferentially hybridize in a base-specific manner to a wild-type nucleic acid sequence or complement sequence thereof, thereby interfering with polymerase extension or ligation during reaction of a primer or probes hybridized in a base-specific manner to the DNA repair enzyme and DNA deaminase enzyme-treated unmethylated sequence or complement sequence thereof; or

b) contacting the sample with DNA repair enzymes to repair damaged DNA, abasic sites, oxidized bases, or nicks in the DNA; or

c) contacting the sample with at least a first methylation sensitive enzyme to form one or more restriction enzyme reaction mixtures prior to, or concurrent with, said blending to form one or more polymerase extension reaction mixtures, wherein said first methylation sensitive enzyme cleaves nucleic acid molecules in the sample that contain one or more unmethylated residues within at least one methylation sensitive enzyme recognition sequence, and whereby said detecting involves detection of one or more parent nucleic acid molecules containing the target nucleotide sequence, wherein said parent nucleic acid molecules originally contained one or more methylated or hydroxymethylated residues; or

d) contacting the sample with an immobilized methylated or hydroxymethylated nucleic acid binding protein or antibody to selectively bind and enrich for methylated or hydroxymethylated nucleic acid in the sample; or

II. wherein:

a) the DNA repair enzyme is the ten-eleven translocation (TET2) dioxygenase and the DNA deaminase enzyme is an apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC cytidine deaminase); or

b) one or more primary or secondary oligonucleotide primers comprises a portion that has no or one nucleotide sequence mismatch when hybridized in a base-specific manner to the target nucleic acid sequence or DNA repair enzyme and DNA deaminase enzyme-treated methylated or hydroxymethylated nucleic acid sequence or complement sequence thereof, but have one or more additional nucleotide sequence mismatches that interferes with polymerase extension when said primary or secondary oligonucleotide primers hybridize in a base-specific manner to a corresponding nucleotide sequence portion in DNA repair enzyme and DNA deaminase enzyme-treated unmethylated nucleic acid sequence or complement sequence thereof; or

c) one or both primary oligonucleotide primers of the primary oligonucleotide primer set and/or one or both secondary oligonucleotide primers of the secondary oligonucleotide primer set have a 3’ portion comprising a cleavable nucleotide or nucleotide analogue and a blocking group, such that the 3’ end of said primer or primers is unsuitable for polymerase extension, said method further comprising:

cleaving the cleavable nucleotide or nucleotide analog of one or both oligonucleotide primers during said hybridization treatment, thereby liberating free 3’OH ends on one or both oligonucleotide primers prior to said extension treatment, optionally wherein:

i) one or more primary or secondary oligonucleotide primers comprises a sequence that differs from the target nucleic acid sequence or DNA repair enzyme and DNA deaminase enzyme-treated methylated or hydroxymethylated nucleic acid sequence or complement sequence thereof, said difference is located two or three nucleotide bases from the liberated free 3’OH end; or

ii) the cleavable nucleotide comprises one or more RNA bases.

6. The method of claim 1, wherein the first secondary oligonucleotide primer has a 5’ primer-specific portion and the second secondary oligonucleotide primer has a 5’ primer-specific portion, said one or more secondary oligonucleotide primer sets further comprising a third secondary oligonucleotide primer comprising the same nucleotide sequence as the 5’ primer-specific portion of the first secondary oligonucleotide primer and (d) a fourth secondary oligonucleotide primer comprising the same nucleotide sequence as the 5’ primer-specific portion of the second secondary oligonucleotide primer.

7. The method of any one of claims 1 to 3 further comprising:

providing one or more third primary oligonucleotide primers comprising the same nucleotide sequence as the 5’ primer-specific portion of the first or second primary oligonucleotide primer; and

blending the one or more third primary oligonucleotide primers in the one or more first polymerase chain reaction mixtures.

8. The method of claim 3, wherein:

a) the second oligonucleotide probe of the oligonucleotide probe set further comprises a unitaq detection portion, thereby forming ligated product sequences comprising the 5’ primer-specific portion, the target-specific portions, the unitaq detection portion, and the 3’ primer-specific portion, said method further comprising:

providing one or more unitaq detection probes, wherein each unitaq detection probe hybridizes to a complementary unitaq detection portion and said detection probe comprises a quencher molecule and a detectable label separated from the quencher molecule;

adding the one or more unitaq detection probes to the second polymerase chain reaction mixture; and

hybridizing the one or more unitaq detection probes to complementary unitaq detection portions on the ligated product sequence or complement thereof during said subjecting the second polymerase chain reaction mixture to conditions suitable for one or more polymerase chain reaction cycles, wherein the quencher molecule and the detectable label are cleaved from the one or more unitaq detection probes during the extension treatment and said detecting involves the detection of the cleaved detectable label; or

b) one or both oligonucleotide probes of the oligonucleotide probe set comprises a portion that has no or one nucleotide sequence mismatch when hybridized in a base-specific manner to the target nucleic acid sequence or DNA repair enzyme and DNA deaminase enzyme-treated methylated or hydroxymethylated nucleic acid sequence or complement sequence thereof, but have one or more additional nucleotide sequence mismatches that interferes with ligation when said oligonucleotide probe hybridizes in a base-specific manner to a corresponding nucleotide sequence portion in the DNA repair enzyme and DNA deaminase enzyme-treated unmethylated nucleic acid sequence or complement sequence thereof; or

c) the 3’ portion of the first oligonucleotide probe of the oligonucleotide probe set comprises a cleavable nucleotide or nucleotide analogue and a blocking group, such that the 3’ end is unsuitable for polymerase extension or ligation, said method further comprising;

cleaving the cleavable nucleotide or nucleotide analog of the first oligonucleotide probe when said probe is hybridized to its complementary target nucleotide sequence of the primary extension product, thereby liberating a 3'OH on the first oligonucleotide probe prior to said ligating,

optionally wherein one or more first oligonucleotide probe of the oligonucleotide probe set comprises a sequence that differs from the target nucleic acid sequence or DNA repair enzyme and DNA deaminase enzyme-treated methylated or hydroxymethylated nucleic acid sequence or complement sequence thereof, said difference is located two or three nucleotide bases from the liberated free 3'OH end; or

d) the second oligonucleotide probe has, at its 5' end, an overlapping identical nucleotide with the 3' end of the first oligonucleotide probe, and, upon hybridization of the first and second oligonucleotide probes of a probe set at adjacent positions on a complementary target nucleotide sequence of a primary extension product to form a junction, the overlapping identical nucleotide of the second oligonucleotide probe forms a flap at the junction with the first oligonucleotide probe, said method further comprising:

cleaving the overlapping identical nucleotide of the second oligonucleotide probe with an enzyme having 5' nuclease activity thereby liberating a phosphate at the 5' end of the second oligonucleotide probe prior to said ligating; or

e) the one or more oligonucleotide probe sets further comprise a third oligonucleotide probe having a target-specific portion, wherein the second and third oligonucleotide probes of a probe set are configured to hybridize adjacent to one another on the target nucleotide sequence with a junction between them to allow ligation between the second and third oligonucleotide probes to form a ligated product sequence comprising the first, second, and third oligonucleotide probes of a probe set.

9. The method of any one of claims 1, 3 and 4, wherein one primary oligonucleotide primer or one secondary oligonucleotide primer further comprises a unitaq detection portion, thereby forming extension product sequences comprising the 5' primer-specific portion, the target-specific portions, the unitaq detection portion, and the complement of the other 5' primer-specific portion, and complements thereof, said method further comprising:

providing one or more unitaq detection probes, wherein each unitaq detection probe hybridizes to a complementary unitaq detection portion and said detection probe comprises a quencher molecule and a detectable label separated from the quencher molecule;

adding the one or more unitaq detection probes to the one or more polymerase chain reaction mixtures; and

hybridizing the one or more unitaq detection probes to complementary unitaq detection portions on the ligated product sequence or complement thereof during polymerase chain reaction cycles after the first polymerase chain reaction, wherein the quencher molecule and the detectable label are cleaved from the one or more unitaq detection probes during the extension treatment and said detecting involves the detection of the cleaved detectable label.

10. The method of any one of claims 1 to 9:

I. wherein:

a) the one or more target nucleotide sequences are low-abundance nucleic acid molecules comprising one or more nucleotide base mutations, insertions, deletions, translocations, splice variants, mRNA, lncRNA, ncRNA, miRNA variants, alternative transcripts, alternative start sites, alternative coding sequences, alternative non-coding sequences, alternative splicing, exon insertions, exon deletions, intron insertions, or other rearrangement at the genome level and/or methylated or hydroxymethylated nucleotide bases, optionally wherein the low-abundance nucleic acid molecules with one or more nucleotide base mutations, insertions, deletions, translocations, splice variants, mRNA, lncRNA, ncRNA, miRNA variants, alternative transcripts, alternative start sites, alternative coding sequences, alternative non-coding sequences, alternative splicings, exon insertions, exon deletions, intron insertions, or other rearrangement at the genome level, and/or methylated or hydroxymethylated nucleotide bases are identified and distinguished from a high-abundance of nucleic acid molecules in the sample having a similar nucleotide sequence as the low abundance nucleic acid molecules but without the one or more nucleotide base mutations, insertions, deletions, translocations, splice variants, mRNA, lncRNA, ncRNA, miRNA variants, alternative transcripts, alternative start sites, alternative coding sequences, alternative non-coding sequences, alternative splicing, exon insertions, exon deletions, intron insertions, or other rearrangement at the genome level, and/or methylated or hydroxymethylated nucleotide bases, and further optionally wherein the copy number of one or more low-abundance target nucleotide sequences are quantified relative to the copy number of the high-abundance nucleic acid molecules in the sample; or

b) the sample is selected from the group consisting of tissue, cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, cell-free circulating nucleic acids, cell-free circulating tumor nucleic acids, cell-free circulating fetal nucleic acids in pregnant woman, circulating tumor cells, tumor, tumor biopsy, and exosomes; or

c) the one or more target nucleotide sequences are quantified or enumerated, optionally wherein the one or more target nucleotide sequences are quantified or enumerated relative to other nucleotide sequences in the sample or other samples undergoing the identical subsequent steps, and further optionally wherein the relative copy number of one or more target nucleotide sequences are quantified or enumerated; or

II. further comprising:

a) diagnosing or prognosing a disease state based on said identifying; or

b) distinguishing a genotype or disease predisposition based on said identifying.

11. A method of diagnosing or prognosing a disease state of cells or tissue based on identifying the presence or level of a plurality of disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers in a biological sample of an individual, wherein the plurality of markers is in a set comprising from 6-12 markers, 12-24 markers, 24-36 markers, 36-48 markers, 48-72 markers, 72-96 markers, or > 96 markers, wherein each marker in a given set is selected by having any one or more of the following criteria:

present, or above a cutoff level, in > 50% of biological samples of the disease cells or tissue from individuals diagnosed with the disease state;

absent, or below a cutoff level, in > 95% of biological samples of the normal cells or tissue from individuals without the disease state;

present, or above a cutoff level, in > 50% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with the disease state;

absent, or below a cutoff level, in > 95% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals without the disease state;

present with a z-value of > 1.65 in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with the disease state;

and, wherein at least 50% of the markers in a set each comprise one or more methylated or hydroxymethylated residues, and/or wherein at least 50% of the markers in a set that are present, or above a cutoff level, or present with a z-value of > 1.65 comprise of one or more methylated or hydroxymethylated residues, in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from at least 50% of individuals diagnosed with the disease state, said method comprising:

obtaining the biological sample including cell-free DNA, RNA, and/or protein originating from the cells or tissue and from one or more other tissues or cells, wherein the biological sample is selected from the group consisting of cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, and fractions thereof;

fractionating the sample into one or more fractions, wherein at least one fraction comprises exosomes, tumor-associated vesicles, other protected states, or cell-free DNA, RNA, and/or protein;

subjecting nucleic acid molecules in one or more fractions to a treatment with one or more DNA repair enzymes under conditions suitable to convert 5-methylated and 5-hydroxymethylated cytosine residues to 5-carboxycytosine residues, followed by treatment with one or more DNA deamination enzymes under conditions suitable to convert unmethylated cytosine but not 5-carboxycytosine residues into dexoyuracil (dU) residues;

carrying out at least two enrichment steps for 50% or more disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers during either said fractionating and/or by carrying out a nucleic acid amplification step; and

performing one or more assays to detect and distinguish the plurality of disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers, thereby identifying their presence or levels in the sample, wherein individuals are diagnosed or prognosed with the disease state if a minimum of 2 or 3 markers are present or above a cutoff level in a marker set comprising from 6-12 markers; or a minimum of 3, 4, or 5 markers are present or above a cutoff level in a marker set comprising from 12-24 markers; or a minimum of 3, 4, 5, or 6 markers are present or above a cutoff level in a marker set comprising from 24-36 markers; or a minimum of 4, 5, 6, 7, or 8 markers are present or above a cutoff level in a marker set comprising from 36-48 markers; or a minimum of 6, 7, 8, 9, 10, 11, or 12 markers are present or above a cutoff level in a marker set comprising from 48-72 markers, or a minimum of 7, 8, 9, 10, 11, 12 or 13 markers are present or above a cutoff level in a marker set comprising from 72-96 markers, or a minimum of 8, 9, 10, 11, 12, 13 or "n"/12 markers are present or above a cutoff level in a marker set comprising 96 to "n" markers, when "n" > 168 markers.

12. A method of diagnosing or prognosing a disease state of a solid tissue cancer including colorectal adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, uterine carcinosarcoma, lung adenocarcinoma, lung squamous cell carcinoma, head & neck squamous cell carcinoma, prostate adenocarcinoma, invasive

urothelial bladder cancer, liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma, based on identifying the presence or level of a plurality of disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers in a biological sample of an individual, wherein the plurality of markers is in a set comprising from 48-72 total cancer markers, 72-96 total cancer markers or $\geq$ 96 total cancer markers, wherein on average greater than one quarter such markers in a given set cover each of the aforementioned major cancers being tested, wherein each marker in a given set for a given solid tissue cancer is selected by having any one or more of the following criteria for that solid tissue cancer:

present, or above a cutoff level, in > 50% of biological samples of a given cancer tissue from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples of the normal tissue from individuals without that given solid tissue cancer;

present, or above a cutoff level, in > 50% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals without that given solid tissue cancer;

present with a z-value of > 1.65 in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer;

and, wherein at least 50% of the markers in a set each comprise one or more methylated residues, and/or wherein at least 50% of the markers in a set that are present, or above a cutoff level, or present with a z-value of > 1.65 comprise of one or more methylated residues, in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from at least 50% of individuals diagnosed with a given solid tissue cancer, said method comprising:

obtaining a biological sample, the biological sample including cell-free DNA, RNA, and/or protein originating from the cells or tissue and from one or more other tissues or cells, wherein the biological sample is selected from the group consisting of cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, and fractions thereof;

fractionating the sample into one or more fractions, wherein at least one fraction comprises exosomes, tumor-associated vesicles, other protected states, or cell-free DNA, RNA, and/or protein;

subjecting the nucleic acid molecules in one or more fractions to a treatment with one or more DNA repair enzymes under conditions suitable to convert 5-methylated and 5-hydroxymethylated cytosine residues to 5-carboxycytosine residues, followed by treatment with one or more DNA deamination enzymes under conditions suitable to convert unmethylated cytosine but not 5-carboxycytosine residues into dexoyuracil (dU) residues;

carrying out at least two enrichment steps for 50% or more disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers during either said fractionating and/or by carrying out a nucleic acid amplification step; and

preforming one or more assays to detect and distinguish the plurality of cancer -specific and/or cell/tissue-specific DNA, RNA, and/or protein markers, thereby identifying their presence or levels in the sample, wherein individuals are diagnosed or prognosed with a solid-tissue cancer if a minimum of 4 markers are present or are above a cutoff level in a marker set comprising from 48-72 total cancer markers; or a minimum of 5 markers are present or are above a cutoff level in a marker set comprising from 72-96 total cancer markers; or a minimum of 6 or "n"/18 markers are present or are above a cutoff level in a marker set comprising 96 to "n" total cancer markers, when "n" > 96 total cancer markers, optionally wherein each marker in a given set for a given solid tissue cancer is selected by having any one or more of the following criteria for that solid tissue cancer:

present, or above a cutoff level, in > 66% of biological samples of a given cancer tissue from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples of the normal tissue from individuals without that given solid tissue cancer;

present, or above a cutoff level, in > 66% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals without that given solid tissue cancer;

present with a z-value of > 1.65 in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions,

bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer.

13. A method of diagnosing or prognosing a disease state of and identifying the most likely specific tissue(s) of origin of a solid tissue cancer in the following groups: Group 1 (colorectal adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma); Group 2 (breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, uterine carcinosarcoma); Group 3 (lung adenocarcinoma, lung squamous cell carcinoma, head & neck squamous cell carcinoma); Group 4 (prostate adenocarcinoma, invasive urothelial bladder cancer); and/or Group 5 (liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma) based on identifying the presence or level of a plurality of disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers in a biological sample of an individual, wherein the plurality of markers is in a set comprising from 36-48 group-specific cancer markers, 48-64 group-specific cancer markers or $\geq$ 64 group-specific cancer markers, wherein on average greater than one third such markers in a given set cover each of the aforementioned cancers being tested within that group, wherein each marker in a given set for a given solid tissue cancer is selected by having any one or more of the following criteria for that solid tissue cancer:

present, or above a cutoff level, in > 50% of biological samples of a given cancer tissue from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples of the normal tissue from individuals without that given solid tissue cancer;

present, or above a cutoff level, in > 50% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals without that given solid tissue cancer;

present with a z-value of > 1.65 in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer;

and, wherein at least 50% of the markers in a set each comprise one or more methylated residues, and/or wherein at least 50% of the markers in a set that are

present, or above a cutoff level, or present with a z-value of > 1.65 comprise one or more methylated residues, in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from at least 50% of individuals diagnosed with a given solid tissue cancer, said method comprising:

obtaining the biological sample, the biological sample including cell-free DNA, RNA, and/or protein originating from the cells or tissue and from one or more other tissues or cells, wherein the biological sample is selected from the group consisting of cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, and fractions thereof;

fractionating the sample into one or more fractions, wherein at least one fraction comprises exosomes, tumor-associated vesicles, other protected states, or cell-free DNA, RNA, and/or protein;

subjecting the nucleic acid molecules in one or more fractions to a treatment with one or more DNA repair enzymes under conditions suitable to convert 5-methylated and 5-hydroxymethylated cytosine residues to 5-carboxycytosine residues, followed by treatment with one or more DNA deamination enzymes under conditions suitable to convert unmethylated cytosine but not 5-carboxycytosine residues into dexoyuracil (dU) residues;

carrying out at least two enrichment steps for 50% or more disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers during either said fractionating and/or by carrying out a nucleic acid amplification step; and

preforming one or more assays to detect and distinguish the plurality of cancer -specific and/or cell/tissue-specific DNA, RNA, and/or protein markers, thereby identifying their presence or levels in the sample, wherein individuals are diagnosed or prognosed with a solid-tissue cancer if a minimum of 4 markers are present or are above a cutoff level in a marker set comprising from 36-48 group-specific cancer markers; or a minimum of 5 markers are present or are above a cutoff level in a marker set comprising from 48-64 group-specific cancer markers; or a minimum of 6 or “n”/12 markers are present or are above a cutoff level in a marker set comprising 64 to “n” group-specific cancer markers, when “n” > 64 group-specific cancer markers, optionally wherein each marker in a given set for a given solid tissue cancer is selected by having any one or more of the following criteria for that solid tissue cancer:

present, or above a cutoff level, in > 66% of biological samples of a given cancer tissue from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples of the normal tissue from individuals without that given solid tissue cancer;

present, or above a cutoff level, in > 66% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals without that given solid tissue cancer;

present with a z-value of > 1.65 in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer.

14. A method of diagnosing or prognosing a disease state of a gastrointestinal cancer including colorectal adenocarcinoma, stomach adenocarcinoma, or esophageal carcinoma, based on identifying the presence or level of a plurality of disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers in a biological sample of an individual, wherein the plurality of markers is in a set comprising from 6-12 markers, 12-18 markers, 18-24 markers, 24-36 markers, 36-48 markers or ≥ 48 markers, wherein each marker is selected by having any one or more of the following criteria for gastrointestinal cancer:

present, or above a cutoff level, in > 75% of biological samples of a given cancer tissue from individuals diagnosed with gastrointestinal cancer;

absent, or below a cutoff level, in > 95% of biological samples of the normal tissue from individuals without gastrointestinal cancer;

present, or above a cutoff level, in > 75% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with gastrointestinal cancer;

absent, or below a cutoff level, in > 95% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals without gastrointestinal cancer;

present with a z-value of > 1.65 in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with gastrointestinal cancer;

and, wherein at least 50% of the markers in a set each comprise one or more methylated residues, and/or wherein at least 50% of the markers in a set that are

present, or above a cutoff level, or present with a z-value of > 1.65 comprise one or more methylated residues, in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from at least 50% of individuals diagnosed with gastrointestinal cancer, said method comprising:

obtaining the biological sample, the biological sample including cell-free DNA, RNA, and/or protein originating from the cells or tissue and from one or more other tissues or cells, wherein the biological sample is selected from the group consisting of cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, and fractions thereof;

fractionating the sample into one or more fractions, wherein at least one fraction comprises exosomes, tumor-associated vesicles, other protected states, or cell-free DNA, RNA, and/or protein;

subjecting the nucleic acid molecules in one or more fractions to a treatment with one or more DNA repair enzymes under conditions suitable to convert 5-methylated and 5-hydroxymethylated cytosine residues to 5-carboxycytosine residues, followed by treatment with one or more DNA deamination enzymes under conditions suitable to convert unmethylated cytosine but not 5-carboxycytosine residues into dexoyuracil (dU) residues;

carrying out at least two enrichment steps for 50% or more disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers during either said fractionating step and/or by carrying out a nucleic acid amplification step; and

preforming one or more assays to detect and distinguish the plurality of cancer -specific and/or cell/tissue-specific DNA, RNA, and/or protein markers, thereby identifying their presence or levels in the sample, wherein individuals are diagnosed or prognosed with gastrointestinal cancer if a minimum of 2, 3 or 4 markers are present or are above a cutoff level in a marker set comprising from 6-12 markers; or a minimum of 2, 3, 4, or 5 markers are present or are above a cutoff level in a marker set comprising from 12-18 markers; or a minimum of 3, 4, 5, or 6 markers are present or are above a cutoff level in a marker set comprising from 18-24 markers; or a minimum of 3, 4, 5, 6, 7, or 8 markers are present or are above a cutoff level in a marker set comprising from 24-36 markers; or a minimum of 4, 5, 6, 7, 8, 9, or 10 markers are present or are above a cutoff level in a marker set comprising from 36-48 markers; or a minimum of 5, 6, 7, 8, 9, 10, 11, 12, or "n"/12 markers are present or are above a cutoff level in a marker set comprising 48 to "n" markers, when "n" > 48 markers.

15. A method of diagnosing or prognosing a disease state of a solid tissue cancer including colorectal adenocarcinoma, stomach adenocarcinoma, esophageal

carcinoma, breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, uterine carcinosarcoma, lung adenocarcinoma, lung squamous cell carcinoma, head & neck squamous cell carcinoma, prostate adenocarcinoma, invasive urothelial bladder cancer, liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma, based on identifying the presence or level of a plurality of disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers in a biological sample of an individual, wherein the plurality of markers is in a set comprising from 36-48 total cancer markers, 48-64 total cancer markers, or $\geq$ 64 total cancer markers, wherein on average greater than half of such markers in a given set cover each of the aforementioned major cancers being tested, wherein each marker in a given set for a given solid tissue cancer is selected by having any one or more of the following criteria for that solid tissue cancer:

present, or above a cutoff level, in > 75% of biological samples of a given cancer tissue from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples of the normal tissue from individuals without that given solid tissue cancer;

present, or above a cutoff level, in > 75% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals without that given solid tissue cancer;

present with a z-value of > 1.65 in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer;

and, wherein at least 50% of the markers in a set each comprise one or more methylated residues, and/or wherein at least 50% of the markers in a set that are present, or above a cutoff level, or present with a z-value of > 1.65 comprise one or more methylated residues, in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from at least 50% of individuals diagnosed with a given solid tissue cancer, said method comprising:

obtaining the biological sample, the biological sample including cell-free DNA, RNA, and/or protein originating from the cells or tissue and from one or more other

tissues or cells, wherein the biological sample is selected from the group consisting of cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, and fractions thereof;

fractionating the sample into one or more fractions, wherein at least one fraction comprises exosomes, tumor-associated vesicles, other protected states, or cell-free DNA, RNA, and/or protein;

subjecting the nucleic acid molecules in one or more fractions to a treatment with one or more DNA repair enzymes under conditions suitable to convert 5-methylated and 5-hydroxymethylated cytosine residues to 5-carboxycytosine residues, followed by treatment with one or more DNA deamination enzymes under conditions suitable to convert unmethylated cytosine but not 5-carboxycytosine residues into dexoyuracil (dU) residues;

carrying out at least two enrichment steps for 50% or more disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers during either said fractionating step and/or by carrying out a nucleic acid amplification step; and

preforming one or more assays to detect and distinguish the plurality of cancer -specific and/or cell/tissue-specific DNA, RNA, and/or protein markers, thereby identifying their presence or levels in the sample, wherein individuals are diagnosed or prognosed with a solid-tissue cancer if a minimum of 4 markers are present or are above a cutoff level in a marker set comprising from 36-48 total cancer markers; or a minimum of 5 markers are present or are above a cutoff level in a marker set comprising from 48-64 total cancer markers; or a minimum of 6 or "n"/12 markers are present or are above a cutoff level in a marker set comprising 64 to "n" total cancer markers, when "n" > 96 total cancer markers.

16. A method of diagnosing or prognosing a disease state of and identifying the most likely specific tissue(s) of origin of a solid tissue cancer in the following groups: Group 1 (colorectal adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma); Group 2 (breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, uterine carcinosarcoma); Group 3 (lung adenocarcinoma, lung squamous cell carcinoma, head & neck squamous cell carcinoma); Group 4 (prostate adenocarcinoma, invasive urothelial bladder cancer); and/or Group 5 (liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma) based on identifying the presence or level of a plurality of disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers in a biological sample of an individual, wherein the plurality of markers is in a set comprising from 24-36 group-specific cancer markers, 36-48 group-specific cancer markers, or ≥ 48 group-

specific cancer markers, wherein on average greater than one half of such markers in a given set cover each of the aforementioned cancers being tested within that group, wherein each marker in a given set for a given solid tissue cancer is selected by having any one or more of the following criteria for that solid tissue cancer:

present, or above a cutoff level, in > 75% of biological samples of a given cancer tissue from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples of the normal tissue from individuals without that given solid tissue cancer;

present, or above a cutoff level, in > 75% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals without that given solid tissue cancer;

present with a z-value of > 1.65 in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer;

and, wherein at least 50% of the markers in a set each comprise one or more methylated residues, and/or wherein at least 50% of the markers in a set that are present, or above a cutoff level, or present with a z-value of > 1.65 comprise one or more methylated residues, in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from at least 50% of individuals diagnosed with a given solid tissue cancer, said method comprising:

obtaining the biological sample, the biological sample including cell-free DNA, RNA, and/or protein originating from the cells or tissue and from one or more other tissues or cells, wherein the biological sample is selected from the group consisting of cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, and fractions thereof;

fractionating the sample into one or more fractions, wherein at least one fraction comprises exosomes, tumor-associated vesicles, other protected states, or cell-free DNA, RNA, and/or protein;

subjecting the nucleic acid molecules in one or more fractions to a treatment with one or more DNA repair enzymes under conditions suitable to convert 5-methylated and 5-hydroxymethylated cytosine residues to 5-carboxycytosine residues,

followed by treatment with one or more DNA deamination enzymes under conditions suitable to convert unmethylated cytosine but not 5-carboxycytosine residues into dexoyuracil (dU) residues;

carrying out at least two enrichment steps for 50% or more disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers during either said fractionating step and/or by carrying out a nucleic acid amplification step; and

performing one or more assays to detect and distinguish the plurality of cancer -specific and/or cell/tissue-specific DNA, RNA, and/or protein markers, thereby identifying their presence or levels in the sample, wherein individuals are diagnosed or prognosed with a solid-tissue cancer if a minimum of 4 markers are present or are above a cutoff level in a marker set comprising from 24-36 group-specific cancer markers; or a minimum of 5 markers are present or are above a cutoff level in a marker set comprising from 36-48 group-specific cancer markers; or a minimum of 6 or "n"/8 markers are present or are above a cutoff level in a marker set comprising 48 to "n" group-specific cancer markers, when "n" > 48 group-specific cancer markers.

17. A method of diagnosing or prognosing a disease state to guide and monitor treatment of a solid tissue cancer in one or more of the following groups; Group 1 (colorectal adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma); Group 2 (breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, uterine carcinosarcoma); Group 3 (lung adenocarcinoma, lung squamous cell carcinoma, head & neck squamous cell carcinoma); Group 4 (prostate adenocarcinoma, invasive urothelial bladder cancer); and/or Group 5 (liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma) based on identifying the presence or level of a plurality of disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers in a biological sample of an individual, wherein the plurality of markers is in a set comprising from 24-36 group-specific cancer markers, 36-48 group-specific cancer markers, or ≥ 48 group-specific cancer markers, wherein on average greater than one half of such markers in a given set cover each of the aforementioned cancers being tested within that group, wherein each marker in a given set for a given solid tissue cancer is selected by having any one or more of the following criteria for that solid tissue cancer:

present, or above a cutoff level, in > 75% of biological samples of a given cancer tissue from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples of the normal tissue from individuals without that given solid tissue cancer;

present, or above a cutoff level, in > 75% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals without that given solid tissue cancer;

present with a z-value of > 1.65 in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer;

and, wherein at least 50% of the markers in a set each comprise of one or more methylated residues, and/or wherein at least 50% of the markers in a set that are present, or above a cutoff level, or present with a z-value of > 1.65 comprise of one or more methylated residues, in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from at least 50% of individuals diagnosed with a given solid tissue cancer, said method comprising:

obtaining the biological sample, the biological sample including cell-free DNA, RNA, and/or protein originating from the cells or tissue and from one or more other tissues or cells, wherein the biological sample is selected from the group consisting of cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, and fractions thereof;

fractionating the sample into one or more fractions, wherein at least one fraction comprises exosomes, tumor-associated vesicles, other protected states, or cell-free DNA, RNA, and/or protein;

subjecting the nucleic acid molecules in one or more fractions to a treatment with one or more DNA repair enzymes under conditions suitable to convert 5-methylated and 5-hydroxymethylated cytosine residues to 5-carboxycytosine residues, followed by treatment with one or more DNA deamination enzymes under conditions suitable to convert unmethylated cytosine but not 5-carboxycytosine residues into dexoyuracil (dU) residues;

carrying out at least two enrichment steps for 50% or more disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers during either said fractionating step and/or by carrying out a nucleic acid amplification step; and

performing one or more assays to detect and distinguish the plurality of cancer -specific and/or cell/tissue-specific DNA, RNA, and/or protein markers, thereby

identifying their presence or levels in the sample, wherein individuals with a given tissue-specific cancer will on average have from approximately one-quarter to about one-half or more of the markers scored as present, or are above a cutoff level in the tested marker set, wherein to guide and monitor subsequent treatment, a portion or all of the identified markers scored as present or the identified markers as above a cutoff level in the tested marker set are deemed the "patient-specific marker set", and retested on a subsequent biological sample from the individual during the treatment protocol, to monitor for loss of marker signal, wherein if a minimum of 3 markers remain present or remain above a cutoff level in a patient-specific marker set comprising from 12-24 markers; or if a minimum of 4 markers remain present or remain above a cutoff level in a patient-specific marker set comprising from 24-36 markers; or a minimum of 5 markers remain present or remain above a cutoff level in a patient-specific marker set comprising from 36-48 markers; or a minimum of 6 or "n"/8 markers remain present or remain above a cutoff level in a patient-specific marker set comprising 48 to "n" markers, when "n" > 48 markers after the treatment protocol has been administered, then the continuing presence of said markers may guide a decision to change the cancer treatment therapy.

18. A method of diagnosing or prognosing a disease state for recurrence of a solid tissue cancer in one or more of the following groups; Group 1 (colorectal adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma); Group 2 (breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, uterine carcinosarcoma); Group 3 (lung adenocarcinoma, lung squamous cell carcinoma, head & neck squamous cell carcinoma); Group 4 (prostate adenocarcinoma, invasive urothelial bladder cancer); and/or Group 5 (liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma) based on identifying the presence or level of a plurality of disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers in a biological sample of an individual, wherein the plurality of markers is in a set comprising from 24-36 group-specific cancer markers, 36-48 group-specific cancer markers, or $\geq$ 48 group-specific cancer markers, wherein on average greater than one half of such markers in a given set cover each of the aforementioned cancers being tested within that group, wherein each marker in a given set for a given solid tissue cancer is selected by having any one or more of the following criteria for that solid tissue cancer:

present, or above a cutoff level, in > 75% of biological samples of a given cancer tissue from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples of the normal tissue from individuals without that given solid tissue cancer;

present, or above a cutoff level, in > 75% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer;

absent, or below a cutoff level, in > 95% of biological samples comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals without that given solid tissue cancer;

present with a z-value of > 1.65 in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from individuals diagnosed with a given solid tissue cancer;

and, wherein at least 50% of the markers in a set each comprise of one or more methylated residues, and/or wherein at least 50% of the markers in a set that are present, or above a cutoff level, or present with a z-value of > 1.65 comprise of one or more methylated residues, in the biological sample comprising cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, or fractions thereof, from at least 50% of individuals diagnosed with a given solid tissue cancer, said method comprising:

obtaining the biological sample, the biological sample including cell-free DNA, RNA, and/or protein originating from the cells or tissue and from one or more other tissues or cells, wherein the biological sample is selected from the group consisting of cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, and fractions thereof;

fractionating the sample into one or more fractions, wherein at least one fraction comprises exosomes, tumor-associated vesicles, other protected states, or cell-free DNA, RNA, and/or protein;

subjecting the nucleic acid molecules in one or more fractions to a treatment with one or more DNA repair enzymes under conditions suitable to convert 5-methylated and 5-hydroxymethylated cytosine residues to 5-carboxycytosine residues, followed by treatment with one or more DNA deamination enzymes under conditions suitable to convert unmethylated cytosine but not 5-carboxycytosine residues into dexoyuracil (dU) residues;

carrying out at least two enrichment steps for 50% or more disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers during either said fractionating step and/or by carrying out a nucleic acid amplification step; and

preforming one or more assays to detect and distinguish the plurality of cancer -specific and/or cell/tissue-specific DNA, RNA, and/or protein markers, thereby

identifying their presence or levels in the sample, wherein individuals with a given tissue-specific cancer will on average have from approximately one-quarter to about one-half or more of the markers scored as present, or are above a cutoff level in the tested marker set, wherein to monitor for recurrence, a portion or all of the markers scored as being present, or the markers scored as above a cutoff level in the tested marker set are deemed the "patient-specific marker set", and retested on subsequent biological samples from the individual after a successful treatment, to monitor for gain of marker signal, wherein if a minimum of 3 markers reappear or rise above a cutoff level in a patient-specific marker set comprising from 12-24 markers; or if a minimum of 4 markers reappear or rise above a cutoff level in a patient-specific marker set comprising from 24-36 markers; or a minimum of 5 markers reappear or rise above a cutoff level in a patient-specific marker set comprising from 36-48 markers; or a minimum of 6 or "n"/8 markers reappear or rise above a cutoff level in a patient-specific marker set comprising 48 to "n" markers, when "n" > 48 markers after the treatment protocol has been administered, then the reappearance or rise or rise above a cutoff level in a patient-specific marker set may guide a decision to resume the cancer treatment therapy or change to a new cancer treatment therapy.

19. The method of any one of claims 11 to 18, wherein:

a) the at least two enrichment steps comprise of one or more of the following steps:

capturing or separating exosomes or extracellular vesicles or markers in other protected states; capturing or separating a platelet fraction; capturing or separating circulating tumor cells; capturing or separating RNA-containing complexes; capturing or separating cfDNA-nucleosome or differentially modified cfDNA-histone complexes; capturing or separating protein targets or protein target complexes; capturing or separating auto-antibodies; capturing or separating cytokines; capturing or separating methylated or hydroxymethylated cfDNA; capturing or separating marker specific DNA, cDNA, miRNA, lncRNA, ncRNA, or mRNA, or amplified complements, by hybridization to complementary capture probes in solution, on magnetic beads, or on a microarray; amplifying miRNA markers, non-coding RNA markers (lncRNA & ncRNA markers), mRNA markers, exon markers, splice-variant markers, translocation markers, or copy number variation markers in a linear or exponential manner via a polymerase extension reaction, polymerase chain reaction, DNA repair enzyme and DNA deaminase enzyme-treated -methyl-specific polymerase chain reaction, reverse-transcription reaction, DNA repair enzyme and DNA deaminase enzyme-treated -methyl-specific ligation reaction, and/or ligation reaction, using DNA polymerase, reverse transcriptase, DNA ligase, RNA ligase, DNA repair enzyme, DNA deaminase enzyme, RNase, RNaseH2,

endonuclease, restriction endonuclease, exonuclease, CRISPR, DNA glycosylase or combinations thereof; selectively amplifying one or more target regions containing mutation markers or DNA repair enzyme and DNA deaminase enzyme-treated -converted DNA methylation markers, while suppressing amplification of the target regions containing DNA repair enzyme and DNA deaminase enzyme-treated unmethylated sequence or complement sequence thereof, in a linear or exponential manner via a polymerase extension reaction, polymerase chain reaction, DNA repair enzyme and DNA deaminase enzyme-treated -methyl-specific polymerase chain reaction, reverse-transcription reaction, DNA repair enzyme and DNA deaminase enzyme-treated -methyl-specific ligation reaction, and/or ligation reaction, using DNA polymerase, reverse transcriptase, DNA ligase, RNA ligase, DNA repair enzyme, DNA deaminase enzyme, RNase, RNaseH2, endonuclease, restriction endonuclease, exonuclease, CRISPR, DNA glycosylase or combinations thereof; preferentially extending, ligating, or amplifying one or more primers or probes whose 3'-OH end has been liberated in an enzyme and sequence-dependent process; using one or more blocking oligonucleotide primers comprising one or more mismatched bases at the 3' end or comprising one or more nucleotide analogs and a blocking group at the 3' end under conditions that interfere with polymerase extension or ligation during said reaction of target-specific primer or probes hybridized in a base-specific manner to DNA repair enzyme and DNA deaminase enzyme-treated unmethylated sequence or complement sequence thereof; and/or

b) the one or more assays to detect and distinguish the plurality of disease-specific and/or cell/tissue-specific DNA, RNA, or protein markers comprise one or more of the following:

a quantitative real-time PCR method (qPCR); a reverse transcriptase-polymerase chain reaction (RTPCR) method; a DNA repair enzyme and DNA deaminase-treated- qPCR method; a digital PCR method (dPCR); a DNA repair enzyme and DNA deaminase-treated- dPCR method; a ligation detection method, a ligase chain reaction, a restriction endonuclease cleavage method; a DNA or RNA nuclease cleavage method; a micro-array hybridization method; a peptide-array binding method; an antibody-array method; a Mass spectrometry method; a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method; a capillary or gel electrophoresis method; a chemiluminescence method; a fluorescence method; a DNA sequencing method; a DNA repair enzyme and DNA deaminase-treated -DNA sequencing method; an RNA sequencing method; a proximity ligation method; a proximity PCR method; a method comprising immobilizing an antibody-target complex; a method comprising immobilizing an aptamer-target complex; an immunoassay method; a method comprising a Western blot assay; a method comprising an enzyme linked immunosorbent assay (ELISA); a method comprising a high-throughput microarray-based enzyme-linked immunosorbent

assay (ELISA); a method comprising a high-throughput flow-cytometry-based enzyme-linked immunosorbent assay (ELISA); and/or

c) the one or more cutoff levels of the one or more assays to detect and distinguish the plurality of disease-specific and/or cell/tissue-specific DNA, RNA, or protein markers comprise one or more of the following calculations, comparisons, or determinations, in the one or more marker assays comparing samples from the disease vs. normal individual:

the marker ΔCt value is > 2; the marker ΔCt value is > 4; the ratio of detected marker-specific signal is > 1.5; the ratio of detected marker-specific signal is > 3; the ratio of marker concentrations is > 1.5; the ratio of marker concentrations is > 3; the enumerated marker-specific signals differ by > 20%; the enumerated marker-specific signals differ by > 50%; the marker-specific signal from a given disease sample is > 85%; > 90%; > 95%; > 96%; > 97%; or > 98% of the same marker-specific signals from a set of normal samples; the marker-specific signal from a given disease sample has a z-score of > 1.03; > 1.28; > 1.65; > 1.75; > 1.88; or > 2.05 compared to the same marker-specific signals from a set of normal samples.

20. A two-step method of diagnosing or prognosing a disease state of cells or tissue based on identifying the presence or level of a plurality of disease-specific and/or cell/tissue-specific DNA, RNA, and/or protein markers in a biological sample of an individual, said two-step method comprising:

obtaining a biological sample, the biological sample including exosomes, tumor-associated vesicles, markers within other protected states, cell-free DNA, RNA, and/or protein originating from the potentially disease state cells or tissue and from one or more other tissues or cells, wherein the biological sample is selected from the group consisting of cells, serum, blood, plasma, amniotic fluid, sputum, urine, bodily fluids, bodily secretions, bodily excretions, and fractions thereof;

applying a first step to the biological samples with an overall sensitivity of > 80% and an overall specificity of > 90% or an overall Z-score of > 1.28 to identify individuals more likely to be diagnosed or prognosed with the disease state; and

applying a second step to biological samples from those individuals identified in the first step with an overall specificity of > 95% or an overall Z-score of > 1.65 to diagnose or prognose individuals with the disease state, wherein said applying the first step and/or said applying the second step is carried out using the method of one of claims 11 to 19.

21. The method of any one of claims 11 to 20, wherein the disease state is:

a) a solid tissue cancer including colorectal adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, uterine carcinosarcoma, lung adenocarcinoma, lung squamous cell carcinoma, head & neck squamous cell carcinoma, prostate adenocarcinoma, invasive urothelial bladder cancer, liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma, wherein at least 50% of the markers in a set each comprise one or more methylated cytosine residues of a CpG sequence, or the complement of one or more methylated cytosine residues of a CpG sequence selected from the list in Figure 42 or in Figure 58; or

b) a solid tissue cancer including colorectal adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, uterine carcinosarcoma, lung adenocarcinoma, lung squamous cell carcinoma, head & neck squamous cell carcinoma, prostate adenocarcinoma, invasive urothelial bladder cancer, liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma, wherein at least 50% of the markers in a set each comprise one or more methylated residues of one or more chromosomal sub-regions selected from the list in Figure 43 or in Figure 59; or

c) a solid tissue cancer including colorectal adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, uterine carcinosarcoma, lung adenocarcinoma, lung squamous cell carcinoma, head & neck squamous cell carcinoma, prostate adenocarcinoma, invasive urothelial bladder cancer, liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma, wherein the one or more markers in a set comprise one or more miRNA sequences selected from the group consisting of (mir ID , Gene ID): hsa-mir-21 , MIR21; hsa-mir-182 , MIR182; hsa-mir-454 , MIR454; hsa-mir-96 , MIR96; hsa-mir-183 , MIR183; hsa-mir-549 , MIR549; hsa-mir-301a , MIR301A; hsa-mir-548f-1 , MIR548F1; hsa-mir-301b , MIR301B; hsa-mir-103-1 , MIR1031; hsa-mir-18a , MIR18A; hsa-mir-147b , MIR147B; hsa-mir-4326, MIR4326; and hsa-mir-573, MIR573 or one or more lncRNA or ncRNA sequences selected from the list in Figure 39; or

d) a solid tissue cancer including colorectal adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, uterine carcinosarcoma, lung adenocarcinoma, lung squamous cell carcinoma, head & neck squamous cell carcinoma, prostate

adenocarcinoma, invasive urothelial bladder cancer, liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma, wherein the one or more markers in a set comprise one or more Exon RNA sequences selected from the list in Figure 40; or

e) a solid tissue cancer including colorectal adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, uterine carcinosarcoma, lung adenocarcinoma, lung squamous cell carcinoma, head & neck squamous cell carcinoma, prostate adenocarcinoma, invasive urothelial bladder cancer, liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma, wherein, the one or more markers in a set comprise one or more mRNA sequences, protein expression levels, protein product concentrations, cytokines, or autoantibody to the protein product selected from the list in Figure 41 or from the group consisting of : (Protein name , UniProt ID); Uncharacterized protein C19orf48 , Q6RUI8; Protein FAM72B , Q86X60; Protein FAM72D , Q6L9T8; Hydroxyacylglutathione hydrolase-like protein , Q6PII5; Putative methyltransferase NSUN5 , Q96P11; RNA pseudouridylate synthase domain-containing protein 1 , Q9UJJ7; Collagen triple helix repeat-containing protein 1 , Q96CG8; Interleukin-11 . P20809; Stromelysin-2 , P09238; Matrix metalloproteinase-9 , P14780; Podocan-like protein 1 , Q6PEZ8;Putative peptide YY-2 , Q9NRI6; Osteopontin , P10451; Sulfhydryl oxidase 2 , Q6ZRP7; Glypican-2 , Q8N158; Macrophage migration inhibitory factor , P14174; Peptidyl-prolyl cis-trans isomerase A , P62937; and Calreticulin , P27797; or

f) a solid tissue cancer including colorectal adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, uterine carcinosarcoma, lung adenocarcinoma, lung squamous cell carcinoma, head & neck squamous cell carcinoma, prostate adenocarcinoma, invasive urothelial bladder cancer, liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma, wherein the one or more markers in a set comprise one or more mutations, insertions, deletions, copy number changes, or expression changes in a gene selected from the group consisting of TP53 (tumor protein p53), TTN (titin), MUC16 (mucin 16), and KRAS (Ki-ras2 Kirsten rat sarcoma viral oncogene homolog); or

g) colon adenocarcinoma, rectal adenocarcinoma, stomach adenocarcinoma, or esophageal carcinoma, wherein at least 50% of the markers in a set each comprise one or more methylated cytosine residues of a CpG sequence, or the

complement of one or more methylated cytosine residues of a CpG sequence selected from the list in Figure 28 or in Figure 45 or in Figure 60; or

h) colon adenocarcinoma, rectal adenocarcinoma, stomach adenocarcinoma, or esophageal carcinoma, wherein at least 50% of the markers in a set each comprise of one or more methylated residues of one or more chromosomal sub-regions selected from the list in Figure 29 or in Figure 46 or in Figure 61; or

i) colon adenocarcinoma, rectal adenocarcinoma, stomach adenocarcinoma, or esophageal carcinoma, wherein the one or more markers in a set comprise one or more miRNA sequences selected from the list in Figure 23 or the group of (mir ID , Gene ID): hsa-mir-624 , MIR624, or one or more lncRNA or ncRNA sequences selected from the list in Figure 24 or the group of [Gene ID, Coordinate (GRCh38)], ENSEMBL ID: LINC01558, chr6:167784537-167796859, or ENSG00000146521.8; or

j) colon adenocarcinoma, rectal adenocarcinoma, stomach adenocarcinoma, or esophageal carcinoma, wherein the one or more markers in a set comprise one or more Exon RNA sequences selected from the list in Figure 25 or in Figure 44; or

k) colon adenocarcinoma, rectal adenocarcinoma, stomach adenocarcinoma, or esophageal carcinoma, wherein, the one or more markers in a set comprise one or more mRNA sequences, protein expression levels, protein product concentrations, cytokines, or autoantibody to the protein product selected from the list in Figure 26 or Figure 27, or from the group consisting of: (Gene Symbol , Chromosome Band , Gene Title , UniProt ID): SELE , 1q22-q25 , selectin E , P16581; OTUD4 , 4q31.21 , OTU domain containing 4 , Q01804; BPI , 20q11.23 , bactericidal/permeability-increasing protein , P17213; ASB4 , 7q21-q22 , ankyrin repeat and SOCS box containing 4 , Q9Y574; C6orf123 , 6q27 , chromosome 6 open reading frame 123 , Q9Y6Z2; KPNA3 , 13q14.3 , karyopherin alpha 3 (importin alpha 4) , and O00505; NUP98 , 11p15 , nucleoporin 98kDa , P52948 or group of : (Protein name , UniProt ID); Bactericidal permeability-increasing protein (BPI) (CAP 57), or P17213; or

l) colon adenocarcinoma, rectal adenocarcinoma, stomach adenocarcinoma, or esophageal carcinoma, wherein the one or more markers in a set comprise one or more mutations, insertions, deletions, copy number changes, or expression changes in a gene selected from the group consisting of APC (APC regulator of WNT signaling pathway), ATM (ATM serine/threonine kinase), CSMD1 (CUB and Sushi multiple domains 1), DNAH11 (dynein axonemal heavy chain 11), DST (dystonin), EP400 (E1A binding protein p400), FAT3 (FAT atypical cadherin 3), FAT4 (FAT atypical cadherin 4), FLG (filaggrin), GLI3 (GLI family zinc finger 3), KRAS (Ki-ras2 Kirsten rat sarcoma viral oncogene homolog), LRP1B (LDL receptor related protein 1B), MUC16 (mucin 16,

cell surface associated), OBSCN (obscurin, cytoskeletal calmodulin and titin-interacting RhoGEF), PCLO (piccolo presynaptic cytomatrix protein), PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha), RYR2 (ryanodine receptor 2), SYNE1 (spectrin repeat containing nuclear envelope protein 1), TP53 (tumor protein p53), TTN (titin), and UNC13C (unc-13 homolog C); or

m) breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, or uterine carcinosarcoma, wherein , at least 50% of the markers in a set each comprise one or more methylated cytosine residues of a CpG sequence, or the complement of one or more methylated cytosine residues of a CpG sequence selected from the list in Figure 47 or in Figure 62; or

n) breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, or uterine carcinosarcoma, wherein at least 50% of the markers in a set each comprise one or more methylated residues of one or more chromosomal sub-regions selected from the list in Figure 48 or in Figure 63; or

o) breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, or uterine carcinosarcoma, wherein the one or more markers in a set comprise one or more miRNA sequences (mir ID , Gene ID) selected from hsa-mir-1265 , MIR1265; or

p) breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, or uterine carcinosarcoma, wherein the one or more markers in a set comprise one or more Exon RNA sequences selected from the group consisting of (Exon location, Gene): chr2:179209013-179209087:+ , OSBPL6; chr2:179251788-179251866:+ , OSBPL6; and chr2:179253736-179253880:+ , OSBPL6; or

q) breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and adenocarcinoma, or uterine carcinosarcoma, wherein the one or more markers in a set comprise one or more mRNA sequences, protein expression levels, protein product concentrations, cytokines, or autoantibody to the protein product selected from the group consisting of (Gene Symbol , Chromosome Band , Gene Title , UniProt ID): RSPO2 , 8q23.1 , R-spondin 2 , Q6UXX9; KLC4 , 6p21.1 , kinesin light chain 4 , Q9NSK0; GLRX , 5q14 , glutaredoxin (thioltransferase) , P35754 and (Protein name, UniProt ID): R-spondin-2 (Roof plate-specific spondin-2) (hRspo2),or Q6UXX9; or

r) breast lobular and ductal carcinoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and

adenocarcinoma, or uterine carcinosarcoma, wherein the one or more markers in a set comprise one or more mutations, insertions, deletions, copy number changes, or expression changes in a gene selected from the group consisting of PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha), and TTN (titin); or

s) lung adenocarcinoma, lung squamous cell carcinoma, or head & neck squamous cell carcinoma, wherein at least 50% of the markers in a set each comprise one or more methylated cytosine residues of a CpG sequence, or the complement of one or more methylated cytosine residues of a CpG sequence selected from the list in Figure 49 or in Figure 64; or

t) lung adenocarcinoma, lung squamous cell carcinoma, or head & neck squamous cell carcinoma, wherein at least 50% of the markers in a set each comprise one or more methylated residues of one or more chromosomal sub-regions selected from the list in Figure 50 or in Figure 65; or

u) lung adenocarcinoma, lung squamous cell carcinoma, or head & neck squamous cell carcinoma, wherein the one or more markers in a set comprise one or more miRNA sequences selected from (mir ID , Gene ID): hsa-mir-28 , MIR28; or

v) lung adenocarcinoma, lung squamous cell carcinoma, or head & neck squamous cell carcinoma, wherein the one or more markers in a set comprise one or more Exon RNA sequences selected from the group consisting of (Exon location, Gene): chr2: chr1:93307721-93309752:- , FAM69A; chr1:93312740-93312916:- , FAM69A; chr1:93316405-93316512:- , FAM69A; chr1:93341853-93342152:- , FAM69A; chr1:93426933-93427079:- , FAM69A; chr7:40221554-40221627:+ , C7orf10; chr7:40234539-40234659:+ , C7orf10;chr8:22265823-22266009:+, SLC39A14; chr8:22272293-22272415:+, SLC39A14; chr14:39509936-39510091:-, SEC23A; and chr14:39511990-39512076:- , SEC23A; or

w) is lung adenocarcinoma, lung squamous cell carcinoma, or head & neck squamous cell carcinoma, wherein the one or more markers in a set comprise one or more mRNA sequences, protein expression levels, protein product concentrations, cytokines, or autoantibody to the protein product selected from the group consisting of (Gene Symbol , Chromosome Band , Gene Title , UniProt ID): STRN3 , 14q13-q21 , striatin, calmodulin binding protein 3 , Q13033; LRRC17 , 7q22.1 , leucine rich repeat containing 17 , Q8N6Y2; FAM69A , 1p22 , family with sequence similarity 69, member A , Q5T7M9; ATF2 , 2q32 , activating transcription factor 2 , P15336; BHMT , 5q14.1 , betaine--homocysteine S-methyltransferase , Q93088; ODZ3/TENM3 , 4q34.3-q35.1 , teneurin transmembrane protein 3 , Q9P273; ZFHX4 , 8q21.11 , zinc finger homeobox 4 , Q86UP3 or (Protein name , UniProt ID): Leucine-rich repeat-containing protein 17 (p37NB) , Q8N6Y2; or

x) lung adenocarcinoma, lung squamous cell carcinoma, or head & neck squamous cell carcinoma, wherein the one or more markers in a set comprise one or more mutations, insertions, deletions, copy number changes, or expression changes in a gene selected from the group consisting of CSMD3 (CUB and Sushi multiple domains 3), DNAH5 (dynein axonemal heavy chain 5), FAT1 (FAT atypical cadherin 1), FLG (filaggrin), KRAS (Ki-ras2 Kirsten rat sarcoma viral oncogene homolog), LRP1B (LDL receptor related protein 1B), MUC16 (mucin 16, cell surface associated), PCLO (piccolo presynaptic cytomatrix protein), PKHD1L1 (PKHD1 like 1), RELN (reelin), RYR2 (ryanodine receptor 2), SI (sucrase-isomaltase), SYNE1 (spectrin repeat containing nuclear envelope protein 1), TP53 (tumor protein p53), TTN (titin), USH2A (usherin), and XIRP2 (xin actin binding repeat containing 2); or

y) prostate adenocarcinoma or invasive urothelial bladder cancer, wherein at least 50% of the markers in a set each comprise one or more methylated cytosine residues of a CpG sequence, or the complement of one or more methylated cytosine residues of a CpG sequence selected from the list in Figure 51 or in Figure 66; or

z) prostate adenocarcinoma or invasive urothelial bladder cancer, wherein at least 50% of the markers in a set each comprise one or more methylated residues of one or more chromosomal sub-regions selected from the list in Figure 52 or in Figure 67; or

aa) prostate adenocarcinoma or invasive urothelial bladder cancer, wherein the one or more markers in a set comprise one or more miRNA sequences selected from the list in Figure 74 or one or more lncRNA or ncRNA sequences selected from the group consisting of (mir ID , Gene ID): hsa-mir-491 , MIR491; hsa-mir-1468 , MIR1468 and one or more lncRNA or ncRNA sequences selected from the group consisting of [Gene ID , Coordinate (GRCh38) , ENSEMBL ID]: AC007383.3 , chr2:206084605-206086564 , ENSG00000227946.1; and LINC00324 , chr17:8220642-8224043 , ENSG00000178977.3; or

ba) prostate adenocarcinoma or invasive urothelial bladder cancer, wherein the one or more markers in a set compriseing one or more Exon RNA sequences (Exon location, Gene) selected from: chr21:45555942-45556055:+ , C21orf33; or

ca) prostate adenocarcinoma or invasive urothelial bladder cancer, wherein the one or more markers in a set comprise one or more mRNA sequences, protein expression levels, protein product concentrations, cytokines, or autoantibody to the protein product selected from the group:(Gene Symbol , Chromosome Band , Gene Title , UniProt ID): PMM1 , 22q13 , phosphomannomutase 1 , Q92871; or

da) prostate adenocarcinoma or invasive urothelial bladder cancer, wherein the one or more markers in a set comprise one or more mutations, insertions, deletions, copy number changes, or expression changes in a gene selected from the group

consisting of BAGE2 (BAGE family member 2), DNM1P47 (dynamin 1 pseudogene 47), FRG1BP (region gene 1 family member B, pseudogene), KRAS (Ki-ras2 Kirsten rat sarcoma viral oncogene homolog), RP11-156P1.3, TTN (titin), and TUBB8P7 (tubulin beta 8 class VIII pseudogene 7); or

ea) liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma, wherein at least 50% of the markers in a set each comprise one or more methylated cytosine residues of a CpG sequence, or the complement of one or more methylated cytosine residues of a CpG sequence selected from the list in Figure 56 or in Figure 68; or

fa) liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma, wherein at least 50% of the markers in a set each comprise one or more methylated residues of one or more chromosomal sub-regions selected from the list in Figure 57 or in Figure 69; or

ga) liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma, wherein the one or more markers in a set comprise one or more miRNA sequences selected from (mir ID , Gene ID): hsa-mir-132 , MIR132 and one or more lncRNA or ncRNA sequences selected from the list in Figure 53; or

ha) liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma, wherein the one or more markers in a set comprise one or more Exon RNA sequences selected from the list in Figure 54; or

ia) liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma, wherein the one or more markers in a set comprise one or more mRNA sequences, protein expression levels, protein product concentrations, cytokines, or autoantibody to the protein product selected from the list in Figure 55 or from the group consisting of (Protein name , UniProt ID); Gelsolin (AGEL) (Actin-depolymerizing factor) (ADF) (Brevin) , P06396; Pro-neuregulin-2 , O14511; CD59 glycoprotein (1F5 antigen) (20 kDa homologous restriction factor) (HRF-20) (HRF20) (MAC-inhibitory protein) (MAC-IP) (MEM43 antigen) (Membrane attack complex inhibition factor) (MACIF) (Membrane inhibitor of reactive lysis) (MIRL) (Protectin) (CD antigen CD59) , P13987; and Divergent protein kinase domain 2B (Deleted in autism-related protein 1) , Q9H7Y0; or

ja) liver hepatoceullular carcinoma, pancreatic ductal adenocarcinoma, or gallbladder adenocarcinoma, wherein the one or more markers in a set comprise one or more mutations, insertions, deletions, copy number changes, or expression changes in a gene selected from the group consisting of KRAS (Ki-ras2 Kirsten rat sarcoma viral oncogene homolog), MUC16 (mucin 16, cell surface associated), MUC4 (mucin 4, cell surface associated), TP53 (tumor protein p53), and TTN (titin).