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Methods, treatment, and compositions for characterizing thyroid nodule

Abstract

The current disclosure provides, inter alia, method of determining benign nodules from thyroid cancer in a subject that is found to have a thyroid nodule, method of treating thyroid cancer in a subject detected to have thyroid cancer by the method of the current disclosure, compositions for determining benign nodules from thyroid cancer in a subject, and kits including reagents and composition for determining benign nodules from thyroid cancer in a subject.

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Background/Summary

CROSS-REFERENCE TO RELATED APPLICATIONS (1) This application is a continuation of U.S. patent application Ser. No. 15/217,645, filed Jul. 22, 2016, now U.S. Pat. No. 11,505,829, issued on Nov. 22, 2022, which claims the benefit of priority under 35 U.S.C. § 119 (e) to U.S. Provisional Application No. 62/196,678, filed Jul. 24, 2015, the content of which are incorporated herein by reference in their entireties.

INCORPORATION-BY-REFERENCE OF SEQUENCE LISTING
(1) The content of the XML file named "048440-573C01US_Sequence_Listing.xml", which was created on Dec. 2, 2022, and is 22,950 kilobytes in size, is hereby incorporated by reference in its

entirety.

BACKGROUND OF THE DISCLOSURE

(2) Palpable thyroid nodules are typically detected in 2-6% of the population, and this increases to 19-35% with ultrasound detection (Dean D S and Gharib H. Best Pract Res Clin Endocrinol Metab 2008; 22:901-11). Approximately 5-15% of thyroid nodules are found to be thyroid cancer, making the existence of a nodule clinically relevant. Fine needle aspiration (FNA) with cytology is currently the standard diagnostic procedure used to evaluate thyroid nodules. However, in as many as 30% of cases, the cytological diagnosis is indeterminate because of cytological features that overlap between benign and malignant nodules. For most indeterminate cases half or the entire thyroid is resected, yet as many as 80% of these cases are found to be benign.

(3) Most thyroid nodules do not cause symptoms. Often, thyroid nodules are discovered incidentally during a routine physical examination or on imaging tests like CT scans or neck ultrasound done for completely unrelated reasons. Occasionally, patients themselves find thyroid nodules by noticing a lump in their neck while looking in a mirror, buttoning their collar, or fastening a necklace. Abnormal thyroid function tests may occasionally be the reason a thyroid nodule is found. Thyroid nodules may produce excess amounts of thyroid hormone causing hyperthyroidism. However, most thyroid nodules, including those that cancerous, are actually non-functioning, meaning current diagnostic test readouts such as the level of Thyroid-Stimulating Hormone (TSH) are normal. Rarely, patients with thyroid nodules may complain of pain in the neck, jaw, or ear. If a nodule is large enough to compress the windpipe or esophagus, it may cause difficulty with breathing, swallowing, or cause a “tickle in the throat”. Even less commonly, hoarseness can be caused if the nodule invades the nerve that controls the vocal cords but this is usually related to thyroid cancer.

(4) Molecular testing is a potential alternative to cytopathological examination. However, FNA molecular testing based on DNA mutations frequently fails. There are two major reasons for this failure: (i) not all papillary thyroid carcinoma (PTC) specimens are characterized by a common set of cancer associated mutations, and (ii) cancer associated mutations like KRAS are frequently found in benign thyroid nodule (BTN) specimens. At the same time commercial diagnostic tests for FNA based on transcriptional activity and currently implemented in clinical practice is complicated due to RNA instability and associated with only an approximately 50% positive predictive value. Thus, there is an urgent need for highly sensitive, low cost biomarker panels that can accurately diagnose thyroid nodules from FNA biopsies.

BRIEF SUMMARY OF THE DISCLOSURE

(5) The present subject matter provides, inter alia, a method of determining benign nodules from thyroid cancer in a subject that is found to have a thyroid nodule, a method of treating thyroid cancer in a subject detected to have thyroid cancer, compositions for determining benign nodules from thyroid cancer in a subject, and kits including reagents and compositions for determining benign nodules from thyroid cancer in a subject.

(6) In embodiments, aspects of the present subject matter provide a method of detecting methylation or unmethylation of a thyroid nodule DNA of a subject, the method including: (i) isolating DNA from a thyroid nodule of the subject thereby forming isolated thyroid nodule DNA, (ii) contacting the isolated thyroid nodule DNA with a bisulfite salt (such as sodium bisulfite) thereby forming a reacted thyroid nodule DNA, (iii) detecting the presence or absence of uracil in the reacted thyroid nodule DNA at a methylation site set forth in Table 1, thereby detecting methylation or unmethylation of the thyroid nodule DNA of the subject.

(7) Also provided is a method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof. The method includes isolating DNA from a thyroid nodule of the subject thereby forming isolated thyroid nodule DNA. The isolated thyroid nodule DNA is contacted with sodium bisulfite thereby forming a reacted thyroid nodule DNA. The presence or absence of uracil is detected in the reacted thyroid nodule DNA at a methylation site set forth in Table 1 thereby determining thyroid cancer in the subject.

(8) In embodiments, provided herein is a method of treating thyroid cancer in a subject by

administering to the subject an active agent for treating thyroid cancer. The method includes identifying the subject for treatment by a method including isolating DNA from a thyroid nodule of the subject thereby forming isolated thyroid nodule DNA. The isolated thyroid nodule DNA is contacted with sodium bisulfite thereby forming a reacted thyroid nodule DNA. The presence or absence of uracil in the reacted thyroid nodule DNA is detected at a methylation site set forth in Table 1 thereby determining thyroid cancer in the subject.

(9) Also included herein is a deoxyribonucleic acid 5 to 100, 5 to 200, 5 to 300, or at least about 5, 50, 100, 150, 200, 250, 300, or more nucleotides in length including a uracil-containing sequence identical to at least a 5 contiguous nucleotides within a sequence including SEQ ID NO: 1 to SEQ ID NO:550.

(10) In embodiments, provided herein is an oligonucleotide 5 to 100, 5 to 200, 5 to 300, or at least about 5, 50, 100, 150, 200, 250, 300, or more nucleotides in length including identical or complementary to at least 5, 10, 20, 25, 50, 100, 150, 200, 250, or 300 contiguous nucleotides within a sequence including SEQ ID NO:1 to SEQ ID NO:550.

(11) Aspects of the present subject matter also include a deoxyribonucleic acid including SEQ ID NO: 551 to SEQ ID NO: 782, in which the nucleic acid is hybridized to a complementary DNA sequence having uridine or cytosine.

(12) Also provided is a kit including a plurality (e.g., at least about 10, 20, 40, 50, 100, 150, 200, 225, or 232) nucleic acids each independently comprising SEQ ID NO: 551 to SEQ ID NO: 782, in which the nucleic acids do not simultaneously include the same sequence of SEQ ID NO: 551 to SEQ ID NO: 782.

(13) Aspects of the present subject matter also provide a system for detecting methylation or unmethylation of a thyroid nodule deoxyribonucleic acid (DNA) of a subject. The system can include at least one processor; and at least one memory including program code which when executed by the at least one memory provides operations. The operations can include: isolating DNA from a thyroid nodule of the subject thereby forming isolated thyroid nodule DNA; contacting the isolated thyroid nodule DNA with bisulfite salt thereby forming a reacted thyroid nodule DNA; detecting a presence or absence of uracil in the reacted thyroid nodule DNA at a plurality of methylation sites set forth in Table 1, thereby detecting methylation or unmethylation of the thyroid nodule DNA of the subject; and generating a diagnosis for the subject based at least in part on the presence or absence of uracil in the reacted thyroid nodule DNA at the plurality of methylation sites set forth in Table 1; and providing, via a user interface, the diagnosis for the subject.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

(1) FIGS. **1**A-**1**B show a drawing defining a threshold for thyroid adenoma specific signature for individual cytosine regions. FIG. **1**A: Adenoma specific hypomethylation signature. FIG. **1**B: Adenoma specific hypermethylation signature.

(2) FIGS. **2**A and **2**B show 364 cytosines associated with BTN or PTC specific DNA methylation changes. Legend (FIG. **2**A): Cancer specific signature (gray); benign specific signature (black). FIG. **2**B: 364 CpG sites associated with benign- and thyroid cancer-specific DNA methylation changes. Each row represents a single cytosine. Each column represents tissue specimen. Dark gray, light gray and black indicate high, low and medium levels of DNA methylation, respectively. Abbreviation “A” is for thyroid benign nodule and “T” is for thyroid cancer.

(3) FIGS. **3**A-**3**C depict exemplary thyroid cancer diagnostics based on DNA methylation signatures. FIG. **3**A: Thyroid cancer diagnostics based on benign DNA methylation signature, cancer DNA methylation signature and cancer risk scores. FIG. **3**B: DNA methylation signatures for malignant and benign thyroid nodules according to leave one-out-cross-validation technique. Specimens with indeterminate epigenetic signature are underlined. Abbreviation “A” is for thyroid benign nodule and “T” is for thyroid cancer. FIG. **3**C: Algorithm for the diagnosis prediction based on BTN, PTC and

cancer risk scores.
(4) FIG. **4** depicts a block diagram illustrating an exemplary thyroid cancer diagnostics system.
(5) FIG. **5** depicts a flowchart illustrating an exemplary process for diagnosing thyroid cancer.
(6) FIG. **6** depicts a flowchart illustrating an exemplary process for diagnosing thyroid cancer.
DETAILED DESCRIPTION OF THE DISCLOSURE
(7) Provided herein are, inter alia, compositions, methods, kits, and systems for detecting unmethylated DNA. In embodiments, compositions, methods, kits, and systems for detecting unmethylated DNA from thyroid nodule are included herein.
(8) The following definitions are included for the purpose of understanding the present subject matter and for constructing the appended patent claims. Abbreviations used herein have their conventional meaning within the chemical and biological arts.
Definitions
(9) The term “thyroid nodule” is used according to its plain ordinary meaning and refers to an abnormal growth of thyroid cells. The abnormal growth may form, for example, a mass or lump within or on the thyroid gland. The mass or lump may be fluid-filled or solid. The thyroid nodules may be benign (noncancerous) or cancerous.
(10) Thyroid fine needle aspiration biopsy (FNA or FNAB): For a fine needle biopsy, a needle is used to withdraw cells from a thyroid nodule. In embodiments, several samples are taken from different parts of the nodule, e.g., to increase the chance of finding cancerous cells if they are present. In embodiments, a sample is taken from one part of the nodule. In embodiments, examination of the cells under a microscope is not necessary. In non-limiting examples, the needle used for FNA is a 20-35 gauge needle (such as a 23, 24 or 25 gauge needle).
(11) The term “disease” refers to any deviation from the normal health of a mammal and includes a state when disease symptoms are present, as well as conditions in which a deviation (e.g., infection, gene mutation, genetic defect, etc.) has occurred, but symptoms are not yet manifested. According to the present disclosure, the methods disclosed herein are suitable for use in a patient that is a member of the Vertebrate class, Mammalia, including, without limitation, primates, livestock and domestic pets (e.g., a companion animal). Typically, a patient will be a human patient. As used herein, a “symptom” of a disease includes and clinical or laboratory manifestation associated with the disease, and is not limited to what a subject can feel or observe.
(12) The terms “subject,” “patient,” “individual,” and the like as used herein are not intended to be limiting and can be generally interchanged. That is, an individual described as a “patient” does not necessarily have a given disease, but may be merely seeking medical advice.
(13) The term “subject” as used herein includes all members of the animal kingdom that may suffer from the indicated disorder. In some aspects, the subject is a mammal, and in some aspects, the subject is a human.
(14) It must be noted that as used herein and in the appended embodiments, the singular forms “a,” “an,” and “the” include the plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to “a disease,” “a disease state”, “a nucleic acid” or “a CpG site” is a reference to one or more such embodiments, and includes equivalents thereof known to those skilled in the art and so forth.
(15) Throughout the description and claims of this specification the word “comprise” and other forms of the word, such as “comprising” and “comprises,” means including but not limited to, and is not intended to exclude, for example, other components.
(16) A “control” sample or value refers to a sample that serves as a reference, usually a known reference, for comparison to a test sample. For example, a test sample can be taken from a patient suspected or at risk of having thyroid cancer and compared to samples from a known thyroid cancer patient, or a known normal (non-disease) individual. A control can also represent an average value gathered from a population of similar individuals, e.g., thyroid cancer patients or healthy individuals with a similar medical background, same age, weight, etc. A control value can also be obtained from the same individual, e.g., from an earlier-obtained sample, prior to disease, or prior to treatment. One

of skill will recognize that controls can be designed for assessment of any number of parameters.
(17) One of skill in the art will understand which controls are valuable in a given situation and be able to analyze data based on comparisons to control values. Controls are also valuable for determining the significance of data. For example, if values for a given parameter are widely variant in controls, variation in test samples will not be considered as significant.
(18) The term “diagnosis” refers to a relative probability that a disease is present in the subject. Similarly, the term “prognosis” refers to a relative probability that a certain future outcome may occur in the subject. For example, in the context of the present disclosure, prognosis can refer to the likelihood that an individual will develop a disease, or the likely severity of the disease (e.g., severity of symptoms, rate of functional decline, survival, etc.). The terms are not intended to be absolute, as will be appreciated by any one of skill in the field of medical diagnostics.
(19) “Nucleic acid” or “oligonucleotide” or “polynucleotide” or grammatical equivalents used herein means at least two nucleotides covalently linked together. Oligonucleotides are typically from about 5, 6, 7, 8, 9, 10, 12, 15, 25, 30, 40, 50 or more nucleotides in length, up to about 100 nucleotides in length. Nucleic acids, including ribonucleic acids (RNA) and deoxyribonucleic acids (DNA), and polynucleotides are a polymers of any length, including longer lengths, e.g., 200, 300, 500, 1000, 2000, 3000, 5000, 7000, 10,000, etc. A nucleic acid of the present invention will generally contain phosphodiester bonds, although in some cases, nucleic acid analogs are included that may have alternate backbones, comprising, e.g., phosphoramidate, phosphorothioate, phosphorodithioate, or O-methylphophoroamidite linkages (see Eckstein, Oligonucleotides and Analogues: A Practical Approach, Oxford University Press); and peptide nucleic acid backbones and linkages. Other analog nucleic acids include those with positive backbones; non-ionic backbones, and non-ribose backbones, including those described in U.S. Pat. Nos. 5,235,033 and 5,034,506, and Chapters 6 and 7, ASC Symposium Series 580, *Carbohydrate Modifications in Antisense Research*, Sanghui & Cook, eds. Nucleic acids containing one or more carbocyclic sugars are also included within one definition of nucleic acids. Modifications of the ribose-phosphate backbone may be done for a variety of reasons, e.g., to increase the stability and half-life of such molecules in physiological environments or as probes on a biochip. Mixtures of naturally occurring nucleic acids and analogs can be made; alternatively, mixtures of different nucleic acid analogs, and mixtures of naturally occurring nucleic acids and analogs may be made.
(20) The term “bp” and the like refer, in the usual and customary sense, to the indicated number of base pairs.
(21) The terms “identical” or percent “identity,” in the context of two or more nucleic acids (e.g., genomic sequences or subsequences or coding sequences) or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (i.e., 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity over a specified region), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Such sequences are then said to be “substantially identical.” This definition also refers to the compliment of a test sequence. Optionally, the identity exists over a region that is at least about 10 to about 100, about 20 to about 75, about 30 to about 50 amino acids or nucleotides in length.
(22) An example of algorithms suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al., *Nuc. Acids Res.* 25:3389-3402 (1977) and Altschul et al., *J. Mol. Biol.* 215:403-410 (1990), respectively. As will be appreciated by one of skill in the art, the software for performing BLAST analyses is publicly available through the website of the National Center for Biotechnology Information.
(23) A “label” or a “detectable moiety” is a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. For example, useful labels include .sup.32P, fluorescent dyes, electron-dense reagents, enzymes (e.g., as commonly used in an ELISA),

biotin, digoxigenin, or haptens and proteins or other entities which can be made detectable, e.g., by incorporating a radiolabel into a peptide or antibody specifically reactive with a target peptide. Any method known in the art for conjugating an antibody to the label may be employed, e.g., using methods described in Hermanson, Bioconjugate Techniques 1996, Academic Press, Inc., San Diego.
(24) The term “associated” or “associated with” in the context of a substance (e.g., level of uracil or methylation level in a thyroid nodule) does not necessarily mean that the disease is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function (i.e., level of uracil in the regions of chromosomes assayed).
(25) The term “unmethylated DNA” or “demethylated DNA” means DNA that lacks a methyl group conjugated to cytosine in a segment of the DNA. DNA methylation typically occurs in a CpG dinucleotide context. DNA methylation at 5′ position of cytosine may have the specific effect on gene expression in vivo. DNA methylation may also form the basis of epigenetic structure, which typically enables a single cell to grow into multiple organs or perform multiple functions.
(26) The CpG sites or CG sites are regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide in the linear sequence of bases along its length. “CpG” is shorthand for “-C-phosphate-G-”, that is, cytosine and guanine separated by only one phosphate; phosphate links any two nucleosides together in DNA. The “CpG” notation is used to distinguish this linear sequence from the CG base-pairing of cytosine and guanine. The CpG notation can also be interpreted as the cytosine being 5′ prime to the guanine base.
(27) In embodiments, methylation is detected based on a chemical reaction of sodium bisulfite with DNA that converts unmethylated cytosines of CpG dinucleotides to uracil or UpG. However, methylated cytosine is not converted in this process, the methods described herein allow determination of methylation status as methylated or unmethylated.
(28) Evaluation of Thyroid Fine Needle Biopsies by Visual Examination
(29) Cells in a thyroid vine needle biopsy sample may be examined under a microscope by, e.g., a pathologist. The report of a thyroid fine needle biopsy followed by examination under a microscope will usually indicate one of the following findings:
(30) 1. The nodule is benign (noncancerous). This result is obtained in up to 80% of biopsies. The risk of overlooking a cancer when the biopsy is benign is generally less than 3 in 100 tests or 3%. This is even lower when the biopsy is reviewed by an experienced pathologist at a major medical center. Generally, benign thyroid nodules do not need to be removed unless they are causing symptoms like choking or difficulty swallowing. Follow up ultrasound exams are important. Occasionally, another biopsy may be required in the future, especially if the nodule grows over time.
(31) 2. The nodule is malignant (cancerous) or suspicious for malignancy. A malignant result is obtained in about 5% of biopsies and is most often due to papillary cancer, which is the most common type of thyroid cancer. A malignant diagnosis has a >99% risk of cancer in the nodule. A suspicious biopsy has a 50-75% risk of cancer in the nodule. These diagnoses require surgical removal of the thyroid after consultation with the endocrinologist and surgeon.
(32) 3. The nodule is indeterminate. This is actually a group of several diagnoses that may occur in up to 30% of cases. An indeterminate finding means that even though an adequate number of cells was removed during the fine needle biopsy, examination with a microscope cannot reliably classify the result as benign or cancer. The biopsy may be indeterminate because the nodule is described as a Follicular Lesion. These nodules are cancerous 20-30% of the time. However, under the current state of the art, the diagnosis can only be made by surgery. Because the odds that the nodule is not a cancer are much better by surgery (70-80%), only the side of the thyroid with the nodule is usually removed. If a cancer is found, the remaining thyroid gland is usually removed as well. If the surgery confirms that no cancer is present, no additional surgery to “complete” the thyroidectomy is necessary.
(33) The biopsy may also be indeterminate because the cells from the nodule have features that cannot be placed in one of the other diagnostic categories. This diagnosis is called atypia, or a follicular lesion of undetermined significance. Diagnoses in this category will contain cancer rarely, so repeat evaluation with FNA or surgical biopsy to remove half of the thyroid containing the nodule

is usually recommended.
(34) 4. The biopsy may also be non-diagnostic or inadequate. This result indicates that not enough cells were obtained to make a diagnosis but is a common result if the nodule is a cyst. These nodules may require reevaluation with second fine needle biopsy, or may need to be removed surgically depending on the clinical judgment of the doctor.
(35) Methods, compositions, kits, and systems provided herein provide significant advantages over the visual examination of biopsies.
(36) Method of Detection Methylation Status of a Thyroid Nodule DNA
(37) In an aspect, provided herein is a method of detecting methylation or unmethylation of a thyroid nodule DNA of a subject. The method includes: (i) isolating a thyroid nodule DNA molecule from a thyroid nodule of the subject thereby forming an isolated thyroid nodule DNA molecule, (ii) contacting the isolated thyroid nodule DNA molecule with a bisulfite salt (such as sodium bisulfite) thereby forming a reacted thyroid nodule DNA molecule, (iii) detecting the presence or absence of uracil in the reacted thyroid nodule DNA molecule at a methylation site set forth in Table 1, thereby detecting methylation or unmethylation of the thyroid nodule DNA molecule of the subject. In embodiments, contacting the isolated thyroid nodule DNA with a bisulfite salt comprises adding a solution comprising the bisulfite salt to a solution comprising the isolated single stranded DNA.
(38) In an aspect, provided herein is a method of detecting methylation or unmethylation of a thyroid nodule DNA molecule of a subject comprising (i) isolating a plurality of thyroid nodule DNA molecules from the thyroid nodule of the subject thereby forming a plurality of isolated thyroid nodule DNA molecules, (ii) contacting the plurality of isolated thyroid nodule DNA molecules with the bisulfite salt thereby forming a plurality of reacted thyroid nodule DNA molecules, (iii) detecting the level of reacted thyroid nodule DNA molecules in the plurality of reacted thyroid nodule DNA molecules having a uracil at a methylation site set forth in Table 1, thereby detecting the level of methylation or unmethylation in the plurality of thyroid nodule DNA molecules of the subject.
(39) In an aspect, provided herein is a method of detecting methylation or unmethylation of a thyroid nodule DNA molecule of a subject comprising (i) isolating a plurality of thyroid nodule DNA molecules from the thyroid nodule of the subject thereby forming a plurality of isolated thyroid nodule DNA molecules, (ii) contacting the plurality of isolated thyroid nodule DNA molecules with the bisulfite salt thereby forming a plurality of reacted thyroid nodule DNA molecules, (iii) detecting the presence or absence of uracil in a reacted thyroid nodule DNA molecule at a methylation site set forth in Table 1, thereby detecting methylation or unmethylation of the thyroid nodule DNA molecule of the subject.
(40) In an aspect, provided herein is a method of detecting methylation or unmethylation of a thyroid nodule DNA of a subject. The method includes: (i) isolating a thyroid nodule DNA molecule from a thyroid nodule of the subject thereby forming an isolated thyroid nodule DNA molecule, (ii) contacting the isolated thyroid nodule DNA molecule with a bisulfite salt (such as sodium bisulfite) thereby forming a reacted thyroid nodule DNA molecule, (iii) amplifying the reacted thyroid nodule DNA molecule thereby forming a reacted thyroid nodule DNA amplicon molecule, (iv) detecting the presence or absence of thymidine in a reacted thyroid nodule DNA amplicon molecule at a methylation site set forth in Table 1, thereby detecting methylation or unmethylation of the thyroid nodule DNA molecule of the subject. In embodiments, contacting the isolated thyroid nodule DNA with a bisulfite salt comprises adding a solution comprising the bisulfite salt to a solution comprising the isolated single stranded DNA.
(41) In an aspect, provided herein is a method of detecting methylation or unmethylation of a thyroid nodule DNA molecule of a subject comprising (i) isolating a plurality of thyroid nodule DNA molecules from the thyroid nodule of the subject thereby forming a plurality of isolated thyroid nodule DNA molecules, (ii) contacting the plurality of isolated thyroid nodule DNA molecules with the bisulfite salt thereby forming a plurality of reacted thyroid nodule DNA molecules, (iii) amplifying the plurality of reacted thyroid nodule DNA molecules thereby forming a plurality of reacted thyroid nodule DNA amplicon molecules, (iv) detecting one or more thyroid nodule DNA

amplicon molecules within the plurality of reacted thyroid nodule DNA amplicon molecules having a thymidine at a methylation site set forth in Table 1, thereby detecting methylation or unmethylation of the thyroid nodule DNA molecule of the subject.

(42) In embodiments, detecting one or more thyroid nodule DNA amplicon molecules comprises detecting the level of one or more one or more thyroid nodule DNA amplicon molecules. In embodiments, detecting one or more thyroid nodule DNA amplicon molecules comprises detecting the level of reacted thyroid nodule DNA amplicon molecules in the plurality of reacted thyroid nodule DNA amplicon molecules having a thymidine at a methylation site set forth in Table 1, thereby detecting the level of methylation or unmethylation in the plurality of thyroid nodule DNA molecules of the subject.

(43) In embodiments, detecting a level includes determining the number (e.g. quantitating) or molecules having, e.g., a thymidine or a uracil. In embodiments, detecting a level includes detecting the portion or proportion of a population or plurality of molecules having, e.g., a thymidine or a uracil.

(44) In embodiments, the isolated thyroid nodule DNA sample is treated with a bisulfite reagent, e.g., a bisulfite salt (i.e., a process called DNA bisulfite conversion). Non-limiting examples of bisulfite salts include sodium bisulfite, potassium bisulfite, ammonium bisulfite, magnesium bisulfite, sodium metabisulfite, potassium metabisulfite, ammonium metabisulfite and magnesium metabisulfite. Bisulfite salts such as sodium bisulfite or ammonium bisulfite can convert cytosine to uracil and leave 5-methylcytosine (5-mC) the same. Thus after bisulfite treatment methylated cytosine in the DNA remains the same and unmodified cytosines will be changed to uracil. The bisulfite treatment can be performed by using the methods disclosed herein or in the art, and/or with commercial kits such as the Bisulflash DNA Modification Kit (Epigentek) and Imprint DNA Modification Kit (Sigma). For achieving the optimal bisulfite conversion, the bisulfite reaction should be carried out in an appropriate concentration of bisulfite reagents, appropriate temperature and appropriate reaction time period. A reagent such as potassium chloride that reduces thermophilic DNA degradation could also be used in bisulfite treatment so that the DNA bisulfite process can be much shorter without interrupting a completed conversion of unmethylated cytosine to uracil and without a significant thermodegradation of DNA resulted from depurination. In embodiments, a commercially available bisulfite treatment kit is used. A non-limiting example of such a kit is EZ DNA Methylation-Gold™ Kit (Zymo Research, Irvine, CA, USA).

(45) In embodiments, once DNA bisulfite conversion is complete, DNA is captured, desulphonated and washed. In embodiments, the bisulfite-treated DNA can be captured by, e.g., a solid matrix selected from silica salt, silica dioxide, silica polymers, magnetic beads, glass fiber, celite diatoms and nitrocellulose in the presence of high concentrations of chaotropic or non-chaotropic salts. In embodiments, the bisulfite-treated DNA is further desulphonated with an alkalized solution, preferably sodium hydroxide at concentrations from 10 mM to 300 mM. In embodiments, the DNA is then eluted and collected into a capped microcentrifuge tube. Non-limiting examples of elution solutions include DEPC-treated water and TE buffer (10 mM Tris-HCL, pH 8.0, and 1 mM EDTA).

(46) In embodiments, the reacted thyroid nodule DNA resulting from bisulfite treatment is amplified. In embodiments, detecting the presence or absence of uracil in reacted thyroid nodule DNA molecule at a methylation site comprises amplifying the reacted thyroid nodule DNA molecule thereby forming a reacted thyroid nodule DNA amplicon molecule, and detecting the presence or absence of thymidine in a reacted thyroid nodule DNA amplicon molecule at the methylation site. In embodiments, a polymerase chain reaction (PCR) method is used for amplifying the reacted thyroid nodule DNA. PCR methods are known to those of ordinary skill in the art. In general, the PCR reactions can be set up by adding sample, dNTPs, and appropriate polymerase such as Taq polymerase, primers, and a buffer.

(47) In embodiments, the method of detecting methylation or unmethylation of a thyroid nodule DNA of a subject, includes detecting methylation or unmethylation at a plurality of methylation sites set forth in Table 1. In embodiments, the plurality of methylation sites comprises at least about 2, 3, 4, 5,

10, 25, 50, 75, 80, 85, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 550, or 5-550 methylation sites. In embodiments, the plurality of methylation sites comprises less than about 550, 500, 450, 400, 350, 300, 250, 200, 150, 100, 90, 85, 80, 75, 50, 25, or 10 methylation sites. In embodiments, the plurality of methylation sites is about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 50, 75, 80, 85, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 550, or 5-550 methylation sites. In embodiments, the plurality of methylation sites includes two or more methylation sites set forth in Table 1 and no other methylation sites.

(48) In embodiments, the method includes detecting methylation or unmethylation of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 50, 100, 200, 300, 400, or 500 of the following sites: Chromosome 1 (Chr1) position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chromosome 2 (Chr2) position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chromosome 3 (Chr3) position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chromosome 4 (Chr4) position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chromosome 5 (Chr5) position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chromosome 6 (Chr6) position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chromosome 7 (Chr7) position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position 105079565, Chr7 position 105079631, Chr7 position 151425103, Chr7 position 151425104, Chromosome 8 (Chr8) position 11764017, Chr8 position 21647308, Chr8 position 22548399, Chr8 position 22548483, Chr8 position 133570537, Chr8 position 141320393, Chr8 position 141320410, Chromosome 9 (Chr9) position 6566568, Chr9 position 16197862, Chr9 position 34591313, Chr9 position 98225096, Chr9 position 126126741, Chr9 position 132083428, Chr9 position 136077410, Chr9 position 139655018, Chr9 position 140205985, Chr9 position 140205985, Chr9 position 140205997, Chromosome 10 (Chr10) position 3929071, Chr10 position 30047012, Chr10 position 79702989, Chr10 position 87984905, Chr10 position 94838789, Chr10 position 102131187, Chr10 position 104196489, Chr10 position 111766879, Chr10 position 112258886, Chr10 position 112258984, Chr10 position 112259015, Chr10 position 116391763, Chr10 position 120011530, Chr10 position 126172714, Chr10 position 126172747, Chromosome 11 (Chr11) position 556355, Chr11 position 821282, Chr11 position 12188937, Chr11 position 12188948, Chr11 position 12188995, Chr11 position 36057726, Chr11 position 48070143, Chr11 position 48070163, Chr11 position 48070166, Chr11 position 48070174, Chr11 position 65158294, Chr11 position 65158342, Chr11 position 65297089, Chr11

position 66104481, Chr11 position 66104485, Chr11 position 66104578, Chr11 position 68608767, Chr11 position 70236292, Chr11 position 70236320, Chr11 position 70236331, Chr11 position 115530032, Chr11 position 117950310, Chr11 position 117950329, Chr11 position 117950361, Chr11 position 117950362, Chr11 position 119293593, Chromosome 12 (Chr12) position 679803, Chr12 position 26039132, Chr12 position 31004558, Chr12 position 45610695, Chr12 position 45610701, Chr12 position 45610702, Chr12 position 45610706, Chr12 position 50286016, Chr12 position 52243258, Chr12 position 52243286, Chr12 position 54145732, Chr12 position 54145741, Chr12 position 54145825, Chr12 position 56115043, Chr12 position 66262229, Chr12 position 66262230, Chr12 position 66262233, Chr12 position 66262234, Chr12 position 77266621, Chr12 position 117580102, Chr12 position 123435962, Chr12 position 123436011, Chr12 position 123436065, Chr12 position 123540893, Chromosome 13 (Chr13) position 20735797, Chr13 position 23500419, Chr13 position 46771519, Chr13 position 46771520, Chr13 position 53313426, Chr13 position 113807393, Chromosome 14 (Chr14) position 38599118, Chr14 position 69170010, Chr14 position 75701632, Chr14 position 75701643, Chr14 position 90850454, Chr14 position 97524282, Chr14 position 103541602, Chr14 position 103768055, Chr14 position 104209000, Chr14 position 104209068, Chr14 position 104354645, Chr14 position 104360487, Chromosome 15 (Chr15) position 41068807, Chr15 position 61152225, Chr15 position 61152253, Chr15 position 61152313, Chr15 position 65186440, Chr15 position 68851629, Chr15 position 70667596, Chr15 position 70767206, Chr15 position 75251486, Chr15 position 77984014, Chr15 position 77989064, Chr15 position 83952081, Chr15 position 85402496, Chr15 position 85402497, Chr15 position 99417337, Chromosome 16 (Chr16) position 1231873, Chr16 position 1458639, Chr16 position 3023231, Chr16 position 23135832, Chr16 position 29616265, Chr16 position 31009547, Chr16 position 31009548, Chr16 position 31009590, Chr16 position 57793674, Chr16 position 57793715, Chr16 position 57793727, Chr16 position 70771056, Chr16 position 70771079, Chr16 position 70771141, Chr16 position 77332010, Chr16 position 78540378, Chr16 position 79333435, Chr16 position 84262419, Chr16 position 88701114, Chr16 position 89988308, Chr16 position 89988644, Chromosome 17 (Chr17) position 1509928, Chr17 position 1509945, Chr17 position 1509952, Chr17 position 1509953, Chr17 position 7644013, Chr17 position 16323460, Chr17 position 16323473, Chr17 position 16924561, Chr17 position 16924562, Chr17 position 16924594, Chr17 position 17717918, Chr17 position 17718591, Chr17 position 18139506, Chr17 position 35278031, Chr17 position 39677570, Chr17 position 40826257, Chr17 position 43037426, Chr17 position 43200096, Chr17 position 43200239, Chr17 position 43510142, Chr17 position 47987828, Chr17 position 48178379, Chr17 position 48596391, Chr17 position 48764165, Chr17 position 55701962, Chr17 position 73584599, Chr17 position 73993165, Chr17 position 75827716, Chr17 position 76882243, Chr17 position 78765910, Chr17 position 79544478, Chr17 position 80696474, Chromosome 18 (Chr18) position 19751759, Chr18 position 21440760, Chr18 position 45555437, Chr18 position 45555438, Chr18 position 46547891, Chr18 position 55888885, Chr18 position 56452096, Chr18 position 56452476, Chr18 position 56887181, Chr18 position 76002973, Chr18 position 77331090, Chromosome 19 (Chr19) position 677895, Chr19 position 884044, Chr19 position 884059, Chr19 position 884105, Chr19 position 884115, Chr19 position 1136511, Chr19 position 1177605, Chr19 position 1177612, Chr19 position 1177640, Chr19 position 1860601, Chr19 position 1860607, Chr19 position 2503954, Chr19 position 3434917, Chr19 position 3434921, Chr19 position 3434930, Chr19 position 3434939, Chr19 position 3434952, Chr19 position 3434954, Chr19 position 3434962, Chr19 position 3434964, Chr19 position 3434979, Chr19 position 3434985, Chr19 position 4052713, Chr19 position 4052714, Chr19 position 4052749, Chr19 position 4374591, Chr19 position 5013982, Chr19 position 5048836, Chr19 position 5048867, Chr19 position 5048877, Chr19 position 8367279, Chr19 position 8428573, Chr19 position 10254577, Chr19 position 10254578, Chr19 position 10463956, Chr19 position 10464137, Chr19 position 13203671, Chr19 position 13266925, Chr19 position 13266934, Chr19 position 13266970, Chr19 position 13842142, Chr19 position 14248494, Chr19 position 15375465, Chr19 position 17218912, Chr19 position 17346702, Chr19 position 17346702, Chr19 position 18157161, Chr19 position 18157221, Chr19 position 18157258, Chr19 position

18415877, Chr19 position 18415890, Chr19 position 30606642, Chr19 position 35531842, Chr19 position 44303112, Chr19 position 47173037, Chr19 position 47316268, Chr19 position 47778278, Chr19 position 47778298, Chromosome 20 (Chr20) position 34206950, Chr20 position 36771969, Chr20 position 48993661, Chr20 position 58406398, Chr20 position 61976049, Chr20 position 61976073, Chr20 position 62588571, Chr20 position 62588579, Chromosome 22 (Chr22) position 19738127, Chr22 position 35965176, Chr22 position 36549809, Chr22 position 36973375, Chr22 position 37447953, Chr22 position 37914998, Chr22 position 38307317, Chr22 position 39662794, and Chr22 position 45622980.

(49) In embodiments, the method includes detecting methylation or unmethylation of at least 1 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chr6 position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chr7 position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position 105079565, Chr7 position 105079631, Chr7 position 151425103, Chr7 position 151425104, Chr8 position 11764017, Chr8 position 21647308, Chr8 position 22548399, Chr8 position 22548483, Chr8 position 133570537, Chr8 position 141320393, Chr8 position 141320410, Chr9 position 6566568, Chr9 position 16197862, Chr9 position 34591313, Chr9 position 98225096, Chr9 position 126126741, Chr9 position 132083428, Chr9 position 136077410, Chr9 position 139655018, Chr9 position 140205985, Chr9 position 140205985, Chr9 position 140205997, Chr10 position 3929071, Chr10 position 30047012, Chr10 position 79702989, Chr10 position 87984905, Chr10 position 94838789, Chr10 position 102131187, Chr10 position 104196489, Chr10 position 111766879, Chr10 position 112258886, Chr10 position 112258984, Chr10 position 112259015, Chr10 position 116391763, Chr10 position 120011530, Chr10 position 126172714, Chr10 position 126172747, Chr11 position 556355, Chr11 position 821282, Chr11 position 12188937, Chr11 position 12188948, Chr11 position 12188995, Chr11 position 36057726, Chr11 position 48070143, Chr11 position 48070163, Chr11 position 48070166, Chr11 position 48070174, Chr11 position 65158294, Chr11 position 65158342, Chr11 position 65297089, Chr11 position 66104481, Chr11 position 66104485, Chr11 position 66104578, Chr11 position 68608767, Chr11 position 70236292, Chr11 position

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48993661, Chr20 position 58406398, Chr20 position 61976049, Chr20 position 61976073, Chr20 position 62588571, Chr20 position 62588579, Chr22 position 19738127, Chr22 position 35965176, Chr22 position 36549809, Chr22 position 36973375, Chr22 position 37447953, Chr22 position 37914998, Chr22 position 38307317, Chr22 position 39662794, and Chr22 position 45622980.

(50) In embodiments, the method includes detecting methylation or unmethylation of at least 2 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chr6 position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chr7 position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position 105079565, Chr7 position 105079631, Chr7 position 151425103, Chr7 position 151425104, Chr8 position 11764017, Chr8 position 21647308, Chr8 position 22548399, Chr8 position 22548483, Chr8 position 133570537, Chr8 position 141320393, Chr8 position 141320410, Chr9 position 6566568, Chr9 position 16197862, Chr9 position 34591313, Chr9 position 98225096, Chr9 position 126126741, Chr9 position 132083428, Chr9 position 136077410, Chr9 position 139655018, Chr9 position 140205985, Chr9 position 140205985, Chr9 position 140205997, Chr10 position 3929071, Chr10 position 30047012, Chr10 position 79702989, Chr10 position 87984905, Chr10 position 94838789, Chr10 position 102131187, Chr10 position 104196489, Chr10 position 111766879, Chr10 position 112258886, Chr10 position 112258984, Chr10 position 112259015, Chr10 position 116391763, Chr10 position 120011530, Chr10 position 126172714, Chr10 position 126172747, Chr11 position 556355, Chr11 position 821282, Chr11 position 12188937, Chr11 position 12188948, Chr11 position 12188995, Chr11 position 36057726, Chr11 position 48070143, Chr11 position 48070163, Chr11 position 48070166, Chr11 position 48070174, Chr11 position 65158294, Chr11 position 65158342, Chr11 position 65297089, Chr11 position 66104481, Chr11 position 66104485, Chr11 position 66104578, Chr11 position 68608767, Chr11 position 70236292, Chr11 position 70236320, Chr11 position 70236331, Chr11 position 115530032, Chr11 position 117950310, Chr11 position 117950329, Chr11 position 117950361, Chr11 position 117950362, Chr11 position 119293593, Chr12 position 679803, Chr12 position 26039132, Chr12 position 31004558, Chr12 position 45610695, Chr12 position 45610701, Chr12 position 45610702, Chr12 position 45610706,

Chr12 position 50286016, Chr12 position 52243258, Chr12 position 52243286, Chr12 position 54145732, Chr12 position 54145741, Chr12 position 54145825, Chr12 position 56115043, Chr12 position 66262229, Chr12 position 66262230, Chr12 position 66262233, Chr12 position 66262234, Chr12 position 77266621, Chr12 position 117580102, Chr12 position 123435962, Chr12 position 123436011, Chr12 position 123436065, Chr12 position 123540893, Chr13 position 20735797, Chr13 position 23500419, Chr13 position 46771519, Chr13 position 46771520, Chr13 position 53313426, Chr13 position 113807393, Chr14 position 38599118, Chr14 position 69170010, Chr14 position 75701632, Chr14 position 75701643, Chr14 position 90850454, Chr14 position 97524282, Chr14 position 103541602, Chr14 position 103768055, Chr14 position 104209000, Chr14 position 104209068, Chr14 position 104354645, Chr14 position 104360487, Chr15 position 41068807, Chr15 position 61152225, Chr15 position 61152253, Chr15 position 61152313, Chr15 position 65186440, Chr15 position 68851629, Chr15 position 70667596, Chr15 position 70767206, Chr15 position 75251486, Chr15 position 77984014, Chr15 position 77989064, Chr15 position 83952081, Chr15 position 85402496, Chr15 position 85402497, Chr15 position 99417337, Chr16 position 1231873, Chr16 position 1458639, Chr16 position 3023231, Chr16 position 23135832, Chr16 position 29616265, Chr16 position 31009547, Chr16 position 31009548, Chr16 position 31009590, Chr16 position 57793674, Chr16 position 57793715, Chr16 position 57793727, Chr16 position 70771056, Chr16 position 70771079, Chr16 position 70771141, Chr16 position 77332010, Chr16 position 78540378, Chr16 position 79333435, Chr16 position 84262419, Chr16 position 88701114, Chr16 position 89988308, Chr16 position 89988644, Chr17 position 1509928, Chr17 position 1509945, Chr17 position 1509952, Chr17 position 1509953, Chr17 position 7644013, Chr17 position 16323460, Chr17 position 16323473, Chr17 position 16924561, Chr17 position 16924562, Chr17 position 16924594, Chr17 position 17717918, Chr17 position 17718591, Chr17 position 18139506, Chr17 position 35278031, Chr17 position 39677570, Chr17 position 40826257, Chr17 position 43037426, Chr17 position 43200096, Chr17 position 43200239, Chr17 position 43510142, Chr17 position 47987828, Chr17 position 48178379, Chr17 position 48596391, Chr17 position 48764165, Chr17 position 55701962, Chr17 position 73584599, Chr17 position 73993165, Chr17 position 75827716, Chr17 position 76882243, Chr17 position 78765910, Chr17 position 79544478, Chr17 position 80696474, Chr18 position 19751759, Chr18 position 21440760, Chr18 position 45555437, Chr18 position 45555438, Chr18 position 46547891, Chr18 position 55888885, Chr18 position 56452096, Chr18 position 56452476, Chr18 position 56887181, Chr18 position 76002973, Chr18 position 77331090, Chr19 position 677895, Chr19 position 884044, Chr19 position 884059, Chr19 position 884105, Chr19 position 884115, Chr19 position 1136511, Chr19 position 1177605, Chr19 position 1177612, Chr19 position 1177640, Chr19 position 1860601, Chr19 position 1860607, Chr19 position 2503954, Chr19 position 3434917, Chr19 position 3434921, Chr19 position 3434930, Chr19 position 3434939, Chr19 position 3434952, Chr19 position 3434954, Chr19 position 3434962, Chr19 position 3434964, Chr19 position 3434979, Chr19 position 3434985, Chr19 position 4052713, Chr19 position 4052714, Chr19 position 4052749, Chr19 position 4374591, Chr19 position 5013982, Chr19 position 5048836, Chr19 position 5048867, Chr19 position 5048877, Chr19 position 8367279, Chr19 position 8428573, Chr19 position 10254577, Chr19 position 10254578, Chr19 position 10463956, Chr19 position 10464137, Chr19 position 13203671, Chr19 position 13266925, Chr19 position 13266934, Chr19 position 13266970, Chr19 position 13842142, Chr19 position 14248494, Chr19 position 15375465, Chr19 position 17218912, Chr19 position 17346702, Chr19 position 17346702, Chr19 position 18157161, Chr19 position 18157221, Chr19 position 18157258, Chr19 position 18415877, Chr19 position 18415890, Chr19 position 30606642, Chr19 position 35531842, Chr19 position 44303112, Chr19 position 47173037, Chr19 position 47316268, Chr19 position 47778278, Chr19 position 47778298, Chr20 position 34206950, Chr20 position 36771969, Chr20 position 48993661, Chr20 position 58406398, Chr20 position 61976049, Chr20 position 61976073, Chr20 position 62588571, Chr20 position 62588579, Chr22 position 19738127, Chr22 position 35965176, Chr22 position 36549809, Chr22 position 36973375, Chr22 position 37447953, Chr22 position 37914998, Chr22 position 38307317, Chr22 position 39662794, and Chr22 position 45622980.

(51) In embodiments, the method includes detecting methylation or unmethylation of at least 3 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chr6 position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chr7 position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position 105079565, Chr7 position 105079631, Chr7 position 151425103, Chr7 position 151425104, Chr8 position 11764017, Chr8 position 21647308, Chr8 position 22548399, Chr8 position 22548483, Chr8 position 133570537, Chr8 position 141320393, Chr8 position 141320410, Chr9 position 6566568, Chr9 position 16197862, Chr9 position 34591313, Chr9 position 98225096, Chr9 position 126126741, Chr9 position 132083428, Chr9 position 136077410, Chr9 position 139655018, Chr9 position 140205985, Chr9 position 140205985, Chr9 position 140205997, Chr10 position 3929071, Chr10 position 30047012, Chr10 position 79702989, Chr10 position 87984905, Chr10 position 94838789, Chr10 position 102131187, Chr10 position 104196489, Chr10 position 111766879, Chr10 position 112258886, Chr10 position 112258984, Chr10 position 112259015, Chr10 position 116391763, Chr10 position 120011530, Chr10 position 126172714, Chr10 position 126172747, Chr11 position 556355, Chr11 position 821282, Chr11 position 12188937, Chr11 position 12188948, Chr11 position 12188995, Chr11 position 36057726, Chr11 position 48070143, Chr11 position 48070163, Chr11 position 48070166, Chr11 position 48070174, Chr11 position 65158294, Chr11 position 65158342, Chr11 position 65297089, Chr11 position 66104481, Chr11 position 66104485, Chr11 position 66104578, Chr11 position 68608767, Chr11 position 70236292, Chr11 position 70236320, Chr11 position 70236331, Chr11 position 115530032, Chr11 position 117950310, Chr11 position 117950329, Chr11 position 117950361, Chr11 position 117950362, Chr11 position 119293593, Chr12 position 679803, Chr12 position 26039132, Chr12 position 31004558, Chr12 position 45610695, Chr12 position 45610701, Chr12 position 45610702, Chr12 position 45610706, Chr12 position 50286016, Chr12 position 52243258, Chr12 position 52243286, Chr12 position 54145732, Chr12 position 54145741, Chr12 position 54145825, Chr12 position 56115043, Chr12 position 66262229, Chr12 position 66262230, Chr12 position 66262233, Chr12 position 66262234, Chr12 position 77266621, Chr12 position 117580102, Chr12 position 123435962, Chr12 position

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(52) In embodiments, the method includes detecting methylation or unmethylation of at least 4 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1

position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chr6 position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chr7 position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position 105079565, Chr7 position 105079631, Chr7 position 151425103, Chr7 position 151425104, Chr8 position 11764017, Chr8 position 21647308, Chr8 position 22548399, Chr8 position 22548483, Chr8 position 133570537, Chr8 position 141320393, Chr8 position 141320410, Chr9 position 6566568, Chr9 position 16197862, Chr9 position 34591313, Chr9 position 98225096, Chr9 position 126126741, Chr9 position 132083428, Chr9 position 136077410, Chr9 position 139655018, Chr9 position 140205985, Chr9 position 140205985, Chr9 position 140205997, Chr10 position 3929071, Chr10 position 30047012, Chr10 position 79702989, Chr10 position 87984905, Chr10 position 94838789, Chr10 position 102131187, Chr10 position 104196489, Chr10 position 111766879, Chr10 position 112258886, Chr10 position 112258984, Chr10 position 112259015, Chr10 position 116391763, Chr10 position 120011530, Chr10 position 126172714, Chr10 position 126172747, Chr11 position 556355, Chr11 position 821282, Chr11 position 12188937, Chr11 position 12188948, Chr11 position 12188995, Chr11 position 36057726, Chr11 position 48070143, Chr11 position 48070163, Chr11 position 48070166, Chr11 position 48070174, Chr11 position 65158294, Chr11 position 65158342, Chr11 position 65297089, Chr11 position 66104481, Chr11 position 66104485, Chr11 position 66104578, Chr11 position 68608767, Chr11 position 70236292, Chr11 position 70236320, Chr11 position 70236331, Chr11 position 115530032, Chr11 position 117950310, Chr11 position 117950329, Chr11 position 117950361, Chr11 position 117950362, Chr11 position 119293593, Chr12 position 679803, Chr12 position 26039132, Chr12 position 31004558, Chr12 position 45610695, Chr12 position 45610701, Chr12 position 45610702, Chr12 position 45610706, Chr12 position 50286016, Chr12 position 52243258, Chr12 position 52243286, Chr12 position 54145732, Chr12 position 54145741, Chr12 position 54145825, Chr12 position 56115043, Chr12 position 66262229, Chr12 position 66262230, Chr12 position 66262233, Chr12 position 66262234, Chr12 position 77266621, Chr12 position 117580102, Chr12 position 123435962, Chr12 position 123436011, Chr12 position 123436065, Chr12 position 123540893, Chr13 position 20735797, Chr13 position 23500419, Chr13 position 46771519, Chr13 position 46771520, Chr13 position 53313426, Chr13 position 113807393, Chr14 position 38599118, Chr14 position 69170010, Chr14 position 75701632, Chr14 position 75701643, Chr14 position 90850454, Chr14 position 97524282, Chr14

position 103541602, Chr14 position 103768055, Chr14 position 104209000, Chr14 position 104209068, Chr14 position 104354645, Chr14 position 104360487, Chr15 position 41068807, Chr15 position 61152225, Chr15 position 61152253, Chr15 position 61152313, Chr15 position 65186440, Chr15 position 68851629, Chr15 position 70667596, Chr15 position 70767206, Chr15 position 75251486, Chr15 position 77984014, Chr15 position 77989064, Chr15 position 83952081, Chr15 position 85402496, Chr15 position 85402497, Chr15 position 99417337, Chr16 position 1231873, Chr16 position 1458639, Chr16 position 3023231, Chr16 position 23135832, Chr16 position 29616265, Chr16 position 31009547, Chr16 position 31009548, Chr16 position 31009590, Chr16 position 57793674, Chr16 position 57793715, Chr16 position 57793727, Chr16 position 70771056, Chr16 position 70771079, Chr16 position 70771141, Chr16 position 77332010, Chr16 position 78540378, Chr16 position 79333435, Chr16 position 84262419, Chr16 position 88701114, Chr16 position 89988308, Chr16 position 89988644, Chr17 position 1509928, Chr17 position 1509945, Chr17 position 1509952, Chr17 position 1509953, Chr17 position 7644013, Chr17 position 16323460, Chr17 position 16323473, Chr17 position 16924561, Chr17 position 16924562, Chr17 position 16924594, Chr17 position 17717918, Chr17 position 17718591, Chr17 position 18139506, Chr17 position 35278031, Chr17 position 39677570, Chr17 position 40826257, Chr17 position 43037426, Chr17 position 43200096, Chr17 position 43200239, Chr17 position 43510142, Chr17 position 47987828, Chr17 position 48178379, Chr17 position 48596391, Chr17 position 48764165, Chr17 position 55701962, Chr17 position 73584599, Chr17 position 73993165, Chr17 position 75827716, Chr17 position 76882243, Chr17 position 78765910, Chr17 position 79544478, Chr17 position 80696474, Chr18 position 19751759, Chr18 position 21440760, Chr18 position 45555437, Chr18 position 45555438, Chr18 position 46547891, Chr18 position 55888885, Chr18 position 56452096, Chr18 position 56452476, Chr18 position 56887181, Chr18 position 76002973, Chr18 position 77331090, Chr19 position 677895, Chr19 position 884044, Chr19 position 884059, Chr19 position 884105, Chr19 position 884115, Chr19 position 1136511, Chr19 position 1177605, Chr19 position 1177612, Chr19 position 1177640, Chr19 position 1860601, Chr19 position 1860607, Chr19 position 2503954, Chr19 position 3434917, Chr19 position 3434921, Chr19 position 3434930, Chr19 position 3434939, Chr19 position 3434952, Chr19 position 3434954, Chr19 position 3434962, Chr19 position 3434964, Chr19 position 3434979, Chr19 position 3434985, Chr19 position 4052713, Chr19 position 4052714, Chr19 position 4052749, Chr19 position 4374591, Chr19 position 5013982, Chr19 position 5048836, Chr19 position 5048867, Chr19 position 5048877, Chr19 position 8367279, Chr19 position 8428573, Chr19 position 10254577, Chr19 position 10254578, Chr19 position 10463956, Chr19 position 10464137, Chr19 position 13203671, Chr19 position 13266925, Chr19 position 13266934, Chr19 position 13266970, Chr19 position 13842142, Chr19 position 14248494, Chr19 position 15375465, Chr19 position 17218912, Chr19 position 17346702, Chr19 position 17346702, Chr19 position 18157161, Chr19 position 18157221, Chr19 position 18157258, Chr19 position 18415877, Chr19 position 18415890, Chr19 position 30606642, Chr19 position 35531842, Chr19 position 44303112, Chr19 position 47173037, Chr19 position 47316268, Chr19 position 47778278, Chr19 position 47778298, Chr20 position 34206950, Chr20 position 36771969, Chr20 position 48993661, Chr20 position 58406398, Chr20 position 61976049, Chr20 position 61976073, Chr20 position 62588571, Chr20 position 62588579, Chr22 position 19738127, Chr22 position 35965176, Chr22 position 36549809, Chr22 position 36973375, Chr22 position 37447953, Chr22 position 37914998, Chr22 position 38307317, Chr22 position 39662794, and Chr22 position 45622980.

(53) In embodiments, the method includes detecting methylation or unmethylation of at least 5 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1

position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chr6 position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chr7 position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position 105079565, Chr7 position 105079631, Chr7 position 151425103, Chr7 position 151425104, Chr8 position 11764017, Chr8 position 21647308, Chr8 position 22548399, Chr8 position 22548483, Chr8 position 133570537, Chr8 position 141320393, Chr8 position 141320410, Chr9 position 6566568, Chr9 position 16197862, Chr9 position 34591313, Chr9 position 98225096, Chr9 position 126126741, Chr9 position 132083428, Chr9 position 136077410, Chr9 position 139655018, Chr9 position 140205985, Chr9 position 140205985, Chr9 position 140205997, Chr10 position 3929071, Chr10 position 30047012, Chr10 position 79702989, Chr10 position 87984905, Chr10 position 94838789, Chr10 position 102131187, Chr10 position 104196489, Chr10 position 111766879, Chr10 position 112258886, Chr10 position 112258984, Chr10 position 112259015, Chr10 position 116391763, Chr10 position 120011530, Chr10 position 126172714, Chr10 position 126172747, Chr11 position 556355, Chr11 position 821282, Chr11 position 12188937, Chr11 position 12188948, Chr11 position 12188995, Chr11 position 36057726, Chr11 position 48070143, Chr11 position 48070163, Chr11 position 48070166, Chr11 position 48070174, Chr11 position 65158294, Chr11 position 65158342, Chr11 position 65297089, Chr11 position 66104481, Chr11 position 66104485, Chr11 position 66104578, Chr11 position 68608767, Chr11 position 70236292, Chr11 position 70236320, Chr11 position 70236331, Chr11 position 115530032, Chr11 position 117950310, Chr11 position 117950329, Chr11 position 117950361, Chr11 position 117950362, Chr11 position 119293593, Chr12 position 679803, Chr12 position 26039132, Chr12 position 31004558, Chr12 position 45610695, Chr12 position 45610701, Chr12 position 45610702, Chr12 position 45610706, Chr12 position 50286016, Chr12 position 52243258, Chr12 position 52243286, Chr12 position 54145732, Chr12 position 54145741, Chr12 position 54145825, Chr12 position 56115043, Chr12 position 66262229, Chr12 position 66262230, Chr12 position 66262233, Chr12 position 66262234, Chr12 position 77266621, Chr12 position 117580102, Chr12 position 123435962, Chr12 position 123436011, Chr12 position 123436065, Chr12 position 123540893, Chr13 position 20735797, Chr13 position 23500419, Chr13 position 46771519, Chr13 position 46771520, Chr13 position 53313426, Chr13 position 113807393, Chr14 position 38599118, Chr14 position 69170010, Chr14 position 75701632, Chr14 position 75701643, Chr14 position 90850454, Chr14 position 97524282, Chr14 position 103541602, Chr14 position 103768055, Chr14 position 104209000, Chr14 position 104209068, Chr14 position 104354645, Chr14 position 104360487, Chr15 position 41068807, Chr15 position 61152225, Chr15 position 61152253, Chr15 position 61152313, Chr15 position 65186440, Chr15 position 68851629, Chr15 position 70667596, Chr15 position 70767206, Chr15 position

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(54) In embodiments, the method includes detecting methylation or unmethylation of at least 6 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2

position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chr6 position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chr7 position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position 105079565, Chr7 position 105079631, Chr7 position 151425103, Chr7 position 151425104, Chr8 position 11764017, Chr8 position 21647308, Chr8 position 22548399, Chr8 position 22548483, Chr8 position 133570537, Chr8 position 141320393, Chr8 position 141320410, Chr9 position 6566568, Chr9 position 16197862, Chr9 position 34591313, Chr9 position 98225096, Chr9 position 126126741, Chr9 position 132083428, Chr9 position 136077410, Chr9 position 139655018, Chr9 position 140205985, Chr9 position 140205985, Chr9 position 140205997, Chr10 position 3929071, Chr10 position 30047012, Chr10 position 79702989, Chr10 position 87984905, Chr10 position 94838789, Chr10 position 102131187, Chr10 position 104196489, Chr10 position 111766879, Chr10 position 112258886, Chr10 position 112258984, Chr10 position 112259015, Chr10 position 116391763, Chr10 position 120011530, Chr10 position 126172714, Chr10 position 126172747, Chr11 position 556355, Chr11 position 821282, Chr11 position 12188937, Chr11 position 12188948, Chr11 position 12188995, Chr11 position 36057726, Chr11 position 48070143, Chr11 position 48070163, Chr11 position 48070166, Chr11 position 48070174, Chr11 position 65158294, Chr11 position 65158342, Chr11 position 65297089, Chr11 position 66104481, Chr11 position 66104485, Chr11 position 66104578, Chr11 position 68608767, Chr11 position 70236292, Chr11 position 70236320, Chr11 position 70236331, Chr11 position 115530032, Chr11 position 117950310, Chr11 position 117950329, Chr11 position 117950361, Chr11 position 117950362, Chr11 position 119293593, Chr12 position 679803, Chr12 position 26039132, Chr12 position 31004558, Chr12 position 45610695, Chr12 position 45610701, Chr12 position 45610702, Chr12 position 45610706, Chr12 position 50286016, Chr12 position 52243258, Chr12 position 52243286, Chr12 position 54145732, Chr12 position 54145741, Chr12 position 54145825, Chr12 position 56115043, Chr12 position 66262229, Chr12 position 66262230, Chr12 position 66262233, Chr12 position 66262234, Chr12 position 77266621, Chr12 position 117580102, Chr12 position 123435962, Chr12 position 123436011, Chr12 position 123436065, Chr12 position 123540893, Chr13 position 20735797, Chr13 position 23500419, Chr13 position 46771519, Chr13 position 46771520, Chr13 position 53313426, Chr13 position 113807393, Chr14 position 38599118, Chr14 position 69170010, Chr14 position 75701632, Chr14 position 75701643, Chr14 position 90850454, Chr14 position 97524282, Chr14 position 103541602, Chr14 position 103768055, Chr14 position 104209000, Chr14 position 104209068, Chr14 position 104354645, Chr14 position 104360487, Chr15 position 41068807, Chr15 position 61152225, Chr15 position 61152253, Chr15 position 61152313, Chr15 position 65186440, Chr15 position 68851629, Chr15 position 70667596, Chr15 position 70767206, Chr15 position 75251486, Chr15 position 77984014, Chr15 position 77989064, Chr15 position 83952081, Chr15 position 85402496, Chr15 position 85402497, Chr15 position 99417337, Chr16 position 1231873, Chr16 position 1458639, Chr16 position 3023231, Chr16 position 23135832, Chr16 position 29616265, Chr16 position 31009547, Chr16 position 31009548, Chr16 position 31009590, Chr16

position 57793674, Chr16 position 57793715, Chr16 position 57793727, Chr16 position 70771056, Chr16 position 70771079, Chr16 position 70771141, Chr16 position 77332010, Chr16 position 78540378, Chr16 position 79333435, Chr16 position 84262419, Chr16 position 88701114, Chr16 position 89988308, Chr16 position 89988644, Chr17 position 1509928, Chr17 position 1509945, Chr17 position 1509952, Chr17 position 1509953, Chr17 position 7644013, Chr17 position 16323460, Chr17 position 16323473, Chr17 position 16924561, Chr17 position 16924562, Chr17 position 16924594, Chr17 position 17717918, Chr17 position 17718591, Chr17 position 18139506, Chr17 position 35278031, Chr17 position 39677570, Chr17 position 40826257, Chr17 position 43037426, Chr17 position 43200096, Chr17 position 43200239, Chr17 position 43510142, Chr17 position 47987828, Chr17 position 48178379, Chr17 position 48596391, Chr17 position 48764165, Chr17 position 55701962, Chr17 position 73584599, Chr17 position 73993165, Chr17 position 75827716, Chr17 position 76882243, Chr17 position 78765910, Chr17 position 79544478, Chr17 position 80696474, Chr18 position 19751759, Chr18 position 21440760, Chr18 position 45555437, Chr18 position 45555438, Chr18 position 46547891, Chr18 position 55888885, Chr18 position 56452096, Chr18 position 56452476, Chr18 position 56887181, Chr18 position 76002973, Chr18 position 77331090, Chr19 position 677895, Chr19 position 884044, Chr19 position 884059, Chr19 position 884105, Chr19 position 884115, Chr19 position 1136511, Chr19 position 1177605, Chr19 position 1177612, Chr19 position 1177640, Chr19 position 1860601, Chr19 position 1860607, Chr19 position 2503954, Chr19 position 3434917, Chr19 position 3434921, Chr19 position 3434930, Chr19 position 3434939, Chr19 position 3434952, Chr19 position 3434954, Chr19 position 3434962, Chr19 position 3434964, Chr19 position 3434979, Chr19 position 3434985, Chr19 position 4052713, Chr19 position 4052714, Chr19 position 4052749, Chr19 position 4374591, Chr19 position 5013982, Chr19 position 5048836, Chr19 position 5048867, Chr19 position 5048877, Chr19 position 8367279, Chr19 position 8428573, Chr19 position 10254577, Chr19 position 10254578, Chr19 position 10463956, Chr19 position 10464137, Chr19 position 13203671, Chr19 position 13266925, Chr19 position 13266934, Chr19 position 13266970, Chr19 position 13842142, Chr19 position 14248494, Chr19 position 15375465, Chr19 position 17218912, Chr19 position 17346702, Chr19 position 17346702, Chr19 position 18157161, Chr19 position 18157221, Chr19 position 18157258, Chr19 position 18415877, Chr19 position 18415890, Chr19 position 30606642, Chr19 position 35531842, Chr19 position 44303112, Chr19 position 47173037, Chr19 position 47316268, Chr19 position 47778278, Chr19 position 47778298, Chr20 position 34206950, Chr20 position 36771969, Chr20 position 48993661, Chr20 position 58406398, Chr20 position 61976049, Chr20 position 61976073, Chr20 position 62588571, Chr20 position 62588579, Chr22 position 19738127, Chr22 position 35965176, Chr22 position 36549809, Chr22 position 36973375, Chr22 position 37447953, Chr22 position 37914998, Chr22 position 38307317, Chr22 position 39662794, and Chr22 position 45622980.

(55) In embodiments, the method includes detecting methylation or unmethylation of at least 7 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position

238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chr6 position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chr7 position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position 105079565, Chr7 position 105079631, Chr7 position 151425103, Chr7 position 151425104, Chr8 position 11764017, Chr8 position 21647308, Chr8 position 22548399, Chr8 position 22548483, Chr8 position 133570537, Chr8 position 141320393, Chr8 position 141320410, Chr9 position 6566568, Chr9 position 16197862, Chr9 position 34591313, Chr9 position 98225096, Chr9 position 126126741, Chr9 position 132083428, Chr9 position 136077410, Chr9 position 139655018, Chr9 position 140205985, Chr9 position 140205985, Chr9 position 140205997, Chr10 position 3929071, Chr10 position 30047012, Chr10 position 79702989, Chr10 position 87984905, Chr10 position 94838789, Chr10 position 102131187, Chr10 position 104196489, Chr10 position 111766879, Chr10 position 112258886, Chr10 position 112258984, Chr10 position 112259015, Chr10 position 116391763, Chr10 position 120011530, Chr10 position 126172714, Chr10 position 126172747, Chr11 position 556355, Chr11 position 821282, Chr11 position 12188937, Chr11 position 12188948, Chr11 position 12188995, Chr11 position 36057726, Chr11 position 48070143, Chr11 position 48070163, Chr11 position 48070166, Chr11 position 48070174, Chr11 position 65158294, Chr11 position 65158342, Chr11 position 65297089, Chr11 position 66104481, Chr11 position 66104485, Chr11 position 66104578, Chr11 position 68608767, Chr11 position 70236292, Chr11 position 70236320, Chr11 position 70236331, Chr11 position 115530032, Chr11 position 117950310, Chr11 position 117950329, Chr11 position 117950361, Chr11 position 117950362, Chr11 position 119293593, Chr12 position 679803, Chr12 position 26039132, Chr12 position 31004558, Chr12 position 45610695, Chr12 position 45610701, Chr12 position 45610702, Chr12 position 45610706, Chr12 position 50286016, Chr12 position 52243258, Chr12 position 52243286, Chr12 position 54145732, Chr12 position 54145741, Chr12 position 54145825, Chr12 position 56115043, Chr12 position 66262229, Chr12 position 66262230, Chr12 position 66262233, Chr12 position 66262234, Chr12 position 77266621, Chr12 position 117580102, Chr12 position 123435962, Chr12 position 123436011, Chr12 position 123436065, Chr12 position 123540893, Chr13 position 20735797, Chr13 position 23500419, Chr13 position 46771519, Chr13 position 46771520, Chr13 position 53313426, Chr13 position 113807393, Chr14 position 38599118, Chr14 position 69170010, Chr14 position 75701632, Chr14 position 75701643, Chr14 position 90850454, Chr14 position 97524282, Chr14 position 103541602, Chr14 position 103768055, Chr14 position 104209000, Chr14 position 104209068, Chr14 position 104354645, Chr14 position 104360487, Chr15 position 41068807, Chr15 position 61152225, Chr15 position 61152253, Chr15 position 61152313, Chr15 position 65186440, Chr15 position 68851629, Chr15 position 70667596, Chr15 position 70767206, Chr15 position 75251486, Chr15 position 77984014, Chr15 position 77989064, Chr15 position 83952081, Chr15 position 85402496, Chr15 position 85402497, Chr15 position 99417337, Chr16 position 1231873, Chr16 position 1458639, Chr16 position 3023231, Chr16 position 23135832, Chr16 position 29616265, Chr16 position 31009547, Chr16 position 31009548, Chr16 position 31009590, Chr16 position 57793674, Chr16 position 57793715, Chr16 position 57793727, Chr16 position 70771056, Chr16 position 70771079, Chr16 position 70771141, Chr16 position 77332010, Chr16 position 78540378, Chr16 position 79333435, Chr16 position 84262419, Chr16 position 88701114, Chr16 position 89988308, Chr16 position 89988644, Chr17 position 1509928, Chr17 position 1509945,

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(56) In embodiments, the method includes detecting methylation or unmethylation of at least 8 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4

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43037426, Chr17 position 43200096, Chr17 position 43200239, Chr17 position 43510142, Chr17 position 47987828, Chr17 position 48178379, Chr17 position 48596391, Chr17 position 48764165, Chr17 position 55701962, Chr17 position 73584599, Chr17 position 73993165, Chr17 position 75827716, Chr17 position 76882243, Chr17 position 78765910, Chr17 position 79544478, Chr17 position 80696474, Chr18 position 19751759, Chr18 position 21440760, Chr18 position 45555437, Chr18 position 45555438, Chr18 position 46547891, Chr18 position 55888885, Chr18 position 56452096, Chr18 position 56452476, Chr18 position 56887181, Chr18 position 76002973, Chr18 position 77331090, Chr19 position 677895, Chr19 position 884044, Chr19 position 884059, Chr19 position 884105, Chr19 position 884115, Chr19 position 1136511, Chr19 position 1177605, Chr19 position 1177612, Chr19 position 1177640, Chr19 position 1860601, Chr19 position 1860607, Chr19 position 2503954, Chr19 position 3434917, Chr19 position 3434921, Chr19 position 3434930, Chr19 position 3434939, Chr19 position 3434952, Chr19 position 3434954, Chr19 position 3434962, Chr19 position 3434964, Chr19 position 3434979, Chr19 position 3434985, Chr19 position 4052713, Chr19 position 4052714, Chr19 position 4052749, Chr19 position 4374591, Chr19 position 5013982, Chr19 position 5048836, Chr19 position 5048867, Chr19 position 5048877, Chr19 position 8367279, Chr19 position 8428573, Chr19 position 10254577, Chr19 position 10254578, Chr19 position 10463956, Chr19 position 10464137, Chr19 position 13203671, Chr19 position 13266925, Chr19 position 13266934, Chr19 position 13266970, Chr19 position 13842142, Chr19 position 14248494, Chr19 position 15375465, Chr19 position 17218912, Chr19 position 17346702, Chr19 position 17346702, Chr19 position 18157161, Chr19 position 18157221, Chr19 position 18157258, Chr19 position 18415877, Chr19 position 18415890, Chr19 position 30606642, Chr19 position 35531842, Chr19 position 44303112, Chr19 position 47173037, Chr19 position 47316268, Chr19 position 47778278, Chr19 position 47778298, Chr20 position 34206950, Chr20 position 36771969, Chr20 position 48993661, Chr20 position 58406398, Chr20 position 61976049, Chr20 position 61976073, Chr20 position 62588571, Chr20 position 62588579, Chr22 position 19738127, Chr22 position 35965176, Chr22 position 36549809, Chr22 position 36973375, Chr22 position 37447953, Chr22 position 37914998, Chr22 position 38307317, Chr22 position 39662794, and Chr22 position 45622980.

(57) In embodiments, the method includes detecting methylation or unmethylation of at least 9 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position

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(58) In embodiments, the method includes detecting methylation or unmethylation of at least 10 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chr6 position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chr7 position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position

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(59) In embodiments, the method includes detecting methylation or unmethylation of at least 50 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chr6 position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chr7 position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position 105079565, Chr7 position 105079631, Chr7 position 151425103, Chr7 position 151425104, Chr8 position 11764017, Chr8 position 21647308, Chr8 position 22548399, Chr8 position 22548483, Chr8 position 133570537, Chr8 position 141320393, Chr8 position 141320410, Chr9 position 6566568, Chr9 position 16197862, Chr9 position 34591313, Chr9 position 98225096, Chr9 position

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(60) In embodiments, the method includes detecting methylation or unmethylation of at least 100 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chr6 position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chr7 position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position 105079565, Chr7 position 105079631, Chr7 position 151425103, Chr7 position 151425104, Chr8 position 11764017, Chr8 position 21647308, Chr8 position 22548399, Chr8 position 22548483, Chr8 position 133570537, Chr8 position 141320393, Chr8 position 141320410, Chr9 position 6566568, Chr9 position 16197862, Chr9 position 34591313, Chr9 position 98225096, Chr9 position 126126741, Chr9 position 132083428, Chr9 position 136077410, Chr9 position 139655018, Chr9 position 140205985, Chr9 position 140205985, Chr9 position 140205997, Chr10 position 3929071, Chr10 position 30047012, Chr10 position 79702989, Chr10 position 87984905, Chr10 position 94838789, Chr10 position 102131187, Chr10 position 104196489, Chr10 position 111766879, Chr10

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Chr19 position 10464137, Chr19 position 13203671, Chr19 position 13266925, Chr19 position 13266934, Chr19 position 13266970, Chr19 position 13842142, Chr19 position 14248494, Chr19 position 15375465, Chr19 position 17218912, Chr19 position 17346702, Chr19 position 17346702, Chr19 position 18157161, Chr19 position 18157221, Chr19 position 18157258, Chr19 position 18415877, Chr19 position 18415890, Chr19 position 30606642, Chr19 position 35531842, Chr19 position 44303112, Chr19 position 47173037, Chr19 position 47316268, Chr19 position 47778278, Chr19 position 47778298, Chr20 position 34206950, Chr20 position 36771969, Chr20 position 48993661, Chr20 position 58406398, Chr20 position 61976049, Chr20 position 61976073, Chr20 position 62588571, Chr20 position 62588579, Chr22 position 19738127, Chr22 position 35965176, Chr22 position 36549809, Chr22 position 36973375, Chr22 position 37447953, Chr22 position 37914998, Chr22 position 38307317, Chr22 position 39662794, and Chr22 position 45622980.

(61) In embodiments, the method includes detecting methylation or unmethylation of at least 200 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chr6 position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chr7 position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position 105079565, Chr7 position 105079631, Chr7 position 151425103, Chr7 position 151425104, Chr8 position 11764017, Chr8 position 21647308, Chr8 position 22548399, Chr8 position 22548483, Chr8 position 133570537, Chr8 position 141320393, Chr8 position 141320410, Chr9 position 6566568, Chr9 position 16197862, Chr9 position 34591313, Chr9 position 98225096, Chr9 position 126126741, Chr9 position 132083428, Chr9 position 136077410, Chr9 position 139655018, Chr9 position 140205985, Chr9 position 140205985, Chr9 position 140205997, Chr10 position 3929071, Chr10 position 30047012, Chr10 position 79702989, Chr10 position 87984905, Chr10 position 94838789, Chr10 position 102131187, Chr10 position 104196489, Chr10 position 111766879, Chr10 position 112258886, Chr10 position 112258984, Chr10 position 112259015, Chr10 position 116391763, Chr10 position 120011530, Chr10 position 126172714, Chr10 position 126172747, Chr11 position 556355, Chr11 position 821282, Chr11 position 12188937, Chr11 position 12188948, Chr11 position 12188995, Chr11 position 36057726, Chr11 position 48070143, Chr11 position

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(62) In embodiments, the method includes detecting methylation or unmethylation of at least 300 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chr6 position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chr7 position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position 105079565, Chr7 position 105079631, Chr7 position 151425103, Chr7 position 151425104, Chr8 position 11764017, Chr8 position 21647308, Chr8 position 22548399, Chr8 position 22548483, Chr8 position 133570537, Chr8 position 141320393, Chr8 position 141320410, Chr9 position 6566568, Chr9 position 16197862, Chr9 position 34591313, Chr9 position 98225096, Chr9 position 126126741, Chr9 position 132083428, Chr9 position 136077410, Chr9 position 139655018, Chr9 position 140205985, Chr9 position 140205985, Chr9 position 140205997, Chr10 position 3929071, Chr10 position 30047012, Chr10 position 79702989, Chr10 position 87984905, Chr10 position 94838789, Chr10 position 102131187, Chr10 position 104196489, Chr10 position 111766879, Chr10 position 112258886, Chr10 position 112258984, Chr10 position 112259015, Chr10 position 116391763, Chr10 position 120011530, Chr10 position 126172714, Chr10 position 126172747, Chr11 position 556355, Chr11 position 821282, Chr11 position 12188937, Chr11 position 12188948, Chr11 position 12188995, Chr11 position 36057726, Chr11 position 48070143, Chr11 position 48070163, Chr11 position 48070166, Chr11 position 48070174, Chr11 position 65158294, Chr11 position 65158342, Chr11 position 65297089, Chr11 position 66104481, Chr11 position 66104485, Chr11 position 66104578, Chr11 position 68608767, Chr11 position 70236292, Chr11 position 70236320, Chr11 position 70236331, Chr11 position 115530032, Chr11 position 117950310, Chr11

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position 62588571, Chr20 position 62588579, Chr22 position 19738127, Chr22 position 35965176, Chr22 position 36549809, Chr22 position 36973375, Chr22 position 37447953, Chr22 position 37914998, Chr22 position 38307317, Chr22 position 39662794, and Chr22 position 45622980.

(63) In embodiments, the method includes detecting methylation or unmethylation of at least 400 of the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chr6 position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chr7 position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position 105079565, Chr7 position 105079631, Chr7 position 151425103, Chr7 position 151425104, Chr8 position 11764017, Chr8 position 21647308, Chr8 position 22548399, Chr8 position 22548483, Chr8 position 133570537, Chr8 position 141320393, Chr8 position 141320410, Chr9 position 6566568, Chr9 position 16197862, Chr9 position 34591313, Chr9 position 98225096, Chr9 position 126126741, Chr9 position 132083428, Chr9 position 136077410, Chr9 position 139655018, Chr9 position 140205985, Chr9 position 140205985, Chr9 position 140205997, Chr10 position 3929071, Chr10 position 30047012, Chr10 position 79702989, Chr10 position 87984905, Chr10 position 94838789, Chr10 position 102131187, Chr10 position 104196489, Chr10 position 111766879, Chr10 position 112258886, Chr10 position 112258984, Chr10 position 112259015, Chr10 position 116391763, Chr10 position 120011530, Chr10 position 126172714, Chr10 position 126172747, Chr11 position 556355, Chr11 position 821282, Chr11 position 12188937, Chr11 position 12188948, Chr11 position 12188995, Chr11 position 36057726, Chr11 position 48070143, Chr11 position 48070163, Chr11 position 48070166, Chr11 position 48070174, Chr11 position 65158294, Chr11 position 65158342, Chr11 position 65297089, Chr11 position 66104481, Chr11 position 66104485, Chr11 position 66104578, Chr11 position 68608767, Chr11 position 70236292, Chr11 position 70236320, Chr11 position 70236331, Chr11 position 115530032, Chr11 position 117950310, Chr11 position 117950329, Chr11 position 117950361, Chr11 position 117950362, Chr11 position 119293593, Chr12 position 679803, Chr12 position 26039132, Chr12 position 31004558, Chr12 position 45610695, Chr12 position 45610701, Chr12 position 45610702, Chr12 position 45610706, Chr12 position 50286016, Chr12 position 52243258, Chr12 position 52243286, Chr12 position

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(64) In embodiments, the method includes detecting methylation or unmethylation of at least 500 of

the following sites: Chr1 position 2996653, Chr1 position 11979164, Chr1 position 12655938, Chr1 position 16450525, Chr1 position 16450542, Chr1 position 16450545, Chr1 position 16469987, Chr1 position 17494491, Chr1 position 25473203, Chr1 position 27640460, Chr1 position 29565080, Chr1 position 38493013, Chr1 position 38493030, Chr1 position 38493074, Chr1 position 46713777, Chr1 position 46914121, Chr1 position 46955744, Chr1 position 55008344, Chr1 position 109816092, Chr1 position 109816111, Chr1 position 110074669, Chr1 position 110074681, Chr1 position 110074685, Chr1 position 150949856, Chr1 position 150949857, Chr1 position 153540282, Chr1 position 155162704, Chr1 position 155162714, Chr1 position 156676611, Chr1 position 157611881, Chr1 position 182205324, Chr1 position 204118999, Chr1 position 206741875, Chr1 position 206741989, Chr1 position 212587673, Chr1 position 212841198, Chr1 position 223403952, Chr1 position 233430972, Chr1 position 234342767, Chr2 position 3454277, Chr2 position 8793724, Chr2 position 20412441, Chr2 position 42329402, Chr2 position 42329494, Chr2 position 55289272, Chr2 position 65064865, Chr2 position 70823641, Chr2 position 73143689, Chr2 position 74454110, Chr2 position 122014529, Chr2 position 128158884, Chr2 position 128158910, Chr2 position 203114171, Chr2 position 218221671, Chr2 position 219745335, Chr2 position 238341465, Chr2 position 238341542, Chr2 position 238341546, Chr2 position 238774763, Chr3 position 13323642, Chr3 position 14180153, Chr3 position 45209073, Chr3 position 45209207, Chr3 position 52525100, Chr3 position 62589658, Chr3 position 65388317, Chr3 position 65388388, Chr3 position 73599302, Chr3 position 195636893, Chr3 position 197093846, Chr4 position 3743223, Chr4 position 5755716, Chr4 position 5755717, Chr4 position 5755728, Chr4 position 5755729, Chr4 position 5755734, Chr4 position 8372861, Chr4 position 57548289, Chr5 position 1118280, Chr5 position 34564389, Chr5 position 73871907, Chr5 position 78013596, Chr5 position 78013643, Chr5 position 137802650, Chr5 position 139051189, Chr5 position 167838221, Chr5 position 177541401, Chr5 position 180018672, Chr5 position 180101026, Chr6 position 3394325, Chr6 position 3887581, Chr6 position 7236568, Chr6 position 7728692, Chr6 position 34203617, Chr6 position 37751320, Chr6 position 41410682, Chr6 position 41438516, Chr6 position 41438575, Chr6 position 43464150, Chr6 position 158734279, Chr7 position 989235, Chr7 position 2673543, Chr7 position 73508602, Chr7 position 105079565, Chr7 position 105079631, Chr7 position 151425103, Chr7 position 151425104, Chr8 position 11764017, Chr8 position 21647308, Chr8 position 22548399, Chr8 position 22548483, Chr8 position 133570537, Chr8 position 141320393, Chr8 position 141320410, Chr9 position 6566568, Chr9 position 16197862, Chr9 position 34591313, Chr9 position 98225096, Chr9 position 126126741, Chr9 position 132083428, Chr9 position 136077410, Chr9 position 139655018, Chr9 position 140205985, Chr9 position 140205985, Chr9 position 140205997, Chr10 position 3929071, Chr10 position 30047012, Chr10 position 79702989, Chr10 position 87984905, Chr10 position 94838789, Chr10 position 102131187, Chr10 position 104196489, Chr10 position 111766879, Chr10 position 112258886, Chr10 position 112258984, Chr10 position 112259015, Chr10 position 116391763, Chr10 position 120011530, Chr10 position 126172714, Chr10 position 126172747, Chr11 position 556355, Chr11 position 821282, Chr11 position 12188937, Chr11 position 12188948, Chr11 position 12188995, Chr11 position 36057726, Chr11 position 48070143, Chr11 position 48070163, Chr11 position 48070166, Chr11 position 48070174, Chr11 position 65158294, Chr11 position 65158342, Chr11 position 65297089, Chr11 position 66104481, Chr11 position 66104485, Chr11 position 66104578, Chr11 position 68608767, Chr11 position 70236292, Chr11 position 70236320, Chr11 position 70236331, Chr11 position 115530032, Chr11 position 117950310, Chr11 position 117950329, Chr11 position 117950361, Chr11 position 117950362, Chr11 position 119293593, Chr12 position 679803, Chr12 position 26039132, Chr12 position 31004558, Chr12 position 45610695, Chr12 position 45610701, Chr12 position 45610702, Chr12 position 45610706, Chr12 position 50286016, Chr12 position 52243258, Chr12 position 52243286, Chr12 position 54145732, Chr12 position 54145741, Chr12 position 54145825, Chr12 position 56115043, Chr12 position 66262229, Chr12 position 66262230, Chr12 position 66262233, Chr12 position 66262234, Chr12 position 77266621, Chr12 position 117580102, Chr12 position 123435962, Chr12 position 123436011, Chr12 position 123436065, Chr12 position 123540893, Chr13 position 20735797, Chr13

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(65) In embodiments, a method provided herein is practiced for a subject more than once over time. In embodiments, methylation or unmethylation of thyroid nodule DNA from a subject is assessed using a method provided herein at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more times. In embodiments, the method is repeated at least once every 4, 6, 8, 12 or 18 months, or at least once every 2, 3, 4, or 5 more years.

(66) In embodiments, the method includes: (i) isolating DNA from multiple cells of a thyroid nodule of the subject thereby forming a plurality of isolated thyroid nodule DNA molecules, (ii) contacting the plurality of isolated thyroid nodule DNA molecules with a bisulfite salt thereby forming a plurality of reacted thyroid nodule DNA molecules, (iii) detecting the proportion of DNA molecules in the plurality of reacted thyroid nodule DNA molecules having a uracil at a methylation site set forth in Table 1, thereby detecting methylation or unmethylation of said thyroid nodule DNA of the subject.

(67) The methylation of a CpG site of interest may vary between individual cells (and even between chromosome pairs of individual cells) in a biological sample. When DNA is obtained from a biological sample and treated with a bisulfite salt to convert unmethylated cytosines to uracils, the bisulfite-treated DNA will typically contain (i) a proportion of DNA molecules with a cytosine at the site of interest (indicating that the site was methylated); and (ii) a proportion of DNA molecules with a uracil at the site of interest (indicating that the site was unmethylated). Since a uracil at a site of interest in bisulfite-treated DNA indicates that the site was unmethylated in the untreated DNA, a thymidine at the corresponding site in an amplicon of the bisulfite-treated DNA (e.g., an amplicon obtained by PCR) also indicates that the site was unmethylated in the untreated DNA.

(68) In embodiments, the level of methylation at a site of interest is the proportion of bisulfite-treated DNA molecules having a cytosine rather than a uracil at that site of interest. In embodiments, the level of methylation at a site of interest is the proportion of amplicons of bisulfite-treated DNA molecules having a cytosine rather than a thymidine at that site of interest.

(69) In embodiments, the level of unmethylation at a site of interest is the proportion of bisulfite-treated DNA molecules having a uracil rather than a cytosine at that site of interest. In embodiments, the level of unmethylation at a site of interest is the proportion of amplicons of bisulfite-treated DNA molecules having a thymidine rather than a cytosine at that site of interest. In Table 1, an indicated level of uracil is the proportion of bisulfite-treated DNA molecules having a uracil rather than a cytosine at the specified methylation site. The same levels listed in Table 1 also apply to the thymidine levels at a site of interest in an amplicon, i.e., the proportion of amplicons (derived from the PCR amplification of bisulfite-treated DNA molecules) having a thymidine rather than a cytosine at the specified methylation site.

(70) The level of DNA methylation at a site of interest (e.g., a methylation site listed in Table 1) may be determined using sequencing technology. Sequencing technology can reveal nucleotide sequence variations in a plurality of DNA molecules at a single nucleotide base resolution. For example, the proportions of corresponding DNA molecules having a uracil, a thymidine, and/or a cytosine at a site may be determined. A non-limiting example of a sequencing-based method for determining the methylation level at a site of interest is described in Masser et al. (2015) Targeted DNA Methylation Analysis by Next-generation Sequencing, J Vis Exp. (96): 52488, the entire content of which is incorporated herein by reference.

(71) The chromosomal positions listed in Tables 1-4 relate to the human genome that is publically accessible in the University of California Santa Cruz (UCSC) genome browser database under accession number HG19, the entire content of which is incorporated herein by reference in its entirety. Non-limiting information regarding the UCSC Genome Browser is provided in Kent W J, Sugnet C W, Furey T S, Roskin K M, Pringle T H, Zahler A M, Haussler D. The human genome browser at UCSC. Genome Res. 2002 June; 12 (6): 996-1006, the entire content of which is incorporated herein by reference. Each methylation site of interest listed in Table 1 may be located in other human genomes (e.g., within the genome of a specific subject or group of subjects) by replacing every U and R in the corresponding sequence with a C and then searching for the location of the X within a reference genome by aligning the sequence against the reference genome. For example, the methylation site of interest “X” in SEQ ID NO: 1 may be located within a genome by replacing each U and R in SEQ ID NO: 1 with a C (to obtain the pre-bisulfite-modified sequence having an X at the site of interest) and then aligning the sequence against the genome using a BLAST algorithm. Also expressly provided, disclosed, and incorporated herein is the non-bisulfite-modified sequence

corresponding to each of SEQ ID NOS: 1-550. The non-bisulfite-modified sequence corresponding to each of SEQ ID NOS: 1-550 is each respective sequence in which each U and R is replaced with a C, where X is the methylation site of interest. For example, the non-bisulfite-modified sequence corresponding to SEQ ID NO: 1 provided herein is a modified version of SEQ ID NO:1 in which each U and R in SEQ ID NO: 1 is replaced with a C, where X is the methylation site of interest; the non-bisulfite-modified sequence corresponding to SEQ ID NO:2 provided herein is a modified version of SEQ ID NO: 2 in which each U and R in SEQ ID NO:2 is replaced with a C, where X is the methylation site of interest; the non-bisulfite-modified sequence corresponding to SEQ ID NO:3 provided herein is a modified version of SEQ ID NO:3 in which each U and R in SEQ ID NO:3 is replaced with a C, where X is the methylation site of interest, and so on.

(72) TABLE-US-00001 TABLE 1 Uracil Uracil Uracil level in level in level in reacted reacted reacted thyroid thyroid thyroid nodule nodule nodule DNA DNA DNA from from from cancer benign benign tissues is tissues is tissues is above above below SEQ ID NO: SEQ ID NO: Chromosome Chr indicated indicated indicated Forward Reverse (chr) Position level* level* level* Strand Strand chr1 2996653 N/A 88.84 N/A 1 2 chr1 11979164 89.29 N/A N/A 3 4 chr1 12655938 N/A N/A 69.23 5 6 chr1 16450525 70.00 N/A N/A 7 8 chr1 16450542 72.00 N/A N/A 7 8 chr1 16450545 73.33 N/A N/A 7 8 chr1 16469987 80.00 N/A N/A 9 10 chr1 17494491 86.00 N/A N/A 11 12 chr1 25473203 88.89 N/A N/A 13 14 chr1 27640460 N/A 80.56 N/A 15 16 chr1 29565080 N/A N/A 60.00 17 18 chr1 38493013 86.36 N/A N/A 19 20 chr1 38493030 79.17 N/A N/A 19 20 chr1 38493074 80.95 N/A N/A 19 20 chr1 46713777 N/A N/A 73.33 21 22 chr1 46914121 N/A N/A 60.00 23 24 chr1 46955744 N/A N/A 77.78 25 26 chr1 55008344 N/A N/A 60.00 27 28 chr1 109816092 80.77 N/A N/A 29 30 chr1 109816111 80.77 N/A N/A 29 30 chr1 110074669 75.00 N/A N/A 31 32 chr1 110074681 71.43 N/A N/A 31 32 chr1 110074685 63.16 N/A N/A 31 32 chr1 150949856 89.29 N/A N/A 33 34 chr1 150949857 88.46 N/A N/A 33 34 chr1 153540282 78.26 N/A N/A 35 36 chr1 155162704 84.21 N/A N/A 37 38 chr1 155162714 88.64 N/A N/A 37 38 chr1 156676611 N/A N/A 84.62 39 40 chr1 157611881 83.05 N/A N/A 41 42 chr1 182205324 77.50 N/A N/A 43 44 chr1 204118999 59.09 N/A N/A 45 46 chr1 206741875 83.33 N/A N/A 47 48 chr1 206741989 66.67 N/A N/A 49 50 chr1 212587673 N/A N/A 80.00 51 52 chr1 212841198 85.29 N/A N/A 53 54 chr1 223403952 79.17 N/A N/A 55 56 chr1 233430972 N/A N/A 86.67 57 58 chr1 234342767 76.67 N/A N/A 59 60 chr10 3929071 88.68 N/A N/A 61 62 chr10 30047012 86.84 N/A N/A 63 64 chr10 79702989 83.33 N/A N/A 65 66 chr10 87984905 86.36 N/A N/A 67 68 chr10 94838789 63.33 N/A N/A 69 70 chr10 102131187 90.00 N/A N/A 71 72 chr10 104196489 75.00 N/A N/A 73 74 chr10 111766879 89.47 N/A N/A 75 76 chr10 112258886 81.82 N/A N/A 77 78 chr10 112258984 83.33 N/A N/A 79 80 chr10 112259015 82.61 N/A N/A 79 80 chr10 116391763 N/A N/A 75.00 81 82 chr10 120011530 79.55 N/A N/A 83 84 chr10 126172714 N/A 80.00 N/A 85 86 chr10 126172747 N/A 84.62 N/A 85 86 chr11 556355 N/A N/A 75.00 87 88 chr11 821282 89.13 N/A N/A 89 90 chr11 12188937 83.33 N/A N/A 91 92 chr11 12188948 77.78 N/A N/A 91 92 chr11 12188995 78.57 N/A N/A 93 94 chr11 36057726 N/A 79.63 N/A 95 96 chr11 48070143 N/A 84.38 N/A 97 98 chr11 48070163 N/A 87.50 N/A 97 98 chr11 48070166 N/A 84.38 N/A 97 98 chr11 48070174 N/A 84.48 N/A 97 98 chr11 65158294 78.00 N/A N/A 99 100 chr11 65158342 85.00 N/A N/A 99 100 chr11 65297089 75.00 N/A N/A 101 102 chr11 66104481 81.58 N/A N/A 103 104 chr11 66104485 83.33 N/A N/A 103 104 chr11 66104578 81.82 N/A N/A 105 106 chr11 68608767 N/A N/A 73.33 107 108 chr11 70236292 89.29 N/A N/A 109 110 chr11 70236320 85.71 N/A N/A 109 110 chr11 70236331 70.83 N/A N/A 109 110 chr11 115530032 N/A N/A 79.49 111 112 chr11 117950310 79.55 N/A N/A 113 114 chr11 117950329 79.55 N/A N/A 113 114 chr11 117950361 80.00 N/A N/A 115 116 chr11 117950362 81.82 N/A N/A 115 116 chr11 119293593 N/A N/A 60.00 117 118 chr12 679803 86.84 N/A N/A 119 120 chr12 26039132 73.91 N/A N/A 121 122 chr12 31004558 N/A N/A 81.82 123 124 chr12 45610695 N/A N/A 83.33 125 126 chr12 45610701 N/A N/A 86.67 125 126 chr12 45610702 N/A N/A 89.47 125 126 chr12 45610706 N/A N/A 80.00 125 126 chr12 50286016 82.14 N/A N/A 127 128 chr12 52243258 82.00 N/A N/A 129 130 chr12 52243286 82.50 N/A N/A 129 130 chr12 54145732 N/A N/A 82.35 131 132 chr12 54145741 N/A N/A 76.47 131 132 chr12 54145825 N/A N/A 70.59 131 132 chr12 56115043 89.29

N/A N/A 133 134 chr12 66262229 72.22 N/A N/A 135 136 chr12 66262230 71.74 N/A N/A 135 136 chr12 66262233 68.27 N/A N/A 135 136 chr12 66262234 71.74 N/A N/A 135 136 chr12 77266621 N/A 73.53 N/A 137 138 chr12 117580102 84.62 N/A N/A 139 140 chr12 123435962 63.89 N/A N/A 141 142 chr12 123436011 71.88 N/A N/A 143 144 chr12 123436065 69.44 N/A N/A 143 144 chr12 123540893 77.27 N/A N/A 145 146 chr13 20735797 N/A N/A 82.35 147 148 chr13 23500419 N/A N/A 68.42 149 150 chr13 46771519 67.65 N/A N/A 151 152 chr13 46771520 73.91 N/A N/A 151 152 chr13 53313426 N/A N/A 60.00 153 154 chr13 113807393 N/A N/A 27.27 155 156 chr14 38599118 65.91 N/A N/A 157 158 chr14 69170010 86.36 N/A N/A 159 160 chr14 75701632 68.42 N/A N/A 161 162 chr14 75701643 68.75 N/A N/A 161 162 chr14 90850454 N/A N/A 54.55 163 164 chr14 97524282 N/A 88.89 N/A 165 166 chr14 103541602 N/A N/A 52.00 167 168 chr14 103768055 76.09 N/A N/A 169 170 chr14 104209000 N/A 80.77 N/A 171 172 chr14 104209068 N/A 83.33 N/A 171 172 chr14 104354645 72.92 N/A N/A 173 174 chr14 104360487 83.33 N/A N/A 175 176 chr15 41068807 69.12 N/A N/A 17 178 chr15 61152225 83.33 N/A N/A 179 180 chr15 61152253 86.67 N/A N/A 181 182 chr15 61152313 86.67 N/A N/A 183 184 chr15 65186440 N/A N/A 55.56 185 186 chr15 68851629 N/A N/A 63.64 187 188 chr15 70667596 83.33 N/A N/A 189 190 chr15 70767206 90.00 N/A N/A 191 192 chr15 75251486 N/A N/A 60.00 193 194 chr15 77984014 N/A 88.89 N/A 195 196 chr15 77989064 73.53 N/A N/A 197 198 chr15 83952081 N/A N/A 72.73 199 200 chr15 85402496 82.10 N/A N/A 201 202 chr15 85402497 79.49 N/A N/A 201 202 chr15 99417337 88.89 N/A N/A 203 204 chr16 1231873 86.36 N/A N/A 205 206 chr16 1458639 N/A N/A 75.00 207 208 chr16 3023231 N/A 84.00 N/A 209 210 chr16 23135832 87.50 N/A N/A 211 212 chr16 29616265 85.71 N/A N/A 213 214 chr16 31009547 84.00 N/A N/A 215 216 chr16 31009548 85.00 N/A N/A 215 216 chr16 31009590 85.00 N/A N/A 215 216 chr16 57793674 80.95 N/A N/A 217 218 chr16 57793715 85.71 N/A N/A 217 218 chr16 57793727 80.95 N/A N/A 217 218 chr16 70771056 68.75 N/A N/A 219 220 chr16 70771079 63.33 N/A N/A 219 220 chr16 70771141 65.79 N/A N/A 219 220 chr16 77332010 72.58 N/A N/A 221 222 chr16 78540378 75.76 N/A N/A 223 224 chr16 79333435 N/A 89.61 N/A 225 226 chr16 84262419 87.23 N/A N/A 227 228 chr16 88701114 N/A N/A 66.67 229 230 chr16 89988308 N/A N/A 83.33 231 232 chr16 89988644 N/A N/A 47.37 233 234 chr17 1509928 N/A 88.46 N/A 235 236 chr17 1509945 N/A 88.46 N/A 235 236 chr17 1509952 N/A 83.93 N/A 235 236 chr17 1509953 N/A 85.00 N/A 235 236 chr17 7644013 N/A 85.42 N/A 237 238 chr17 16323460 85.00 N/A N/A 239 240 chr17 16323473 84.21 N/A N/A 239 240 chr17 16924561 80.36 N/A N/A 241 242 chr17 16924562 75.71 N/A N/A 241 242 chr17 16924594 75.71 N/A N/A 241 242 chr17 17717918 72.73 N/A N/A 243 244 chr17 17718591 84.38 N/A N/A 245 246 chr17 18139506 82.81 N/A N/A 247 248 chr17 35278031 N/A N/A 28.42 249 250 chr17 39677570 71.88 N/A N/A 251 252 chr17 40826257 N/A N/A 23.81 253 254 chr17 43037426 N/A N/A 33.33 255 256 chr17 43200096 77.78 N/A N/A 257 258 chr17 43200239 85.00 N/A N/A 259 260 chr17 43510142 N/A N/A 81.82 261 262 chr17 47987828 N/A N/A 69.23 263 264 chr17 48178379 83.33 N/A N/A 265 266 chr17 48596391 N/A 88.64 N/A 267 268 chr17 48764165 88.89 N/A N/A 269 270 chr17 55701962 68.75 N/A N/A 271 272 chr17 73584599 N/A N/A 60.00 273 274 chr17 73993165 90.00 N/A N/A 275 276 chr17 75827716 78.57 N/A N/A 277 278 chr17 76882243 61.54 N/A N/A 279 280 chr17 78765910 88.71 N/A N/A 281 282 chr17 79544478 83.15 N/A N/A 283 284 chr17 80696474 60.00 N/A N/A 285 286 chr18 19751759 N/A N/A 33.33 287 288 chr18 21440760 67.86 N/A N/A 289 290 chr18 45555437 66.18 N/A N/A 291 292 chr18 45555438 73.68 N/A N/A 291 292 chr18 46547891 76.09 N/A N/A 293 294 chr18 55888885 75.47 N/A N/A 295 296 chr18 56452096 90.00 N/A N/A 297 298 chr18 56452476 81.82 N/A N/A 299 300 chr18 56887181 N/A N/A 60.00 301 302 chr18 76002973 81.58 N/A N/A 303 304 chr18 77331090 81.03 N/A N/A 305 306 chr19 677895 85.29 N/A N/A 307 308 chr19 884044 76.92 N/A N/A 309 310 chr19 884059 76.92 N/A N/A 309 310 chr19 884105 84.62 N/A N/A 311 312 chr19 884115 84.62 N/A N/A 311 312 chr19 1136511 86.96 N/A N/A 313 314 chr19 1177605 73.68 N/A N/A 315 316 chr19 1177612 72.73 N/A N/A 315 316 chr19 1177640 81.82 N/A N/A 315 316 chr19 1860601 88.46 N/A N/A 317 318 chr19 1860607 82.81 N/A N/A 317 318 chr19 2503954 90.00 N/A N/A 319 320 chr19 3434917 N/A N/A 40.00 321 322 chr19 3434921 N/A N/A 42.86 321 322 chr19 3434930 N/A N/A 57.14 321 322 chr19 3434939 N/A

N/A 71.43 321 322 chr19 3434952 N/A N/A 71.43 321 322 chr19 3434954 N/A N/A 60.00 321 322 chr19 3434962 N/A N/A 71.43 321 322 chr19 3434964 N/A N/A 71.43 321 322 chr19 3434979 N/A N/A 66.67 321 322 chr19 3434985 N/A N/A 55.56 321 322 chr19 4052713 85.56 N/A N/A 323 324 chr19 4052714 85.14 N/A N/A 323 324 chr19 4052749 84.62 N/A N/A 323 324 chr19 4374591 82.14 N/A N/A 325 326 chr19 5013982 N/A 83.33 N/A 327 328 chr19 5048836 77.27 N/A N/A 329 330 chr19 5048867 70.59 N/A N/A 329 330 chr19 5048877 73.53 N/A N/A 329 330 chr19 8367279 75.00 N/A N/A 331 332 chr19 8428573 N/A N/A 75.00 333 334 chr19 10254577 76.25 N/A N/A 335 336 chr19 10254578 79.17 N/A N/A 335 336 chr19 10463956 N/A 86.73 N/A 337 338 chr19 10464137 N/A 89.29 N/A 339 340 chr19 13203671 75.86 N/A N/A 341 342 chr19 13266925 N/A N/A 66.67 343 344 chr19 13266934 N/A N/A 66.67 343 344 chr19 13266970 N/A N/A 63.64 343 344 chr19 13842142 N/A N/A 76.47 345 346 chr19 14248494 N/A N/A 73.91 347 348 chr19 15375465 72.22 N/A N/A 349 350 chr19 17218912 81.25 N/A N/A 351 352 chr19 17346702 N/A N/A 85.71 353 354 chr19 17346702 N/A N/A 78.95 353 354 chr19 18157161 88.24 N/A N/A 355 356 chr19 18157221 86.76 N/A N/A 357 358 chr19 18157258 65.22 N/A N/A 359 360 chr19 18415877 N/A N/A 47.83 361 362 chr19 18415890 N/A N/A 47.83 361 362 chr19 30606642 80.56 N/A N/A 363 364 chr19 35531842 N/A N/A 83.33 365 366 chr19 44303112 N/A N/A 77.78 367 368 chr19 47173037 N/A 88.64 N/A 369 370 chr19 47316268 76.67 N/A N/A 371 372 chr19 47778278 N/A N/A 66.67 373 374 chr19 47778298 N/A N/A 83.33 373 374 chr2 3454277 N/A 84.78 N/A 375 376 chr2 8793724 N/A 78.57 N/A 377 378 chr2 20412441 85.71 N/A N/A 379 380 chr2 42329402 N/A N/A 78.95 381 382 chr2 42329494 N/A N/A 60.00 381 382 chr2 55289272 N/A 75.00 N/A 383 384 chr2 65064865 64.71 N/A N/A 385 386 chr2 70823641 79.03 N/A N/A 387 388 chr2 73143689 N/A N/A 77.78 389 390 chr2 74454110 70.00 N/A N/A 391 392 chr2 122014529 N/A 86.36 N/A 393 394 chr2 128158884 85.00 N/A N/A 395 396 chr2 128158910 77.50 N/A N/A 395 396 chr2 203114171 79.63 N/A N/A 397 398 chr2 218221671 N/A 85.19 N/A 399 400 chr2 219745335 N/A N/A 81.82 401 402 chr2 238341465 86.36 N/A N/A 403 404 chr2 238341542 90.00 N/A N/A 405 406 chr2 238341546 87.50 N/A N/A 405 406 chr2 238774763 67.57 N/A N/A 407 408 chr20 31126186 87.50 N/A N/A 409 410 chr20 31126189 84.21 N/A N/A 409 410 chr20 34206950 N/A N/A 76.47 411 412 chr20 36771969 79.31 N/A N/A 413 414 chr20 48993661 80.00 N/A N/A 415 416 chr20 58406398 89.66 N/A N/A 417 418 chr20 61976049 87.93 N/A N/A 419 420 chr20 61976073 89.66 N/A N/A 419 420 chr20 62588571 N/A N/A 50.00 421 422 chr20 62588579 N/A N/A 38.46 421 422 chr22 19738127 70.59 N/A N/A 423 424 chr22 35965176 76.32 N/A N/A 425 426 chr22 36549809 83.33 N/A N/A 427 428 chr22 36973375 80.43 N/A N/A 429 430 chr22 37447953 N/A N/A 73.33 431 432 chr22 37914998 N/A N/A 69.23 433 434 chr22 38307317 N/A 89.66 N/A 435 436 chr22 39662794 84.62 N/A N/A 437 438 chr22 45622980 85.00 N/A N/A 439 440 chr3 13323642 N/A N/A 72.73 441 442 chr3 14180153 57.89 N/A N/A 443 444 chr3 45209073 N/A N/A 60.00 445 446 chr3 45209207 N/A N/A 83.33 447 448 chr3 52525100 79.41 N/A N/A 449 450 chr3 62589658 87.50 N/A N/A 451 452 chr3 65388317 71.43 N/A N/A 453 454 chr3 65388388 79.31 N/A N/A 455 456 chr3 73599302 85.11 N/A N/A 457 458 chr3 195636893 N/A N/A 84.62 459 460 chr3 197093846 80.00 N/A N/A 461 462 chr4 3743223 68.18 N/A N/A 463 464 chr4 5755716 85.48 N/A N/A 465 466 chr4 5755717 80.00 N/A N/A 465 466 chr4 5755728 82.26 N/A N/A 465 466 chr4 5755729 79.17 N/A N/A 465 466 chr4 5755734 79.17 N/A N/A 465 466 chr4 8372861 N/A 85.71 N/A 467 468 chr4 57548289 80.23 N/A N/A 469 470 chr5 1118280 73.08 N/A N/A 471 472 chr5 34564389 89.29 N/A N/A 473 474 chr5 73871907 89.47 N/A N/A 475 476 chr5 78013596 70.00 N/A N/A 477 478 chr5 78013643 80.00 N/A N/A 479 480 chr5 137802650 72.73 N/A N/A 481 482 chr5 139051189 84.09 N/A N/A 483 484 chr5 167838221 68.18 N/A N/A 485 486 chr5 177541401 N/A N/A 69.23 487 488 chr5 180018672 N/A N/A 72.73 489 490 chr5 180101026 N/A N/A 64.71 491 492 chr6 3394325 N/A 87.84 N/A 493 494 chr6 3887581 N/A 85.71 N/A 495 496 chr6 7236568 84.43 N/A N/A 497 498 chr6 7728692 N/A N/A 73.33 499 500 chr6 34203617 N/A N/A 45.45 501 502 chr6 37751320 N/A N/A 78.57 503 504 chr6 41410682 N/A N/A 77.78 505 506 chr6 41438516 N/A N/A 39.13 507 508 chr6 41438575 89.66 N/A N/A 507 508 chr6 43464150 75.76 N/A N/A 509 510 chr6 158734279 N/A 86.84 N/A 511 512 chr7 989235 76.67 N/A N/A 513 514 chr7 2673543 82.14 N/A N/A 515 516 chr7 73508602 N/A N/A

85.71 517 518 chr7 105079565 78.75 N/A N/A 519 520 chr7 105079631 71.25 N/A N/A 519 520 chr7 151425103 86.96 N/A N/A 521 522 chr7 151425104 76.19 N/A N/A 521 522 chr8 11764017 80.77 N/A N/A 523 524 chr8 21647308 N/A N/A 71.43 525 526 chr8 22548399 N/A 88.16 N/A 527 528 chr8 22548483 N/A 87.50 N/A 527 528 chr8 133570537 N/A 80.00 N/A 529 530 chr8 141320393 75.00 N/A N/A 531 532 chr8 141320410 85.00 N/A N/A 531 532 chr9 6566568 86.84 N/A N/A 533 534 chr9 16197862 N/A 86.36 N/A 535 536 chr9 34591313 N/A N/A 80.00 537 538 chr9 98225096 N/A N/A 22.22 539 540 chr9 126126741 86.11 N/A N/A 541 542 chr9 132083428 N/A N/A 70.59 543 544 chr9 136077410 73.91 N/A N/A 545 546 chr9 139655018 83.33 N/A N/A 547 548 chr9 140205985 75.00 N/A N/A 549 550 chr9 140205985 83.33 N/A N/A 549 550 chr9 140205997 79.17 N/A N/A 549 550 *Level values provided are the proportion (percentage) of reacted thyroid nodule DNA molecules having a uracil at the methylation site of interest. When amplicons generated from reacted thyroid nodule DNA molecules (e.g., by PCR) are used to assess the level of methylation, the values provided correspond to the proportion of amplicons having a thymidine at the nucleotide position that corresponds to the methylation site of interest.

(73) In embodiments, the method of detecting methylation or unmethylation of a thyroid nodule DNA of a subject detects an alteration in methylation including increase or loss of uracil level at plurality of methylation sites. In embodiments, the method of detecting methylation or unmethylation of a thyroid nodule DNA of a subject detects an alteration in methylation including increase or loss of thymidine level at plurality of methylation sites. The indicated levels in Tables 1, 2, 3, and 4, are approximate indicated levels, and include values that are within about 15%, about 10%, or about 5% above and below the indicated levels.

(74) In embodiments, the method detects the uracil level above about a threshold as set forth in Table 2 in subjects with a cancerous thyroid nodule. In embodiments, the method detects the thymidine level above about a threshold as set forth in Table 2 in subjects with a cancerous thyroid nodule.

(75) TABLE-US-00002 TABLE 2 Methylation Threshold for Cancerous Thyroid Nodule Uracil level in reacted thyroid nodule DNA from Chromosomal cancer tissues is about Chromosome Position above indicated level* chr1 11979164 89.29 chr1 16450525 70.00 chr1 16450542 72.00 chr1 16450545 73.33 chr1 16469987 80.00 chr1 17494491 86.00 chr1 25473203 88.89 chr1 38493013 86.36 chr1 38493030 79.17 chr1 38493074 80.95 chr1 109816092 80.77 chr1 109816111 80.77 chr1 110074669 75.00 chr1 110074681 71.43 chr1 110074685 63.16 chr1 150949856 89.29 chr1 150949857 88.46 chr1 153540282 78.26 chr1 155162704 84.21 chr1 155162714 88.64 chr1 157611881 83.05 chr1 182205324 77.50 chr1 204118999 59.09 chr1 206741875 83.33 chr1 206741989 66.67 chr1 212841198 85.29 chr1 223403952 79.17 chr1 234342767 76.67 chr10 3929071 88.68 chr10 30047012 86.84 chr10 79702989 83.33 chr10 87984905 86.36 chr10 94838789 63.33 chr10 102131187 90.00 chr10 104196489 75.00 chr10 111766879 89.47 chr10 112258886 81.82 chr10 112258984 83.33 chr10 112259015 82.61 chr10 120011530 79.55 chr11 821282 89.13 chr11 12188937 83.33 chr11 12188948 77.78 chr11 12188995 78.57 chr11 65158294 78.00 chr11 65158342 85.00 chr11 65297089 75.00 chr11 66104481 81.58 chr11 66104485 83.33 chr11 66104578 81.82 chr11 70236292 89.29 chr11 70236320 85.71 chr11 70236331 70.83 chr11 117950310 79.55 chr11 117950329 79.55 chr11 117950361 80.00 chr11 117950362 81.82 chr12 679803 86.84 chr12 26039132 73.91 chr12 50286016 82.14 chr12 52243258 82.00 chr12 52243286 82.50 chr12 56115043 89.29 chr12 66262229 72.22 chr12 66262230 71.74 chr12 66262233 68.27 chr12 66262234 71.74 chr12 117580102 84.62 chr12 123435962 63.89 chr12 123436011 71.88 chr12 123436065 69.44 chr12 123540893 77.27 chr13 46771519 67.65 chr13 46771520 73.91 chr14 38599118 65.91 chr14 69170010 86.36 chr14 75701632 68.42 chr14 75701643 68.75 chr14 103768055 76.09 chr14 104354645 72.92 chr14 104360487 83.33 chr15 41068807 69.12 chr15 61152225 83.33 chr15 61152253 86.67 chr15 61152313 86.67 chr15 70667596 83.33 chr15 70767206 90.00 chr15 77989064 73.53 chr15 85402496 82.10 chr15 85402497 79.49 chr15 99417337 88.89 chr16 1231873 86.36 chr16 23135832 87.50 chr16 29616265 85.71 chr16 31009547 84.00 chr16 31009548 85.00 chr16 31009590 85.00 chr16 57793674 80.95 chr16 57793715 85.71 chr16 57793727 80.95 chr16 70771056 68.75 chr16 70771079 63.33 chr16 70771141 65.79 chr16

77332010 72.58 chr16 78540378 75.76 chr16 84262419 87.23 chr17 16323460 85.00 chr17 16323473 84.21 chr17 16924561 80.36 chr17 16924562 75.71 chr17 16924594 75.71 chr17 17717918 72.73 chr17 17718591 84.38 chr17 18139506 82.81 chr17 39677570 71.88 chr17 43200096 77.78 chr17 43200239 85.00 chr17 48178379 83.33 chr17 48764165 88.89 chr17 55701962 68.75 chr17 73993165 90.00 chr17 75827716 78.57 chr17 76882243 61.54 chr17 78765910 88.71 chr17 79544478 83.15 chr17 80696474 60.00 chr18 21440760 67.86 chr18 45555437 66.18 chr18 45555438 73.68 chr18 46547891 76.09 chr18 55888885 75.47 chr18 56452096 90.00 chr18 56452476 81.82 chr18 76002973 81.58 chr18 77331090 81.03 chr19 677895 85.29 chr19 884044 76.92 chr19 884059 76.92 chr19 884105 84.62 chr19 884115 84.62 chr19 1136511 86.96 chr19 1177605 73.68 chr19 1177612 72.73 chr19 1177640 81.82 chr19 1860601 88.46 chr19 1860607 82.81 chr19 2503954 90.00 chr19 4052713 85.56 chr19 4052714 85.14 chr19 4052749 84.62 chr19 4374591 82.14 chr19 5048836 77.27 chr19 5048867 70.59 chr19 5048877 73.53 chr19 8367279 75.00 chr19 10254577 76.25 chr19 10254578 79.17 chr19 13203671 75.86 chr19 15375465 72.22 chr19 17218912 81.25 chr19 18157161 88.24 chr19 18157221 86.76 chr19 18157258 65.22 chr19 30606642 80.56 chr19 47316268 76.67 chr2 20412441 85.71 chr2 65064865 64.71 chr2 70823641 79.03 chr2 74454110 70.00 chr2 128158884 85.00 chr2 128158910 77.50 chr2 203114171 79.63 chr2 238341465 86.36 chr2 238341542 90.00 chr2 238341546 87.50 chr2 238774763 67.57 chr20 31126186 87.50 chr20 31126189 84.21 chr20 36771969 79.31 chr20 48993661 80.00 chr20 58406398 89.66 chr20 61976049 87.93 chr20 61976073 89.66 chr22 19738127 70.59 chr22 35965176 76.32 chr22 36549809 83.33 chr22 36973375 80.43 chr22 39662794 84.62 chr22 45622980 85.00 chr3 14180153 57.89 chr3 52525100 79.41 chr3 62589658 87.50 chr3 65388317 71.43 chr3 65388388 79.31 chr3 73599302 85.11 chr3 197093846 80.00 chr4 3743223 68.18 chr4 5755716 85.48 chr4 5755717 80.00 chr4 5755728 82.26 chr4 5755729 79.17 chr4 5755734 79.17 chr4 57548289 80.23 chr5 1118280 73.08 chr5 34564389 89.29 chr5 73871907 89.47 chr5 78013596 70.00 chr5 78013643 80.00 chr5 137802650 72.73 chr5 139051189 84.09 chr5 167838221 68.18 chr6 7236568 84.43 chr6 41438575 89.66 chr6 43464150 75.76 chr7 989235 76.67 chr7 2673543 82.14 chr7 105079565 78.75 chr7 105079631 71.25 chr7 151425103 86.96 chr7 151425104 76.19 chr8 11764017 80.77 chr8 141320393 75.00 chr8 141320410 85.00 chr9 6566568 86.84 chr9 126126741 86.11 chr9 136077410 73.91 chr9 139655018 83.33 chr9 140205985 75.00 chr9 140205989 83.33 chr9 140205997 79.17 *Level values provided are the proportion (percentage) of reacted thyroid nodule DNA molecules having a uracil at the methylation site of interest. When amplicons generated from reacted thyroid nodule DNA molecules (e.g., by PCR) are used to assess the level of methylation, the values provided correspond to the proportion of amplicons having a thymidine at the nucleotide position that corresponds to the methylation site of interest.

(76) In embodiments, the uracil level is above a threshold as set forth in Table 3 in subjects with benign thyroid nodules. In embodiments, the thymidine level is above a threshold as set forth in Table 3 in subjects with benign thyroid nodules.

(77) TABLE-US-00003 TABLE 3 Threshold for Benign Thyroid Nodule Uracil level in reacted thyroid nodule DNA from benign tissues is Chromosomal about above Chromosome Position indicated level* chr1 2996653 88.84 chr1 27640460 80.56 chr10 126172714 80.00 chr10 126172747 84.62 chr11 36057726 79.63 chr11 48070143 84.38 chr11 48070163 87.50 chr11 48070166 84.38 chr11 48070174 84.48 chr12 77266621 73.53 chr14 97524282 88.89 chr14 104209000 80.77 chr14 104209068 83.33 chr15 77984014 88.89 chr16 3023231 84.00 chr16 79333435 89.61 chr17 1509928 88.46 chr17 1509945 88.46 chr17 1509952 83.93 chr17 1509953 85.00 chr17 7644013 85.42 chr17 48596391 88.64 chr19 5013982 83.33 chr19 10463956 86.73 chr19 10464137 89.29 chr19 47173037 88.64 chr2 3454277 84.78 chr2 8793724 78.57 chr2 55289272 75.00 chr2 122014529 86.36 chr2 218221671 85.19 chr22 38307317 89.66 chr4 8372861 85.71 chr6 3394325 87.84 chr6 3887581 85.71 chr6 1.59E+08 86.84 chr8 22548399 88.16 chr8 22548483 87.50 chr8 1.34E+08 80.00 chr9 16197862 86.36 *Level values provided are the proportion (percentage) of reacted thyroid nodule DNA molecules having a uracil at the methylation site of interest. When amplicons generated from reacted thyroid nodule DNA molecules (e.g., by PCR) are used to assess the level of methylation, the

values provided correspond to the proportion of amplicons having a thymidine at the nucleotide position that corresponds to the methylation site of interest.

(78) In embodiments, the uracil level is below a threshold as set forth in Table 4 in subjects with benign thyroid nodule. In embodiments, the thymidine level is below a threshold as set forth in Table 4 in subjects with benign thyroid nodule.

(79) TABLE-US-00004 TABLE 4 Methylation Threshold for Benign Thyroid Nodule Uracil level in reacted thyroid nodule DNA from Chromosomal benign tissues is about Chromosome Position below indicated level* chr1 12655938 69.23 chr1 29565080 60.00 chr1 46713777 73.33 chr1 46914121 60.00 chr1 46955744 77.78 chr1 55008344 60.00 chr1 156676611 84.62 chr1 212587673 80.00 chr1 233430972 86.67 chr10 116391763 75.00 chr11 556355 75.00 chr11 68608767 73.33 chr11 115530032 79.49 chr11 119293593 60.00 chr12 31004558 81.82 chr12 45610695 83.33 chr12 45610701 86.67 chr12 45610702 89.47 chr12 45610706 80.00 chr12 54145732 82.35 chr12 54145741 76.47 chr12 54145825 70.59 chr13 20735797 82.35 chr13 23500419 68.42 chr13 53313426 60.00 chr13 113807393 27.27 chr14 90850454 54.55 chr14 103541602 52.00 chr15 65186440 55.56 chr15 68851629 63.64 chr15 75251486 60.00 chr15 83952081 72.73 chr16 1458639 75.00 chr16 88701114 66.67 chr16 89988308 83.33 chr16 89988644 47.37 chr17 35278031 28.42 chr17 40826257 23.81 chr17 43037426 33.33 chr17 43510142 81.82 chr17 47987828 69.23 chr17 73584599 60.00 chr18 19751759 33.33 chr18 56887181 60.00 chr19 3434917 40.00 chr19 3434921 42.86 chr19 3434930 57.14 chr19 3434939 71.43 chr19 3434952 71.43 chr19 3434954 60.00 chr19 3434962 71.43 chr19 3434964 71.43 chr19 3434979 66.67 chr19 3434985 55.56 chr19 8428573 75.00 chr19 13266925 66.67 chr19 13266934 66.67 chr19 13266970 63.64 chr19 13842142 76.47 chr19 14248494 73.91 chr19 17346702 85.71 chr19 17346735 78.95 chr19 18415877 47.83 chr19 18415890 47.83 chr19 35531842 83.33 chr19 44303112 77.78 chr19 47778278 66.67 chr19 47778298 83.33 chr2 42329402 78.95 chr2 42329494 60.00 chr2 73143689 77.78 chr2 219745335 81.82 chr20 34206950 76.47 chr20 62588571 50.00 chr20 62588579 38.46 chr22 37447953 73.33 chr22 37914998 69.23 chr3 13323642 72.73 chr3 45209073 60.00 chr3 45209207 83.33 chr3 195636893 84.62 chr5 177541401 69.23 chr5 180018672 72.73 chr5 180101026 64.71 chr6 7728692 73.33 chr6 34203617 45.45 chr6 37751320 78.57 chr6 41410682 77.78 chr6 41438516 39.13 chr7 73508602 85.71 chr8 21647308 71.43 chr9 34591313 80.00 chr9 98225096 22.22 chr9 132083428 70.59 *Level values provided are the proportion (percentage) of reacted thyroid nodule DNA molecules having a uracil at the methylation site of interest. When amplicons generated from reacted thyroid nodule DNA molecules (e.g., by PCR) are used to assess the level of methylation, the values provided correspond to the proportion of amplicons having a thymidine at the nucleotide position that corresponds to the methylation site of interest.

(80) In embodiments, the method of detecting methylation or unmethylation of a thyroid nodule DNA is of a candidate thyroid cancer patient. In embodiments, the subject is suspected of having thyroid cancer. In embodiments, the subject has thyroid cancer.

(81) In embodiments, the method of detecting methylation or unmethylation of a thyroid nodule DNA is based on the level of uracil as set forth Table 2, in which the uracil level above the threshold identifies the thyroid nodule as a cancerous thyroid nodule. In embodiments, the method of detecting methylation or unmethylation of a thyroid nodule DNA is based on a level of thymidine indicated in Table 2, in which the thymidine level above the threshold identifies the thyroid nodule as a cancerous thyroid nodule. In embodiments, the level is the proportion of molecules (e.g., in a plurality of reacted thyroid nodule DNA molecules or a plurality of reacted thyroid nodule DNA amplicons) having a uracil or thymidine as determined by a quantitation method. Non-limiting examples of quantitation methods include sequencing and microarray methods.

(82) In embodiments, the method of detecting methylation or unmethylation of a thyroid nodule DNA is based on the level of uracil as set forth Table 3, in which the uracil level above the threshold identifies the thyroid nodule as a benign thyroid nodule. In embodiments, the method of detecting methylation or unmethylation of a thyroid nodule DNA is based on a level of thymidine indicated in Table 3, in which the thymidine level above the threshold identifies the thyroid nodule as a benign

thyroid nodule. In embodiments, the level is the proportion of molecules (e.g., in a plurality of reacted thyroid nodule DNA molecules or a plurality of reacted thyroid nodule DNA amplicons) having a uracil or thymidine as determined by a quantitation method.

(83) In embodiments, the method of detecting methylation or unmethylation of a thyroid nodule DNA is based on the level of uracil as set forth Table 4, in which the uracil level below the threshold identifies the thyroid nodule as a benign thyroid nodule. In embodiments, the method of detecting methylation or unmethylation of a thyroid nodule DNA is based on a level of thymidine indicated in Table 4, in which the thymidine level below the threshold identifies the thyroid nodule as a benign thyroid nodule. In embodiments, the level is the proportion of molecules (e.g., in a plurality of reacted thyroid nodule DNA molecules or a plurality of reacted thyroid nodule DNA amplicons) having a uracil or thymidine as determined by a quantitation method.

(84) In embodiments, the thyroid nodule is a specimen obtained by biopsy or by surgical resection of a subject.

(85) In embodiments, the subject has undergone thyroid surgery, radiation therapy, radioactive iodine therapy, chemotherapy, thyroid hormone therapy, and administration of an active agent before the subject undergoes the method of detecting methylation or unmethylation of a thyroid nodule DNA.

(86) In embodiments, the method includes a determination of prognosis for local recurrence in thyroid cancer. In embodiments, the method includes determination of prognosis of distant recurrence of thyroid cancer.

(87) In embodiments, the method of detecting DNA methylation level in DNA of thyroid nodule may lead to changes in therapeutic regimen for treating the subject. In embodiments a subject identified as having thyroid cancer may be treated with tyrosine kinase inhibitors.

(88) In embodiments, the active agent administered to a subject before or after detecting the level of methylation or unmethylation is: Cabozantinib-S-Malate, Caprelsa® (Vandetanib), Cometriq® (Cabozantinib-S-Malate), Doxorubicin Hydrochloride, Lenvatinib Mesylate, Lenvima® (Lenvatinib Mesylate), Nexavar® (Sorafenib Tosylate), Sorafenib Tosylate, and/or Vandetanib.

(89) Method of Determining Thyroid Cancer or Risk of Developing Thyroid Cancer

(90) In an aspect, provided herein is a method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof. The method involves: (i) isolating a thyroid nodule DNA molecule from a thyroid nodule of the subject thereby forming an isolated thyroid nodule DNA molecule; (ii) contacting the isolated thyroid nodule DNA molecule with a bisulfite salt (such as sodium bisulfite) thereby forming a reacted thyroid nodule DNA molecule; and (iii) detecting the presence or absence of uracil in the reacted thyroid nodule DNA molecule at a methylation site set forth in Table 1; thereby detecting the thyroid cancer in the subject.

(91) In an aspect, provided herein is a method of detecting a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof, comprising (i) isolating a plurality of thyroid nodule DNA molecules from the thyroid nodule of the subject thereby forming a plurality of isolated thyroid nodule DNA molecules, (ii) contacting the plurality of isolated thyroid nodule DNA molecules with the bisulfite salt thereby forming a plurality of reacted thyroid nodule DNA molecules, (iii) detecting the level of reacted thyroid nodule DNA molecules in the plurality of reacted thyroid nodule DNA molecules having a uracil at a methylation site set forth in Table 1; thereby detecting the thyroid cancer in the subject.

(92) In an aspect, provided herein is a method of detecting a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof, comprising (i) isolating a plurality of thyroid nodule DNA molecules from the thyroid nodule of the subject thereby forming a plurality of isolated thyroid nodule DNA molecules, (ii) contacting the plurality of isolated thyroid nodule DNA molecules with the bisulfite salt thereby forming a plurality of reacted thyroid nodule DNA molecules, (iii) detecting the presence or absence of uracil in a reacted thyroid nodule DNA molecule at a methylation site set forth in Table 1, thereby detecting methylation or unmethylation of the thyroid nodule DNA molecule of the subject.

(93) In an aspect, provided herein is a method of detecting a thyroid cancer or risk of developing

thyroid cancer in a subject in need thereof. The method includes: (i) isolating a thyroid nodule DNA molecule from a thyroid nodule of the subject thereby forming an isolated thyroid nodule DNA molecule, (ii) contacting the isolated thyroid nodule DNA molecule with a bisulfite salt (such as sodium bisulfite) thereby forming a reacted thyroid nodule DNA molecule, (iii) amplifying the reacted thyroid nodule DNA molecule thereby forming a reacted thyroid nodule DNA amplicon molecule, (iv) detecting the presence or absence of thymidine in a reacted thyroid nodule DNA amplicon molecule at a methylation site set forth in Table 1, thereby detecting methylation or unmethylation of the thyroid nodule DNA molecule of the subject. In embodiments, contacting the isolated thyroid nodule DNA with a bisulfite salt comprises adding a solution comprising the bisulfite salt to a solution comprising the isolated single stranded DNA.

(94) In an aspect, provided herein is a method of detecting a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof, comprising (i) isolating a plurality of thyroid nodule DNA molecules from the thyroid nodule of the subject thereby forming a plurality of isolated thyroid nodule DNA molecules, (ii) contacting the plurality of isolated thyroid nodule DNA molecules with the bisulfite salt thereby forming a plurality of reacted thyroid nodule DNA molecules, (iii) amplifying the plurality of reacted thyroid nodule DNA molecules thereby forming a plurality of reacted thyroid nodule DNA amplicon molecules, (iv) detecting one or more thyroid nodule DNA amplicon molecules within the plurality of reacted thyroid nodule DNA amplicon molecules having a thymidine at a methylation site set forth in Table 1, thereby detecting methylation or unmethylation of the thyroid nodule DNA molecule of the subject.

(95) In embodiments, detecting one or more thyroid nodule DNA amplicon molecules comprises detecting the level of one or more one or more thyroid nodule DNA amplicon molecules. In embodiments, detecting one or more thyroid nodule DNA amplicon molecules comprises detecting the level of reacted thyroid nodule DNA amplicon molecules in the plurality of reacted thyroid nodule DNA amplicon molecules having a thymidine at a methylation site set forth in Table 1, thereby detecting the level of methylation or unmethylation in the plurality of thyroid nodule DNA molecules of the subject.

(96) In embodiments, detecting a level includes determining the number (e.g. quantitating) or molecules having, e.g., a thymidine or a uracil. In embodiments, detecting a level includes detecting the portion or proportion of a population or plurality of molecules having, e.g., a thymidine or a uracil.

(97) In embodiments, contacting the isolated thyroid nodule DNA with a bisulfite salt comprises adding a solution comprising the bisulfite salt to a solution comprising the isolated thyroid nodule DNA.

(98) In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes selecting a subject that has or is at risk for developing thyroid cancer. In embodiments, the subject (a) is a woman; (b) is about 20 to about 55 years old; (c) has a mutated Ret Proto-Oncogene; (d) has a grandparent, parent, or sibling who has been diagnosed with thyroid cancer; (e) self-identifies as being Caucasian or Asian; and/or (f) has or has had breast cancer.

(99) In embodiments, the method includes detecting methylation or unmethylation at a plurality of methylation sites set forth in Table 1. In embodiments, the plurality of methylation sites comprises at least about 2, 3, 4, 5, 10, 25, 50, 75, 80, 85, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 550, or 5-550 methylation sites. In embodiments, the plurality of methylation sites comprises less than about 550, 500, 450, 400, 350, 300, 250, 200, 150, 100, 90, 85, 80, 75, 50, 25, or 10 methylation sites. In embodiments, the plurality of methylation sites is about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 50, 75, 80, 85, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 550, or 5-550 methylation sites. In embodiments, the plurality of methylation sites includes two or more methylation sites set forth in Table 1 and no other methylation sites.

(100) In embodiments, a method provided herein is practiced for a subject more than once over time. In embodiments, methylation or unmethylation of thyroid nodule DNA from a subject is assessed using a method provided herein at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more times. In embodiments, the

method is repeated at least once every 4, 6, 8, 12 or 18 months, or at least once every 2, 3, 4, or 5 more years.

(101) In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining alteration in methylation at a plurality of methylation sites set forth in Table 1. In embodiments, the method comprises: (i) isolating DNA from multiple cells of a thyroid nodule of the subject thereby forming a plurality of isolated thyroid nodule DNA molecules, (ii) contacting the plurality of isolated thyroid nodule DNA molecules with a bisulfite salt thereby forming a plurality of reacted thyroid nodule DNA molecules, (iii) detecting the proportion of DNA molecules in the plurality of reacted thyroid nodule DNA molecules having a uracil at a methylation site set forth in Table 1.

(102) In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes alteration, i.e., increase or loss of uracil level at plurality of methylation sites. In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes alteration, i.e., increase or loss of thymidine level at plurality of methylation sites.

(103) In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining a uracil level which is above a threshold as set forth in Table 2. In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining a thymidine level which is above a threshold indicated in Table 2. In embodiments, the level is the proportion of molecules (e.g., in a plurality of reacted thyroid nodule DNA molecules or a plurality of reacted thyroid nodule DNA amplicons) having a uracil or thymidine as determined by a quantitation method.

(104) In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining a uracil level which is above a threshold as set forth in Table 3. In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining a thymidine level which is above a threshold indicated in Table 3. In embodiments, the level is the proportion of molecules (e.g., in a plurality of reacted thyroid nodule DNA molecules or a plurality of reacted thyroid nodule DNA amplicons) having a uracil or thymidine as determined by a quantitation method.

(105) In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining a uracil level which is below a threshold as set forth in Table 4. In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining a thymidine level which is below a threshold indicated in Table 4. In embodiments, the level is the proportion of molecules (e.g., in a plurality of reacted thyroid nodule DNA molecules or a plurality of reacted thyroid nodule DNA amplicons) having a uracil or thymidine as determined by a quantitation method.

(106) In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer involves a candidate thyroid cancer patient. In embodiments, the subject is suspected of having thyroid cancer. In embodiments, the subject has thyroid cancer.

(107) In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining a uracil level in which a threshold above the threshold set forth in Table 2 identifies the thyroid nodule as a cancerous thyroid nodule. In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining a thymidine level in which a threshold above the threshold indicated in Table 2 identifies the thyroid nodule as a cancerous thyroid nodule. In embodiments, the level is the proportion of molecules (e.g., in a plurality of reacted thyroid nodule DNA molecules or a plurality of reacted thyroid nodule DNA amplicons) having a uracil or thymidine as determined by a quantitation method.

(108) In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining a uracil level in which a threshold above the threshold set forth in Table 3 identifies the thyroid nodule as a benign thyroid nodule. In

embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining a thymidine level in which a threshold above the threshold indicated in Table 3 identifies the thyroid nodule as a benign thyroid nodule. In embodiments, the level is the proportion of molecules (e.g., in a plurality of reacted thyroid nodule DNA molecules or a plurality of reacted thyroid nodule DNA amplicons) having a uracil or thymidine as determined by a quantitation method.

(109) In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining a uracil level in which a threshold below the threshold set forth in Table 4 identifies the thyroid nodule as a benign thyroid nodule. In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining a thymidine level in which a threshold below the threshold indicated in Table 4 identifies the thyroid nodule as a benign thyroid nodule. In embodiments, the level is the proportion of molecules (e.g., in a plurality of reacted thyroid nodule DNA molecules or a plurality of reacted thyroid nodule DNA amplicons) having a uracil or thymidine as determined by a quantitation method.

(110) In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining a uracil level in DNA of a thyroid nodule specimen obtained by biopsy or by surgical resection of a subject. In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof includes determining a thymidine level in DNA of a thyroid nodule specimen obtained by biopsy or by surgical resection of a subject.

(111) In embodiments, the method of determining a thyroid cancer or risk of developing thyroid cancer is of a subject who has previously undergone thyroid surgery, radiation therapy, radioactive iodine therapy, chemotherapy, thyroid hormone therapy, and/or administration of an active agent, before the determination.

(112) In embodiments, a subject having thyroid cancer or at risk of developing thyroid cancer was administered an active agent: Cabozantinib-S-Malate, Caprelsa (Vandetanib), Cometriq (Cabozantinib-S-Malate), Doxorubicin Hydrochloride, Lenvatinib Mesylate, Lenvima (Lenvatinib Mesylate), Nexavar (Sorafenib Tosylate), Sorafenib Tosylate, and/or Vandetanib.

(113) In embodiments, the method of determining a thyroid cancer may lead to changes in therapeutic regimen for treating the subject. In embodiments a subject identified as having thyroid cancer may be treated with tyrosine kinase inhibitors. In embodiments, a subject identified as having thyroid cancer or being at risk of developing thyroid cancer according to a method disclosed herein is advised and/or directed to receive additional screening and/or treatment for thyroid cancer.

(114) In embodiments, the active agent administered to a subject after determining thyroid cancer is: Cabozantinib-S-Malate, Caprelsa (Vandetanib), Cometriq (Cabozantinib-S-Malate), Doxorubicin Hydrochloride, Lenvatinib Mesylate, Lenvima (Lenvatinib Mesylate), Nexavar (Sorafenib Tosylate), Sorafenib Tosylate, and/or Vandetanib.

(115) Method of Treating Thyroid Cancer

(116) Also provided herein is a method of treating thyroid cancer in a subject by administering to the subject an active agent for treating thyroid cancer, in which the subject is identified for treatment by a method including isolating a thyroid nodule DNA molecule from a thyroid nodule of the subject thereby forming an isolated thyroid nodule DNA molecule; contacting the isolated thyroid nodule DNA molecule with a bisulfite salt (such as sodium bisulfite) thereby forming a reacted thyroid nodule DNA molecule; and detecting the presence or absence of uracil in the reacted thyroid nodule DNA molecule at a methylation site set forth in Table 1; thereby detecting the thyroid cancer in the subject. In embodiments, contacting the isolated thyroid nodule DNA with a bisulfite salt comprises adding a solution comprising the bisulfite salt to a solution comprising the isolated thyroid nodule DNA.

(117) In embodiments, the method includes detecting methylation or unmethylation at a plurality of methylation sites set forth in Table 1. In embodiments, the plurality of methylation sites comprises at

least about 2, 3, 4, 5, 10, 25, 50, 75, 80, 85, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 550, or 5-550 methylation sites. In embodiments, the plurality of methylation sites comprises less than about 550, 500, 450, 400, 350, 300, 250, 200, 150, 100, 90, 85, 80, 75, 50, 25, or 10 methylation sites. In embodiments, the plurality of methylation sites is about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 50, 75, 80, 85, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 550, or 5-550 methylation sites. In embodiments, the plurality of methylation sites includes two or more methylation sites set forth in Table 1 and no other methylation sites.

(118) In embodiments, a method provided herein is practiced for a subject more than once over time. In embodiments, methylation or unmethylation of thyroid nodule DNA from a subject is assessed using a method provided herein at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more times. In embodiments, the method is repeated at least once every 4, 6, 8, 12 or 18 months, or at least once every 2, 3, 4, or 5 more years.

(119) In embodiments, the method of treating a thyroid cancer in a subject in need thereof includes determining alteration in methylation at a plurality of methylation sites set forth in Table 1.

(120) In embodiments, the method of treating a thyroid cancer in a subject in need thereof includes alteration which includes increase or loss of uracil level at plurality of methylation sites.

(121) In embodiments, the method of treating a thyroid cancer in a subject in need thereof includes determining a uracil level which is above a threshold as set forth in Table 2. In embodiments, the method of treating a thyroid cancer in a subject in need thereof includes determining a thymidine level which is above a threshold indicated in Table 2. In embodiments, the level is the proportion of molecules (e.g., in a plurality of reacted thyroid nodule DNA molecules or a plurality of reacted thyroid nodule DNA amplicons) having a uracil or thymidine as determined by a quantitation method.

(122) In embodiments, the method of treating a thyroid cancer in a subject in need thereof includes determining a uracil level which is above a threshold as set forth in Table 3. In embodiments, the method of treating a thyroid cancer in a subject in need thereof includes determining a thymidine level which is above a threshold indicated in Table 3. In embodiments, the level is the proportion of molecules (e.g., in a plurality of reacted thyroid nodule DNA molecules or a plurality of reacted thyroid nodule DNA amplicons) having a uracil or thymidine as determined by a quantitation method.

(123) In embodiments, the method of treating a thyroid cancer in a subject in need thereof includes determining a uracil level which is below a threshold as set forth in Table 4. In embodiments, the method of treating a thyroid cancer in a subject in need thereof includes determining a thymidne level which is below a threshold indicated in Table 4. In embodiments, the level is the proportion of molecules (e.g., in a plurality of reacted thyroid nodule DNA molecules or a plurality of reacted thyroid nodule DNA amplicons) having a uracil or thymidine as determined by a quantitation method.

(124) In embodiments, the method of treating a thyroid cancer is in a subject who has undergone surgery, radiation therapy, radioactive iodine therapy, chemotherapy, or thyroid hormone therapy, before the detecting thyroid cancer.

(125) In embodiments, an active agent administered to a subject for treating thyroid cancer: Cabozantinib-S-Malate, Caprelsa (Vandetanib), Cometriq (Cabozantinib-S-Malate), Doxorubicin Hydrochloride, Lenvatinib Mesylate, Lenvima (Lenvatinib Mesylate), Nexavar (Sorafenib Tosylate), Sorafenib Tosylate, and/or Vandetanib.

(126) In embodiments, the subject has or is at risk of papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, or anaplastic thyroid cancer.

(127) In embodiments, the method includes determining a papillary thyroid carcinoma (PTC) methylation alteration score for the subject, wherein the PTC methylation alteration score is equal to the number of methylation sites in Table 1 having a uracil level equal to or greater than the corresponding threshold level set forth in Table 2.

(128) In embodiments, the method includes determining a PTC methylation alteration score for the subject, wherein the PTC methylation alteration score is equal to the number of methylation sites in Table 1 having a thymidine level equal to or greater than the corresponding threshold level set forth in Table 2.

(129) In embodiments, the method includes determining a benign thyroid nodule (BTN) methylation alteration score for said subject, wherein the BTN methylation alteration score is equal to: (a) the number of methylation sites in Table 1 having a uracil level equal to or greater than the corresponding threshold level set forth in Table 3; (b) the number of methylation sites in Table 1 having a uracil level equal to or less than the corresponding threshold level set forth in Table 4; or (c) the number of methylation sites in Table 1 having a uracil level equal to or greater than the corresponding threshold level set forth in Table 3 plus the number of methylation sites in Table 1 having a uracil level equal to or less than the corresponding threshold level set forth in Table 4.
(130) In embodiments, the method includes determining a benign thyroid nodule (BTN) methylation alteration score for said subject, wherein the BTN methylation alteration score is equal to: (a) the number of methylation sites in Table 1 having a thymidine level equal to or greater than the corresponding threshold level set forth in Table 3; (b) the number of methylation sites in Table 1 having a thymidine level equal to or less than the corresponding threshold level set forth in Table 4; or (c) the number of methylation sites in Table 1 having a thymidine level equal to or greater than the corresponding threshold level set forth in Table 3 plus the number of methylation sites in Table 1 having a thymidine level equal to or less than the corresponding threshold level set forth in Table 4.
(131) In embodiments, the method comprises calculating a Composite Cancer Risk Score for the subject. In embodiments, the Composite Cancer Risk Score for the subject equals: [the PTC methylation alteration score for said subject]/[BTN methylation alteration score for said subject]. In embodiments, the Composite Cancer Risk Score for the subject equals: [(the PTC methylation alteration score for said subject)+1]/[(BTN methylation alteration score for said subject)+1].
(132) In embodiments, the subject is identified as being at risk of developing thyroid cancer or diagnosed as having thyroid cancer if (a) the PTC methylation alteration score for the subject is at least 5, 6, 7, 8, 9, or 10; (b) the BTN methylation alteration score for the subject is at least 5, 6, 7, 8, 9, or 10; and/or (c) the Composite Cancer Risk Score for the subject is at least about 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0.
(133) In embodiments, the subject receives treatment (e.g., is directed or advised to receive treatment) for thyroid cancer or is directed to receive additional screening for thyroid cancer if (a) the PTC methylation alteration score for the subject is at least 5, 6, 7, 8, 9, or 10; (b) the BTN methylation alteration score for the subject is at least 5, 6, 7, 8, 9, or 10; and/or (c) the Composite Cancer Risk Score for the subject is at least about 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0.
(134) Target Sites for Methylation Level of Thyroid Nodule
(135) In another aspect, provided herein is a deoxyribonucleic acid 5 to 100, 5 to 300, 5 to 300, or at least about 5, 50, 100, 150, 200, 250, 300, or more nucleotides in length including a uracil-containing sequence identical to the sequence of at least 5 contiguous nucleotides within a sequence including SEQ ID NO:1 to SEQ ID NO:550.
(136) SEQ ID NO:1 to SEQ ID NO:500 are 300 bp length sequences that include the target sites (i.e., methylation sites of interest). The sequences provided are as modified after bisulfite conversion. Therefore “C” in the non-CpG context becomes “U”, and C in the CpG context is designated as R or X (either “U” either “C”), where X is the target site. The DNA strands (sense and antisense) are no longer complementary after bisulfite conversion. Therefore, each DNA strand is identified with its unique sequence, and is designated as “forward” and “reverse” respectively, in Table 1.
(137) 5 The sequences listed in Table 1 are provided below with their respective sequence identification number.
(138) TABLE-US-00005 SEQ ID NO: Sequence 1
TUUTTAGUUUTURGTGGRGUUAGAGTTGGTTGUUTUAGTAGRGRGTGUUUAUURGG
UUUAAAGUTGTTUTGUAGUTGGTUAUTGTGGGAGAAGAGAUTGGAAAAGTTUAAAG
GTGGAGAGGRGGUAGRGATUTGGAGUAUTTTTURGUAXGUTGTAAUUUUTGAGAAG
AAAUAAAGAGGAAARGAGGUTGTTTAGATAATUURGGGUUUTGGTGUTTGUATTTA
GAAAAATTAGGUUUTUTGAAAAATTAUAGAATTATGUTGUUAGTGTUAGGTTUUU
AGATAATGATGTGTUTGTGT 2

UAUAGAUAUATUATTATUTGGGAAUUTGAUAUTGGUAGUATAATTUTGTAATTTTT
UAAGAGGGUUTAATTTTTUTAAATGUAAGUAUUAGGGUURGGGATTATUTAAAUAG
UUTRGTTTUUTUTTTGTTTUTTUTUAGGGGTTAUAGXGTGRGGAAAAGTGUTUUAGA
TRGUTGURGUUTUTUUAUUTTTGAAUTTTTUUAGTUTUTTUTUUUAUAGTGAUUAGU
TGUAGAAUAGUTTTGGGURGGGTGGGUARGRGUTAUTGAGGUAAUUAAUTUTGGRG
UUARGGAGGGUTAAGGAU 3
GGGTGAUUAGTGUUAUTAAAAGUAGAGUTTGAGTTTAUTUTUATAAUUATRGGUTG
TGGGUUAGAUATTTGGUTGUTTTGUAGGUAGAUUAGGUTTUURGGTGAGTUATGUT
GUTTAAAATGUTGTUTGGGAARGUAGAGAAAGTUTAAAXGUUAAGARGUTGAGGA
UAGUUURGUAGGTGGAUTGUUATGUURGGUTRGGUUUUTTTTTGGTUUUUAGAGTG
GAUUUTTUTUUTUUUUAUAGAGGGGAGGUATUTGATGGTGGUTTUAGUAGAUAAU
UTGGAGAAGAAUUAUTUAGGGT 4
AUUUTGAGTGGTTUTTUTUUAGGTTGTUTGUTGAAGUAUUATUAGATGUUTUUUU
TUTGTGGGGAGGAGAAGGGTUUAUTUTGGGGAUUAAAAAGGGGURGAGURGGGUA
TGGUAGTUUAUUTGRGGGGUTGTUUTUAGRGTUTTGGXGTTTAGAUTTTUTUTGRGT
TUUUAGAUAGUATTTAAGUAGUATGAUTUAURGGGAAGUUTGGTUTGUUTGUAAA
GUAGUUAAATGTUTGGUUUAUAGURGATGGTTATGAGAGTAAAUTUAAGUTUTGUT
TTTAGTGGUAUTGGTUAUUU 5
CAGUTGGGGAGGGGAUAGGGTAGGTGGUTGUAGAAGGGGGUTGGGTTGAGGTUTU
AGGTGUAGARGAGGAGGGGUTGGGRGGAGGGGGTGAGGAGGGGAGURGGGUTGGG
GGURGGGRGRGUTGUTGGGGTUUUUUTUURGUUURGGGAUXGTURGUTUTTGUUUA
GAUURGTRGGTAAAUAGARGURGTGATGTUARGGGRGURGUTGAUUTGTGGUTGAA
UURGGAGUTGTAAATGAGATGUAAGGTGUUAGUAGUUTURGGURGUAGGGUUTAR
GAGUUAUARGRGUTUUTURGURGG 6
URGGRGGAGGAGRGRGTGTGGUTRGTAGGUUUTGRGGURGGAGGUTGUTGGUAUUT
TGUATUTUATTTAUAGUTURGGGTTUAGUUAUAGGTUAGRGGRGUURGTGAUATUA
RGGRGTUTGTTTAURGARGGGTUTGGGUAAGAGRGGAXGGTUURGGGGRGGGAGGG
GGAUUUUAGUAGRGUUURGGUUUUUAGUURGGUTUUUUTUUTUAUUUUUTURGUU
UAGUUUUTUUTRGTUTGUAUUTGAGAUUTUAAUUUAGUUUUUTTUTGUAGUUAUU
TAUUUTGTUUUUTUUUUAGUTG 7
TTTTUTGTAAAATGGGGURGUUUAUAAAAUTUATAAUAAAGTGTTGAGGTTURGAU
AAGURGAAAUUTGTGAAAAGUTTGTGTAAAUUTUAGAGUTGTAUATGGATGGTTGA
AGGATUTATTTRGAUAGUTURGGGGAGUXGTGGGAGGGAAGUTGAXGGXGGUTUTT
GUTGTTUTUUTAUUTUUUAGUUUTUURGAAGAUTUTGAGUAGUUTGGAGATUAAAG
GTGATTGGGGUUTGUTGGUATGGAGGURGGGUTRGGUAGAAUUTGUTTUURGGUUU
UUTGUUUAUUTUUUAUUUAU 8
GTGGGTGGGAGGTGGGUAGGGGGURGGGAAGUAGGTTUTGURGAGUURGGUUTUU
ATGUUAGUAGGUUUUAATUAUUTTTGATUTUUAGGUTGUTUAGAGTUTTRGGGAGG
GUTGGGAGGTAGGAGAAUAGUAAGAGUXGUXGTUAGUTTUUUTUUUAXGGUTUUU
RGGAGUTGTRGAAATAGATUUTTUAAUUATUUATGTAUAGUTUTGAGGTTTAUAUA
AGUTTTTUAUAGGTTTRGGUTTGTRGGAAUUTUAAUAUTTGTTATGAGTTTTGTGG
GRGGUUUUATTTTAUAGAAAA 9
TGAGUAGTGTTTUAGRGUUUAGAGAGAUAUTGTGGAGAAGGTUUAUUAGGATGUU
TAUUTGUUTTAUAUAAGAGUUTAAUTTTGGUAUAUUTGTGGUAUAUUTGTGGAGAG
UTGTTUTGGUUURGGTTGTUTGGUAGGUUTGGGUTAUTUXGAGUAGGGGAAUTGGG
GUAUAGTGGUTGUAUUTURGGUTATAUUUTGGTTTTTUUAGTTUUTGATGUURGUU
UUTUAGGTGGUAGUATGAGGTGAUTUAGGGAUAGARGUUUTTATRGTGARGUAAGT
UUAGUUUUUAGTGGAGUUUUT 10
AGGGGUTUUAUTGGGGGUTGGAUTTGRGTUARGATAAGGGRGTUTGTUUUTGAGTU
AUUTUATGUTGUUAUUTGAGGGGRGGGUATUAGGAAUTGGAAAAAUUAGGGTATA
GURGGAGGTGUAGUUAUTGTGUUUUAGTTUUUUTGUTXGGAGTAGUUUAGGUUTG

UUAGAUAAURGGGGUUAGAAUAGUTUTUUAUAGGTGTGUUAUAGGTGTGUUAAAG
TTAGGUTUTTGTGTAAGGUAGGTAGGUATUUTGGTGGAUUTTUTUUAUAGTGTUTUT
UTGGGRGUTGAAAUAUTGUTUA 11
TUTTGTAAAATTUUAGAGUUAGGTATAUUUAATrUTGUAARGTGGTAGUTGUATGA
UTGTAUAAGTUUUTTAAUAGUAURGGGUUTUAGTGAUATUATUTGTTAAATGGGTT
GGTGATGATAATGGTUAGUATTTATGGAGGAGUUUAUAXGGTGUTAAGTGUTTrAU
AUATATUAGUTAAUTGAATUUTUAUTGUTGUUAATGAGAUAGGTAUTATTGAATUA
GAGGUURGGAGAGAGUTUUARGRGGTTGGTUATAUTGGTGAAGAGUTTGGTTUAAT
GUUTGGTGAAUTUTRGGUAU 12
GTGURGAGAGTTUAUUAGGUATTGAAUUAAGUTUTTUAUUAGTATGAUUAAURGRG
TGGAGUTUTUTURGGGUUTUTGATTUAATAGTAUUTGTUTUATTGGUAGUAGTGAG
GATTUAGTTAGUTGATATGTGTAAAGUAUTTAGUAUXGTGTGGGUTUUTUUATAAA
TGUTGAUUATTATUATUAUUAAUUUATTTAAUAGATGATGTUAUTGAGGUURGGTG
UTGTTAAGGGAUTTGTAUAGTUATGUAGUTAUUARGTTGUAGAATTGGGTATAUUT
GGUTUTGGAATTTTAUAAGA 13
TURGGAGUUAGTGAAUTTGTGATURGGAGUUAGTTAAUTTUAUAGUTAATGTGUTG
AGUAGUATTUUAGUUAGRGTUTGAAGUUAGAGUAGGGAGGRGGARGGGUUUUAGG
AGTTRGAGGTURGGGAAGURGAAGUAUUAUUAAAUTGAGXGAGGTTUUAAUTUTU
UUTUUUAGGAGGTURGGUTGUUTUUUAUUAGUAGUUUAAUUAUAGGGTUUTGUTU
UAGARGTTAUTATTTTUTUTTTTTUAGTGTGTUUAGUAGUAAUUTRGAUTGUUAAUA
AUAARGTGAAAAATAAUTGUAG 14
UTGUAGTTATTTTTUARGTTGTTGTTGGUAGTRGAGGTTGUTGUTGGAUAUAUTGAA
AAAGAGAAAATAGTAARGTUTGGAGUAGGAUUUTGTGGTTGGGUTGUTGGTGGGAG
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RGUTGGUTGGAATGUTGUTUAGUAUATTAGUTGTGAAGTTAAUTGGUTURGGATUA
UAAGTTUAUTGGUTURGGA 15
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GGAAGUTGAGGUAGGUAAATTGUTTGAAUUTGGGAGGTGGAGGTUAUAGTGAGUU
AAGATTGTGUUAUTGUAUTUUA 16
TGGAGTGUAGTGGUAUAATUTTGGUTUAUTGTGAUUTUUAUUTUUUAGGTTUAAGU
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TGUTTUUAGTTTTGGUAA 17
GGRGGGATURGAGURGAGAUARGTGUTGGAGRGGAGURGUTTUUTUARGGTRGUUA
GURGUAGAUAAUTGAUUTUUURGGUATRGRGTTRGRGGUUUTGUTGUTGGUTURGG
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UUUUATGTUUTGRGGUAAUTT 18
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TGTUTRGGUTRGGATUURGUUU 19

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UAGTTUUTGGATGGATTUUU 22
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UURGGGTGGGGAGGGRGAGTUTGG 23
RGUAGGUURGRGUUURGUTUURGUUURGUUTGURGRGUUTUURGGGGRGUURGUA
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AUAGTRGUTGUAGGGAGGARGRGGGURGTGAGAAUURGGGGAUAGUUTUUUUTUT
TGRGGTUUTGUAGTUURGGAUUUAUTGGGRGGATUAGAAAGTTTGUAGGGAGUUA
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AUURGGGGUTGAAAARGGTGGUAGAAAGTGAGUAAUTTAGGGAGAUAGAAAGAGR
GUAGAAUTRGAAATTURGAGGUAGAGA 26
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TUTGTUUURGAUTRGGTUTTTUTGGUATUUUTUXGUTTTUTUTGTUUUTGRGUTGTU
TGTUTGTUTUUTAGTUUUTGGUTUUUTGUAAAUTTTUTGATURGUUUAGTGGGTURG
GGAUTGUAGGAURGUAAGAGGGGAGGUTGTUUURGGGTTUTUARGGUURGRGTUU
TUUUTGUAGRGAUTGT 27
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TGUTTGUAGGUTGGGGUATGAAGUAUUUTGGTATTTARGUTGGGATTGGTUTUTUA
UTAGGGTTGGGGRGGGUTGTGGTUAUUTGGUURGGRGXGURGUAGAGGUTGGUTUR

GGAGAAGAUUTGGGGGRGUAAGAUTUAGAGGUUAGAGGGTGUAGURGUTGUTGAU
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GAGUUAGGGUUAAATUTGGGT 28
AUUUAGATTTGGUUUTGGUTUTUAAATRGUTUAUAAUAGGGGUTAGRGUTUUTUUU
AGURGUUURGTURGUAAATGAGTUAGUAGRGGUTGUAUUUTUTGGUTUTUTGAGTUT
TGRGUUUUUAGGTUTTUTURGGAGUUAGUUTUTGRGGXGRGURGGGUUAGGTGAU
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GUUAGRGURGGGGTAUAGGUTGA 29
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GUAGUUTUATAUUTUAUATTUTUUTGTGGURGUAUUTUAUAGUUURGUUURGGUU
UAUAGGUATUUTTAAGAAGAAGTGTUTGUUUAUUATUAGXGAGAAGAGUAGUUTU
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GGGUAGURGGGGAGGUUUUUUTUUURGUUUAURGUUURGGUAGAGUUTUUAGGA
GUAGUTGAARGGGGTUATGUUUATRG 30
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GGAGGGGGGUUTUUURGGUTGUUUTUAUTAGRGGAGGAGUUURGGGAAGAUUUTG
TGUATTGUTUUAGGGGGAGUXGUAGGAGGUTGUTUTTUTXGUTGATGGTGGGUAGA
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UAUTUAUUTTTGTGAGGUTGGGU 31
TUAGAATAATGGUTGGTTTGTAGAGATUAGAAATGUUUAUTGUTGTTTUUTGTAT
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UUAUTUAAGGAUAGUAGUTGUTGAUTUAGAXGUTUAAATTUTXGGGXGGAAAAGG
AUUTTAGAGAATGUUTAAAATRGTGGUUUAATUUUTUATTGGAAGUTGGGGUTURG
AAAAGURGGGGUTURGAAAAGUTGGGAGAGUAGUUUAAAGRGTAUTGUUUAUTAA
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UTTTTRGGAGUUURGGUTTTTRGGAGUUUUAGUTTUUAATGAGGGATTGGGUUARG
ATTTTAGGUATTUTUTAAGGTUUTTTTUXGUUXGAGAATTTGAGXGTUTGAGTUAGU
AGUTGUTGTUUTTGAGTGGUTTUTUTUTUUAGGUUURGGAUAGUTTUAGAGGUTUA
GTUTGGGTGGGTGGAGGGATAUAGGAAAUAGUAGTGGGUATTTUTGATUTUTAUAA
AUUAGGUUATTATTUTGGA 33
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UTUAGUUAGUAURGGGATGATGRGAUUAGUTTTGTUAGUAXGUTTGGGGAGUATAU
AUAURGUTTGUUTTGGUTGGAURGGAGAUTGTGATUAUUAUUUTTUUAAUUUATUU
UUUAAUARGUAGGUTGGUATGGUUARGUUUAUAGTGUUUUAAGTGUTGUUTGUUT
TGUAGTGAUTUAUTTUUTUTGTA 34
TAUAGAGGAAGTGAGTUAUTGUAAGGUAGGUAGUAUTTGGGGUAUTGTGGGRGTG
GUUATGUUAGUUTGRGTGTTGGGGGATGGGTTGGAAGGGTGGTGATUAUAGTUTUR
GGTUUAGUUAAGGUAAGRGGTGTGTATGUTUUUUAAGXGTGUTGAUAAAGUTGGTR
GUATUATUURGGTGUTGGUTGAGGUUUAGTTTUUUUTTUTUUATUUAUUTTUTUTTT
TGTUTUUTGGGGGAGGAATATAUUUTUTTATUTTTATTTUTUAGGUUUTGGTTATUU
AAUTTUTGUUUUAGAAUTT 35
TUAGAARGTGUUUAUAUATGUUUATGUUUTUTATUUTGUTGAAATUUAAUUUUUU
UTTUAAAGGUUAUTGUAGGGAGUUTTUUUAGGGUUUAAURGGATTUAGTGTUTAU
UTGTTUTGTUUTGTAUAAAGRGUUUUTTTTGUUUTTTTXGTGTGTAUTTAGAGAATT
UTGATTTTGAUTGAATUAUUTGTGTAUTTGTTTTUTUTUAGUUTUAUUUUUAUATGG
TGAGUTUAURGGTUTTAUTUATTTUTGUATGAGGTAAGGGTUTRGUUUAUAUUAGG
TGUUAAUUAGTGUTTARGGU 36

URGTAAGUAUTGGTTGGUAUUTGGTGTGGGRGAGAUUUTTAUUTUATGUAGAAATG
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GGGAGUUUATUURGUAUTGUTGUAGUUTRGUUAUUTUTUUTAUAUUUAUTGGUA
UTGTUUUTAUAGGTGGUUTGUAUAGTGGAGAG
(139) Also provided herein is a deoxyribonucleic acid identical to 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-100, 100-110, 110-120, 120-130, 130-140, 140-150, 150-160, 160-170, 170-180, 180-190, or 190-200 of contiguous nucleotide sequence of the sequence including a sequence of SEQ ID NO:1 to SEQ ID NO: 550.
(140) In embodiments, provided herein is a deoxyribonucleic acid which includes a methylation site set forth in Table 1.
(141) In embodiments, included herein is a deoxyribonucleic acid in which a plurality of methylation sites set forth in Table 1 are methylated or unmethylated. In embodiments, the plurality of methylation sites comprises at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 550 methylation sites. In embodiments, the plurality of methylation sites comprises between 1-50, 50-100, 100-250, 100-300, 100-400, 100-500, 100-550, 250-550, or 350-500 methylation sites.
(142) Compositions for Detecting Methylation
(143) Also provided herein are probes and primers that are complementary to one or more of SEQ ID NOS: 1-550. In embodiments, pairs of primers complementary to nucleotide sequences on either side of a methylation site of interest listed in Table 1 are provided. In embodiments, a plurality of probes and/or primers are provided to detect and/or amplify a polynucleotide (e.g., a polynucleotide obtained by bisulfite treatment of DNA) comprising a methylation site of interest. In embodiments, a probe or primer is complementary to a polynucleotide sequence that encompasses the methylation site of interest. In embodiments, the probe or primer is complementary to a sequence that is proximal to the methylation site of interest (e.g., within 1000, 900, 800, 700, 600, 500, 400, 300, 200, 100, 75, 50, or 25 nucleotides of the methylation site of interest in a genomic or bisulfite-treatment-derived polynucleotide).
(144) In embodiments, a deoxyribonucleic acid selected from SEQ ID NO:551 to SEQ ID NO: 782 is included. In embodiments, the deoxyribonucleic acid selected from SEQ ID NO:551 to SEQ ID NO: 782 is hybridized to a complementary DNA sequence having uridine or cytosine. In embodiments, each of the nucleic acids is different. In embodiments, each of the nucleic acids does not simultaneously have the same sequence selected from SEQ ID NO:551 to SEQ ID NO: 782.
(145) In embodiments, aspects include a deoxyribonucleic acid selected from SEQ ID NO: 551 to

SEQ ID NO:782, hybridized to corresponding a complementary DNA sequence having uridine or cytosine, and in a complex with an enzyme, e.g., a thermostable DNA polymerase. In embodiments, the thermostable DNA polymerase is Taq DNA polymerase.

(146) In some aspects, the method includes deoxyribonucleic acid that has a sequence that is at least 50%-55%, 55%-60%, 60%-65%, 65%-70%, 70%-75%, 75%-80%, 80%-85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical or homologous to a nucleic acid having a sequence of at least one of SEQ ID NO:551 to SEQ ID NO:782.

(147) TABLE-US-00006 TABLE 5 SEQ ID NO: Sequence, 5′ to 3′ 551 GGGAGAAGAGATTGGAAAA 552 CTAAAAACCTAACACTAACAACATAAT 553 TGTTGTTTAAAATGTTGTTT 554 AACCCTAAATAATTCTTCTC 555 GGGTTGGGTTGAGGTTTT 556 ACACCTTACATCTCATTTACAACTC 557 AATTTGTGAAAAGTTTGTGTA 558 CCCAATCACCTTTAATCT 559 GTTGGGATTTGAAATAGTGA 560 CCTCCACTCACCTAAAACTT 561 TTGGTTAGTGATTATTTATT 562 AAAAATTAATATAAAATTAAAA 563 TTTGTAGGGAGTTAGGGAT 564 TCCTCTATCTCACCCTAAAT 565 TTTGATTGAATTATTTGTGTATT 566 ACTCCCTTACTCCTAAACACT 567 AGTGGAGATEGGTAGGGAGA 568 CCCAAAACTAAAACCAAATATAA 569 TTGTGGTTAAATTTATTG 570 ACCCAACAAAATAATATC 571 TGAGGTAGAGTTGTGTGTATAT 572 ATCAATCAATTCTCATTAAAC 573 GGAAGTTAGGAAGGGTTGT 574 CTCCAACTCCAACTAAAACTC 575 TTEGGGTATTGATTTATTTT 576 AAATTCTACCTACAAACTATACA 577 AGGATGAAGTAATAATTAAATATTG 578 CCCACTCTACCAACTAAAC 579 AGGTTTGTGTTAGTATAAAT 580 TTCTTACCTATATAATTAATAATA 581 GTTGGGTGAATTTTATTAG 582 TCAAAACCTAAACTCTAACA 583 GGATTGGTTTRATATAGAAAGTAT 584 CAAATAATAAATCATAACTCTTAACT 585 TGGGGTAGTTGATGGTTT 586 CTTTCTAACAAAATAAAAAAATTTAA 587 TTGTATTTGAAGTTTGTAGAGATTTATA 588 TTTCCTCCAACAACTCAAT 589 TTATGAGTATGTAGTAGGGTTATTATA 590 AAAATATCAAACAAATTTATCC 591 TGGTTGTTTGTTTTTTATGTATT 592 TCCCTACCTCCCAAATTC 593 TATGATGATTGTTGTAGTGTAGA 594 CCTCCCTAATAACTAAAAATAC 595 GGTGGTTTTGATATTTAGTG 596 CCCAATTACCTAACAAATTA 597 TGGGATAGGTGTAGATATG 598 CAACAAAAACTAAAACACTATAC 599 TTTGGGATTGGTTATTTT 600 AAACCCCTTAACTCTATACC 601 GATTTTTTTGAGAAGAGTATAG 602 AACCACTACCACCTAAATATA 603 GGAGGATAGGGTGTGATT 604 ACATTTTTAACTCTAACTAAAAATAAA 605 TGGAAATGAGGTGAGTTT 606 AAAAAAAAATAAAATAACAATAACTA 607 TGGAGAGTTTAGTTTGTTT 608 CAAAAAAAAATCTAACAAC 609 TGGGTTTTAGTTATGTGGTT 610 ATCAATAATATCCAACAAAATAATAT 611 TTTTTTTAGTTTTTGTATATATATTAG 612 ACCCAAATAATCAACTCTT 613 GTGGTTTTTGGAGATTTA 614 AAACAAACTACAAATAAAATAATAC 615 GGGTTATAGGTTTGAGTTA 616 CCATTAAAAAAAATAAAATC 617 TTGGTAGATTTAGTAAATTTATT 618 AAACTTAAACAACCCTATATAC 619 ATGGTTTTAAAGAGTAGTAGTATAGTT 620 AAATTTACTCATCCCACTTC 621 AGGGGTTGGGATATTGTT 622 AAAAATTTCTCCTTACAAAAAACTAA 623 ATGGGTGTTTGGAATTTTTTA 624 CTACCTCAACCTCCTAAATAACTAA 625 GTGTTTTGTGGTANAGATATAG 626 ATTCTTAAATTAATTCAACTACAT 627 TGGGGGTAAAAGTTATAGTT 628 AAAAAACAAAAAACCAAATAC 629 GTTTTTTGGTTAGTGTGTT 630 CCCCATACTTCTATACTATAAT 631 TTGTTGTTTTTAAAGAAATTATA 632 ATCATCTAAACTTAACTCATCTAA 633 ATTTTTGGGTGTTTTATATT 634 AAACCTCAAACAATAACA 635 ATTAAGGATATTTAGGAGAGTAAG 636 ACACCACAACTTCAAACTAC 637

TGAGGAAGAGAGAAGAGATGATA 638 AAAACTAAACTATAAAACAAAACAAAACTA 639
GGTGGAGGTGTTTTTTATAG 640 CCAAATACTACTTTCAAAATACA 641
ATGGATTATTATTGTGTTATT 642 CATCTCAACCTCATACTAA 643
GGATGATTTAGTAGGGATTGAG 644 ccAAATAAAAACCATTCTCTAAC 645
TTGGATTAAGTATTTTTGATATTA 646 TCCCTAAACCATATATTACTAAA 647
GGGTAGTTTGGTGATTATTATT 648 CCCTTCCCTACTCACAATA 649
ATTTGGTTAGTGATTTAGTTATT 650 TCCCACTTAAAAAATTCTATA 651
AGTGGGGAAGGTAATTGTTAT 652 CTTTCTAATAAAAATTTACTAAAACCTCTA 653
TTTGGTTAGTTTTATTTTTGATTG 654 ATTCCTCCCTATCCCTATTC 655
GGGATAGGGGTTAGAGTAA 656 TCCATAAAAACAAAACACTC 657
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ATAGGGTTGAGGTTAGAGTTAT 662 CCTCCTCTCCACAATAAA 663
TTTAAGTTTTTTTTTAGTTTTGTAGT 664 CCCCATCCTCTCTATCTC 665
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AATTTAGTATAAGATTTGATTTGTTA 672 CCACCTACTCCTTCCTATAC 673
TTTTTTGAAATTGTATGTTAT 674 CAAATCCTTAAAATTCTATAA 675
TTTGAAGTGGTGTTTTAG 676 CCAAAATTCTTCCATACT 677 TGGGTATTTAGTYTTTTGTG
678 AACAAcTACCTCCTTTTACTAAT 679 TATGGTAGGAGGTGGAGTT 680
CCCAATTTTAAAACAATAC 681 AGAGGAAGTAAGGTTATTAGTT 682
ACCAAACAAACAATATCTAA 683 GGTTTTAATTATGATTTAATTAGA 684
CCTACACTCAAATTTACCTCTA 685 AATGGGTAGTTGATATAATTATT 686
CACAAAATCCTAAAACTAAAA 687 AGGATTAGTGGAAATGAAAATA 688
TAACCTCAAAACAACTTCTAAAC 689 TTTTTTTTATAGAGAAGTATTTTAG 690
CCCATTACAAAACTATCC 691 GGTGAGTTTGTGGTTAGTG 692
TTTTCTAAAAAAATCCAATCTA 693 AATGGATAGGTTGGAATAG 694
AAAAAAAAAAAAAAACTAATTAC 695 GAGTTATTTAGTTTGGTTAGGT 696
ACTCAACTTAAAAAATCACTATAC 697 TTTYTTTTGGYTTTTTGGYTTT 698
TCCCCCACACCCATATAA 699 TTAAAAAAAAGTATAATGAGTAGGA 700
CCCACAAAAACTCTCTACA 701 AAAGGAGGTTGAGTTAGAAAGTAG 702
AACTATTTAACTTACTTAACCACACC 703 GGTGTGGTTAAGTAAGTTAAATAGT 704
TACCCCTTCCTCTTCAAC 705 TTTTGATATGATTTATGATTATAT 706
TTTTCCACTAAACAACACTA 707 TTTGAGGGTTGTTTTAGAT 708
ACTCACAAAAAATAACTAATAACTAT 709 AAAGGAGGTAGGGGAGATATA 710
TCAAAATAAAAACCAAAATTCTC 711 AGGTTAAGTTGGTAGAGGTAGA 712
CAAACTCTAAACTCAAAATATATTC 713 TTTTTATTTTAGTTTTTTTGAGTAG 714
CCCTACAACACTCCTATCTA 715 TTTGGAGTTAGGTTGATAG 716
CAACAATACTCTCACTTACAC 717 AGAAAGATTTTTAAATATTTTTAAT 718
AAACCTCTAATACACAACAAA 719 TTTTGAGTTTTTTTTTTTTAAGTAT 720
CAAACAAAACAACACTTAATAC 721 GGTTGAGGTGGGTGGATTA 722
TTTTTTTTTTTTTTTTTTAAAATAAAATCT 723 GGGTGTTTGTAATTTTAGTT 724
ACCTETTAACAACCTAACAATATA 725 GGGTAGATGATATGGTAGTGA 726
AAAAAATAAAAAATAACTAAAACAATAT 727 AGGAAGTGTTTAAGAAGTAGAA 728
CCTAAAACTCTAAATACAATCTC 729 TTTTTAATTTTTGTTTGTATT 730
AAACCACAATCTATTTCTAA 731 TTAGAAAAGAATAATTATAGTTG 732
ACCCTAAAAAAATAAAATC 733 TTGTATTAGTAAATAAAGTGTATTTT 734
AACCCTTTCTACAAATCTAC 735 AGGGGTGGGTGGAAGAAT 736
CTCCTCAATAAAATAAAAATCCTAAAAAATA 737 GGGTTAATTAGTTGTTTTAT 738
CCTACAAATATATCACACACT 739 TTTGTTAAATAGGTGGTTAGA 740

ACCTCAACCTCCTAAATAAC 741 TAGGGTTTAGAGTAGGAGGTAG 742
CAAAAAATATAAATCAAAAACATC 743 GGGATTATAGGTATTTATTAT 744
TAAAAATTAAAAATCATACTTA 745 AAGTGATTTTTAGGGAGTGT 746
TCCATAATAACCTCATTTTAATA 747 TTTTTGGTTGAGGTTTAGT 748
AAACAACACAACTCTTATCAC 749 TATGGTGATTAAAGTATAATAGTT 750
TCCTAAATAAAAAACAACATA 751 TGAAAATGTTTTTAGTTTTTATT 752
AAATACCCTACCTCTTATCTAA 753 GATGGTTAATTTTTTTATTT 754
ACTCCTTCAACAAACTAAC 755 AGGGGATATTTTTAGGTT 756
CCAATCTATTCCTATATAATTAA 757 AGGAGAGTTTGGAAATATAG 758
CAATTCTAAATTAAACCTTATT 759 AATAATGGTAGTAGTTTTATTAG 760
TTCCTATATTAACAACTTACA 761 TTTTTTGGTAGATTTTTAT 762
AAATTAATTTCTATTATTTATATTA 763 AGGTGGTTGGGGAGAGTG 764
CCCTAAAATAAATCAAAAAAAAACCTTAA 765 AGGTTTAGGTGGGGTGAAT 766
TAAAATCATCAAAATCCCTTAAAA 767 TTTTTTTTTAGGTTATACTGAGTATT 768
ATCCCCACAAAACACATA 769 TAGGGTAAATATTGGGATTATT 770
TTTCCACCTCAAAACTTAAC 771 GGGTGTTTGTATTTTTATATT 772
ACCTCCCAAAACCATAAC 773 GATGTGAGTGGTGAGGTGGT 774
CAAACCCTTCCAAAACATAAAC 775 TGGGATTATAGGTATGTATT 776
CAATTTCATTTATAAATATAAATAT 777 AGGGGTTGGTTATTTTTATTTT 778
TTTTTAATATTTAATTTTTACCTTCAACT 779 GGTAAGTTGTGGATGTGAGT 780
AAAAAAAACCAAACCTTATCTA 781 TTTTTAGGATTTGGGTTAG 782
AACCTTATAAATAACAACAAAAC

Kit for Detecting Methylation Level of a Thyroid Nodule

(148) Also provided is a kit including a plurality (e.g., at least about 10, 20, 40, 50, 100, 150, 200, 225, or 232) nucleic acids each independently comprising one sequence selected from SEQ ID NO: 551 to SEQ ID NO:782, in which the nucleic acids do not simultaneously include the same sequence.

(149) In some aspects, the kit includes deoxyribonucleic acid that has a sequence that is at least 50%-55%, 55%-60%, 60%-65%, 65%-70%, 70%-75%, 75%-80%, 80%-85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical or homologous to a nucleic acid having a sequence of at least one of SEQ ID NO:551 to SEQ ID NO:782.

(150) The kit provided herein may include enzymes, reagents for deamination of cytosine, buffers, vials, plasmid vectors, control DNA, devices for collecting thyroid tissue samples, reagents for isolating DNA, reagents for labeling DNA, labels, or any combinations thereof.

(151) The kit provided herein may include enzymes such as thermostable DNA polymerase enzymes, restriction enzymes, and combination thereof.

(152) In embodiments, the kit(s) may further include enzymes, reagents for deamination of cytosine, buffers, vials, control DNA, devices for collecting blood and/or tissue samples, or reagents for labeling DNA, or any combinations thereof.

(153) In embodiments, a kit provided herein may include a solid carrier capable of adsorbing the nucleic acids containing in a sample of a body fluid, for example blood (whole blood, plasma, or serum). The kit may also contain other components for example, reagents, in concentrated or final dilution form, chromatographic materials for the separation of the nucleic acids, aqueous solutions (buffers, optionally also in concentrated form for final adjusting by the user) or chromatographic materials for desalting nucleic acids which have been eluted with sodium chloride.

(154) In embodiments, a kit provided herein includes materials for purifying nucleic acids, for example, inorganic and/or organic carriers and optionally solutions, excipients and/or accessories. Such agents are known and are commercially available. For solid phase nucleic acid isolation methods, many solid supports have been used including membrane filters, magnetic beads, metal oxides, and latex particles.

(155) In addition, a kit can also contain excipients such as, for example, a protease such as proteinase K, or enzymes and other agents for manipulating nucleic acids, e.g., at least one amplification primer,

nucleic acid bases (A, T, G, C, and/or U), and enzymes suitable for amplifying nucleic acids, e.g., DNase, a nucleic acid polymerase and/or at least one restriction endonuclease. Alternatively, a commercial polymerase chain reaction kit may be used to amplify the DNA samples.

(156) Exemplary Techniques for Detecting Specific Sequences

(157) Specific sequences, such as the sequences listed in Table 1 (or portions thereof containing a methylation site of interest), can be detected by numerous methods that are well-established in the art (e.g., PCR-based sequence specific amplification, isozyme markers, northern analysis, sequence specific hybridization, and array based hybridization). In embodiments, the presence or absence of methylation is determined through nucleotide sequencing of the site of interest (e.g., the site in bisulfite-treated DNA or an amplicon thereof). Any of these methods are readily adapted to high throughput analysis.

(158) Some techniques for detecting specific sequences utilize hybridization of a probe nucleic acid to nucleic acids corresponding to the methylation site of interest (e.g., amplified nucleic acids produced using bisulfite-treated DNA as a template or the bisulfite-treated DNA itself). Hybridization formats, including, but not limited to: solution phase, solid phase, mixed phase, or in situ hybridization assays are useful for sequence detection. A non-limiting guide to the hybridization of nucleic acids is found in Tijssen (1993) Laboratory Techniques in Biochemistry and Molecular Biology—Hybridization with Nucleic Acid Probes Elsevier, N.Y., as well as in Sambrook, Berger and Ausubel.

(159) Nucleic acid probes complementary to a methylation site can be cloned and/or synthesized. Any suitable label can be used with a probe. Detectable labels suitable for use with nucleic acid probes include, for example, any composition detectable by spectroscopic, radioisotopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels include biotin for staining with labeled streptavidin conjugate, magnetic beads, fluorescent dyes, radiolabels, enzymes, and colorimetric labels. Other labels include ligands which bind to antibodies labeled with fluorophores, chemiluminescent agents, and enzymes. A probe can also constitute radiolabelled PCR primers that are used to generate a radiolabelled amplicon. Labeling strategies for labeling nucleic acids and corresponding detection strategies can be found, e.g., in Haugland (**2003**) Handbook of Probes and Research Chemicals Ninth Edition by Molecular Probes, Inc. (Eugene Oreg.). Additional non-limiting details regarding sequence detection strategies are found below.

(160) PCR, RT-PCR and LCR are in particularly broad use as amplification and amplification-detection methods for amplifying nucleic acids (e.g., those comprising a methylation site), facilitating detection of the nucleic acids of interest.

(161) In embodiments, real time PCR or LCR is performed on the amplification mixtures described herein, e.g., using molecular beacons or TaqMan™ probes. A molecular beacon (MB) is an oligonucleotide or peptide nucleic acid (PNA) which, under appropriate hybridization conditions, self-hybridizes to form a stem and loop structure. The MB has a label and a quencher at the termini of the oligonucleotide or PNA; thus, under conditions that permit intra-molecular hybridization, the label is typically quenched (or at least altered in its fluorescence) by the quencher. Under conditions where the MB does not display intra-molecular hybridization (e.g., when bound to a target nucleic acid, e.g., to a region of an amplicon during amplification), the MB label is unquenched. Details regarding standard methods of making and using MBs are well established in the literature and MBs are available from a number of commercial reagent sources. See also, e.g., Leone et al. (1995) "Molecular beacon probes combined with amplification by NASBA enable homogenous real-time detection of RNA." Nucleic Acids Res. 26:2150-2155; Tyagi and Kramer (1996) "Molecular beacons: probes that fluoresce upon hybridization" Nature Biotechnology 14:303-308; Blok and Kramer (1997) "Amplifiable hybridization probes containing a molecular switch" Mol Cell Probes 11:187-194; Hsuih et al. (1997) "Novel, ligation-dependent PCR assay for detection of hepatitis C in serum" J Clin Microbiol 34:501-507; Kostrikis et al. (1998) "Molecular beacons: spectral genotyping of human alleles" Science 279:1228-1229; Sokol et al. (1998) "Real time detection of DNA:RNA hybridization in living cells" Proc. Natl. Acad. Sci. U.S.A. 95:11538-11543; Tyagi et al. (1998)

"Multicolor molecular beacons for allele discrimination" Nature Biotechnology 16:49-53; Bonnet et al. (1999) "Thermodynamic basis of the chemical specificity of structured DNA probes" Proc. Natl. Acad. Sci. U.S.A. 96:6171-6176; Fang et al. (1999) "Designing a novel molecular beacon for surface-immobilized DNA hybridization studies" J. Am. Chem. Soc. 121:2921-2922; Marras et al. (1999) "Multiplex detection of single-nucleotide variation using molecular beacons" Genet. Anal. Biomol. Eng. 14:151-156; and Vet et al. (1999) "Multiplex detection of four pathogenic retroviruses using molecular beacons" Proc. Natl. Acad. Sci. U.S.A. 96:6394-6399. Additional details regarding MB construction and use is found in the patent literature, e.g., U.S. Pat. No. 5,925,517 (Jul. 20, 1999) to Tyagi et al. entitled "Detectably labeled dual conformation oligonucleotide probes, assays and kits;" U.S. Pat. No. 6,150,097 to Tyagi et al (Nov. 21, 2000) entitled "Nucleic acid detection probes having non-FRET fluorescence quenching and kits and assays including such probes" and U.S. Pat. No. 6,037,130 to Tyagi et al (Mar. 14, 2000), entitled "Wavelength-shifting probes and primers and their use in assays and kits."

(162) PCR detection and quantification using dual-labeled fluorogenic oligonucleotide probes, commonly referred to as "TaqMan™" probes, can also be performed. These probes are composed of short (e.g., 20-25 base) oligodeoxynucleotides that are labeled with two different fluorescent dyes. On the 5′ terminus of each probe is a reporter dye, and on the 3′ terminus of each probe a quenching dye is found. The oligonucleotide probe sequence is complementary to an internal target sequence present in a PCR amplicon. When the probe is intact, energy transfer occurs between the two fluorophores and emission from the reporter is quenched by the quencher by FRET. During the extension phase of PCR, the probe is cleaved by 5′ nuclease activity of the polymerase used in the reaction, thereby releasing the reporter from the oligonucleotide-quencher and producing an increase in reporter emission intensity. Accordingly, TaqMan™ probes are oligonucleotides that have a label and a quencher, where the label is released during amplification by the exonuclease action of the polymerase used in amplification. This provides a real time measure of amplification during synthesis. A variety of TaqMan™ reagents are commercially available, e.g., from Applied Biosystems (Division Headquarters in Foster City, Calif.) as well as from a variety of specialty vendors such as Biosearch Technologies (e.g., black hole quencher probes). Further details regarding dual-label probe strategies can be found, e.g., in WO92/02638.

(163) Other similar methods include e.g. fluorescence resonance energy transfer between two adjacently hybridized probes, e.g., using the "LightCycler™" format described in U.S. Pat. No. 6,174,670.

(164) Amplification and Sequencing Primers

(165) In embodiments, methylation sites are detected using primers, e.g., to amplify and/or sequence polynucleotides comprising the methylation sites.

(166) Suitable primers can be designed and is not intended that the present subject matter be limited to any particular primer or primer pair. For example, primers can be designed using any suitable software program, such as LASERGENE™, e.g., taking account of publicly available sequence information. Flanking sequences for the methylation sites identified herein are publicly available; accordingly, suitable amplification primers can be constructed based on well understood base-pairing rules. The sequence of any amplicon can be detected as has already been discussed above, e.g., by sequencing, hybridization, array hybridization, PCR, LCR, or the like.

(167) In embodiments, the primers are radiolabelled, or labeled by any suitable means (e.g., using a non-radioactive fluorescent tag), to allow for rapid visualization of differently sized amplicons following an amplification reaction without any additional labeling step or visualization step. In embodiments, the primers are not labeled, and the amplicons are visualized following their size resolution, e.g., following agarose or acrylamide gel electrophoresis. In embodiments, ethidium bromide staining of the PCR amplicons following size resolution allows visualization of the different size amplicons.

(168) It is not intended that the primers be limited to generating an amplicon of any particular size. The primers can generate an amplicon of any suitable length for detection (e.g., by sequencing or

hybridization). In embodiments, amplification produces an amplicon at least 20 nucleotides in length, or alternatively, at least 50 nucleotides in length, or alternatively, at least 100 nucleotides in length, or alternatively, at least 200 nucleotides in length. Amplicons of any size can be detected and/or sequenced using various technologies described herein and known in the art.

(169) Detection of Methylation Levels Using Sequencing

(170) Sequencing is the process of determining the precise order of nucleotides within a DNA molecule. The advent of rapid DNA sequencing methods has greatly accelerated biological and medical research and discovery. Non-limiting examples and descriptions are provided below. However, embodiments are not limited to the use of a particular sequencing assay, technology, or approach.

(171) Sanger sequencing is a method of DNA sequencing based on the selective incorporation of chain-terminating dideoxynucleotides by DNA polymerase during in vitro DNA replication (Sanger F; Coulson A R (May 1975) J. Mol. Biol. 94 (3): 441-8; Sanger et al. (December 1977) Proc. Natl. Acad. Sci. U.S.A. 74 (12): 5463-7).

(172) In embodiments, next-generation sequencing is used. Non-limiting examples of next-generation sequencing methods include massively parallel signature sequencing (MPSS), single-molecule real-time sequencing, ion semiconductor sequencing, pyrosequencing, sequencing by synthesis, sequencing by ligation, chain termination, DNA nanoball sequencing, helicos single molecule sequencing, single molecule real time sequencing, nanopore DNA sequencing, tunnelling currents DNA sequencing, and sequencing by hybridization.

(173) Many commercially available sequencing technologies, devices, and services are available. In embodiments, an Illumina sequencer is used. In embodiments, PCR products are ligated with a linker and sequenced using a high throughput sequencer, such as an Illumina sequencer. In embodiments, the ligation step can be avoided, omitted, or eliminated by adding a linker to amplification primers.

(174) Array-Based Sequence Detection

(175) Array-based detection can be performed using commercially available arrays, e.g., from Affymetrix (Santa Clara, Calif.) or other manufacturers. Reviews regarding the operation of nucleic acid arrays include Sapolsky et al. (1999) “High-throughput polymorphism screening and genotyping with high-density oligonucleotide arrays.” Genetic Analysis: Biomolecular Engineering 14:187-192; Lockhart (1998) “Mutant yeast on drugs” Nature Medicine 4:1235-1236; Fodor (1997) “Genes, Chips and the Human Genome.” FASEB Journal 11:A879; Fodor (1997) “Massively Parallel Genomics.” Science 277:393-395; and Chee et al. (1996) “Accessing Genetic Information with High-Density DNA Arrays.” Science 274:610-614.

(176) A variety of probe arrays have been described in the literature and can be used for detection of methylation. For example, DNA probe array chips or larger DNA probe array wafers (from which individual chips would otherwise be obtained by breaking up the wafer) may be used in embodiments described herein. DNA probe array wafers generally comprise glass wafers on which high density arrays of DNA probes (short segments of DNA) have been placed.

(177) Each of these wafers can hold, for example, approximately 60 million DNA probes that are used to recognize longer sample DNA sequences (e.g., from individuals or populations, e.g., that comprise methylation sites of interest). The recognition of sample DNA by the set of DNA probes on the glass wafer takes place through DNA hybridization. When a DNA sample hybridizes with an array of DNA probes, the sample binds to those probes that are complementary to the sample DNA sequence. By evaluating to which probes the sample DNA for an individual hybridizes more strongly, it is possible to determine whether a known sequence of nucleic acid is present or not in the sample, thereby determining whether a uracil, thymine, or cytosine is present at a polynucleotide site corresponding to a genomic methylation site. One can also use this approach to control the hybridization conditions to permit single nucleotide discrimination, e.g., for the identification of methylation at a site of interest. Arrays provide one convenient embodiment for detecting multiple methylation sites simultaneously (or in series). Of course, any detection technology (PCR, LCR, and/or sequencing etc.) can similarly be used, e.g., with multiplex amplification/detection/sequencing

reactions, or simply by running several separate reactions, e.g., simultaneously or in series.
(178) In embodiments, the use of DNA probe arrays to obtain methylation information involves the following general steps: design and manufacture of DNA probe arrays, preparation of the sample, bisulfite treatment, hybridization of sample DNA to the array, detection of hybridization events and data analysis to determine sequence. In embodiments, an array is used to capture polynucleotides containing a methylation site of interest, and the captured polynucleotides are subsequently amplified and/or sequenced. Preferred wafers are manufactured using a process adapted from semiconductor manufacturing to achieve cost effectiveness and high quality, and are available, e.g., from Affymetrix, Inc. of Santa Clara, Calif.
(179) For example, probe arrays can be manufactured by light-directed chemical synthesis processes, which combine solid-phase chemical synthesis with photolithographic fabrication techniques as employed in the semiconductor industry. Using a series of photolithographic masks to define chip exposure sites, followed by specific chemical synthesis steps, the process constructs high-density arrays of oligonucleotides, with each probe in a predefined position in the array. Multiple probe arrays can be synthesized simultaneously on a large glass wafer. This parallel process enhances reproducibility and helps achieve economies of scale.
(180) In embodiments, DNA probe arrays can be used to obtain data regarding presence of sequences (e.g., corresponding to methylated or unmethylated DNA) of interest. The DNA samples may be tagged with biotin and/or a fluorescent reporter group by standard biochemical methods. The labeled samples are incubated with an array, and segments of the samples bind, or hybridize, with complementary sequences on the array. The array can be washed and/or stained to produce a hybridization pattern. The array is then scanned and the patterns of hybridization are detected by emission of light from the fluorescent reporter groups. Because the identity and position of each probe on the array is known, the nature of the DNA sequences in the sample applied to the array can be determined.
(181) In embodiments, the nucleic acid sample to be analyzed is isolated, bisulfite-treated, amplified and, optionally, labeled with biotin and/or a fluorescent reporter group. The labeled nucleic acid sample may then incubated with the array using a fluidics station and hybridization oven. The array can be washed and or stained or counter-stained, as appropriate to the detection method. After hybridization, washing and staining, the array is inserted into a scanner, where patterns of hybridization are detected. The hybridization data are collected as light emitted from the fluorescent reporter groups already incorporated into the labeled nucleic acid, which is now bound to the probe array. Probes that most clearly match the labeled nucleic acid produce stronger signals than those that have mismatches. Since the sequence and position of each probe on the array are known, by complementarity, the identity of the nucleic acid sample applied to the probe array can be identified. In embodiments, hybridization techniques and conditions that allow only fully complementary nucleotide sequences to hybridize with probes in an array are used.
(182) Prior to amplification and/or detection of a nucleic acid comprising a sequence of interest, the nucleic acid is optionally purified from the samples by any available method, e.g., those taught in Berger and Kimmel, Guide to Molecular Cloning Techniques, Methods in Enzymology volume 152 Academic Press, Inc., San Diego, Calif. (Berger); Sambrook et al., Molecular Cloning—A Laboratory Manual (3rd Ed.), Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 2001 (“Sambrook”); and/or Current Protocols in Molecular Biology, F. M. Ausubel et al., eds., Current Protocols, a joint venture between Greene Publishing Associates, Inc. and John Wiley & Sons, Inc., (supplemented through 2002) (“Ausubel”)). A plethora of kits are also commercially available for the purification of nucleic acids from cells or other samples (see, e.g., EasyPrep™, FlexiPrep™, both from Pharmacia Biotech; StrataClean™, from Stratagene; and, QIAprep™ from Qiagen). Alternately, samples can simply be directly subjected to amplification or detection, e.g., following aliquotting and/or dilution.
(183) Thyroid Cancer Diagnostic System and Processes
(184) FIG. **4** depicts a block diagram illustrating an exemplary thyroid cancer diagnostic system **600**.

Referring to FIG. **4**, the thyroid cancer diagnostic system **600** can include an input module **610**, an isolation module **612**, a conversion module **614**, a detection module **616**, a diagnosis module **618**, a treatment module **620**, and a user interface (UI) module **622**. The thyroid cancer diagnostic system **600** can be configured to provide a diagnosis indicative of a presence of thyroid cancer and/or a risk of developing thyroid cancer. Moreover, the thyroid cancer diagnostic system **600** can be further configured to generate a treatment plan for a subject based on the diagnosis. For instance, when the diagnosis indicates a presence and/or risk of thyroid cancer in a subject, the thyroid cancer diagnostic system **600** can recommend one or more treatments including, for example, thyroid surgery, radiation therapy, radioactive iodine therapy, chemotherapy, thyroid hormone therapy, and administration of an active agent.

(185) One or more modules of the thyroid cancer diagnostic system **600** can be realized in digital electronic circuitry, integrated circuitry, specially designed application specific integrated circuits (ASICs), field programmable gate arrays (FPGAs) computer hardware, firmware, software, and/or combinations thereof. The thyroid cancer diagnostic system **600** can further be communicatively coupled with one or more devices including, for example, a device **630**. The thyroid cancer diagnostic system **600** can communicate with the device **620** via a wired and/or wireless network **640** (e.g., a wide area network (WAN), a local area network (LAN), and/or the Internet). As shown in FIG. **4**, the thyroid cancer diagnostic system **600** can be further coupled with a data store **650**.

(186) The input module **610** can be adapted to receive and/or collect a sample of a thyroid nodule obtained from a subject. The isolation module **612** can be configured to isolate DNA from the thyroid nodule sample received by the input module **610** thereby forming isolated thyroid nodule DNA. The conversion module **614** can be configured to treat the isolated thyroid nodule DNA including by contacting the isolated thyroid nodule DNA with one or more bisulfite reagents including, for example, a bisulfite salt. Exposing the isolated thyroid nodule DNA to one or more bisulfite reagents can convert cytosine to uracil while 5-mC is left unmodified. Thus, the 5-mC present in the isolated thyroid nodule DNA will remain in the reacted thyroid nodule DNA. Meanwhile, any cytosine in the isolated thyroid nodule DNA will be replaced by uracil in the reacted thyroid nodule DNA. In embodiments, the treatment of the isolated thyroid nodule DNA can be performed by applying one or more kits (e.g., the Bisulflash DNA Modification Kit (Epigentek) or Imprint DNA Modification Kit (Sigma)).

(187) In embodiments, the conversion module **614** can be further adapted to ensure optimal bisulfite conversion (e.g., with desired DNA fragment size for post-bisulfite ligation) by controlling one or more of a concentration of the bisulfite reagents, temperature, and reaction time period. It should be appreciated that the conversion module **614** can be adapted to use a different and/or additional type of reagent without departing from the scope of the present subject matter. For example, the conversion module **614** can treat the isolated thyroid nodule DNA with potassium chloride, which may reduce the thermophilic DNA degradation associated with the conversion of cytosine to uracil. Moreover, the conversion module **614** can be configured to perform additional processing of the reacted thyroid nodule DNA including, for example, desulphonation (e.g., with an alkalized solution), cleansing (e.g., by elution), and amplification (e.g., using the PCR method).

(188) The detection module **616** can be configured to detect a methylation and/or unmethylation of the thyroid nodule DNA. For instance, the detection module **616** can detect methylation by detecting a presence of uracil in the reacted thyroid nodule DNA generated by the conversion module **614**. Alternately and/or additionally, the detection module **616** can detect unmethylation by detecting an absence of uracil in the reacted thyroid nodule DNA. In embodiments, the detection module **616** can be configured detect the presence and/or absence of uracil at specific methylation sites. That is, the detection module **616** can be configured to detect the presence and/or absence of uracil at specific chromosomal positions of certain chromosomes. For example, the thyroid cancer diagnostic system **600** can store a plurality of specific methylation sites (e.g., Table 1) in the data store **650**. As such, to detect methylation, the detection module **616** can be configured to obtain, from the data store **650**, one or more specific methylation sites at which to test for the presence and/or absence of uracil.

Moreover, in embodiments, the detection module **616** can be configured to determine a level of methylation and/or unmethylation at the specific methylation sites. The level of methylation at a particular site can correspond to a proportion of the reacted thyroid nodule DNA that has a cytosine rather than a uracil at that site. By contrast, the level of unmethylation at a particular site can correspond to a proportion of reacted thyroid nodule DNA that has a uracil rather than a cytosine at that site.

(189) In embodiments, the conversion module **614** may amplify the reacted thyroid nodule DNA such as by using a PCR method. The detection of methylation and/or unmethylation in amplified reacted thyroid nodule DNA may require detection of a presence and/or absence of thymidine at a site of interest in amplicons amplified from the reacted thyroid nodule DNA. That is, instead of detecting the presence and/or absence of uracil, the detection module **616** can be configured to detect methylation and/or unmethylation of amplified reacted thyroid nodule DNA by detecting a presence and/or absence of thymidine at specific methylation sites (e.g., as set forth in Table 1).

(190) The diagnosis module **618** can be configured to generate a diagnosis for the subject based on whether the detection module **616** detects methylation and/or unmethylation at the plurality of specific methylation sites (e.g., Table 1). Alternately or additionally, the diagnosis module **618** can be configured to generate a diagnosis for the subject based on a level of methylation and/or unmethylation detected by the detection module **616** at the plurality of specific methylation sites. For instance, diagnosis module **618** can determine that the thyroid nodule is malignant (e.g., cancerous) when the unmethylation level (e.g., proportion of uracil) at different methylation sites exceeds the corresponding thresholds (e.g., as set forth in Table 2). In embodiments, the diagnosis module **618** can further generate a diagnosis for the subject based on one or more of the subject's PTC methylation alternation score, a BTN methylation alternation score, and/or a Composite Cancer Risk Score.

(191) In embodiments, the diagnosis module **618** can be configured to determine a PTC methylation alternation score for the subject. In embodiments, the PTC methylation alteration score can correspond to a number of specific methylation sites (e.g., as set forth in Table 1) that have a uracil level (or corresponding thymidine level if amplicons are being analyzed) equal to or greater than the corresponding thresholds (e.g., as set forth in Table 2). Alternately or additionally, the diagnosis module **618** can be configured to determine a BTN methylation alternation score for the subject. The BTN methylation alteration score can correspond to a number of specific methylation sites (e.g., as set forth in Table 1) that have a uracil level (or corresponding thymidine level if amplicons are being analyzed) equal to or greater than the various corresponding threshold level (e.g., as set forth in Table 3 and/or Table 4).

(192) In embodiments, the diagnosis module **618** can further be configured to compute a Composite Cancer Risk Score for the subject. The diagnosis module **618** can compute the Composite Cancer Risk Score based on the PTC methylation alteration score and the BTN methylation alteration score for the subject. For example, the Composite Cancer Risk Score for the subject can be computed based on equation (1):

(193) $$\frac{[\text{thePTCmethylationalterationscoreforthesubject}]}{[\text{BTNmethylationalterationscoreforthesubject}]}. \quad (1)$$

(194) Alternately or additionally, the Composite Cancer Risk Score for the subject can be computed based on equation (2):

(195) $$\frac{[(\text{thePTCmethylationalterationscoreforthesubject}) + 1]}{[(\text{BTNmethylationalterationscoreforthesubject}) + 1]} \quad (2)$$

(196) The treatment module **620** can be configured to formulate a treatment plan for the subject based on the diagnosis generated by the diagnosis module **618**. For instance, when the diagnosis generated by the diagnosis module **618** indicates a presence and/or risk of a malignant (e.g., cancerous) thyroid nodule, the treatment module **620** can prescribe one or more treatments including, for example, thyroid surgery, radiation therapy, radioactive iodine therapy, chemotherapy, thyroid hormone therapy, and administration of an active agent. In embodiments, the treatment module **620** can be configured to provide the treatment plan to the device **630** via the network **640**. Alternately or additionally, the treatment module **620** can store the treatment plan in the data store **650**.

(197) The UI module **622** can be configured to generate a UI through which a user (e.g., a physician) can interface with the thyroid cancer diagnostic system **600**. For example, the UI module **622** can provide one or more graphic user interfaces (GUIs) configured to display the diagnosis and/or treatment plan for the subject.
(198) FIG. **5** depicts a flowchart illustrating an exemplary process **700** for diagnosing thyroid cancer. Referring to FIGS. **4-5**, the process **700** can be performed by the thyroid cancer diagnostic system **600**.
(199) The thyroid cancer diagnostic system **600** (e.g., the input module **610**) can receive a sample of a thyroid nodule from a subject (**702**). The thyroid cancer diagnostic system **600** (e.g., the isolation module **612**) can isolate thyroid nodule DNA from the thyroid nodule sample (**704**). The thyroid cancer diagnostic system **600** (e.g., the conversion module **614**) can treat the isolated thyroid nodule DNA with a bisulfite salt to generate reacted thyroid nodule DNA (**706**). Treating the isolated thyroid nodule DNA with the bisulfite salt can form a reacted thyroid nodule DNA by converting the cytosine present in the isolated thyroid nodule DNA to uracil. In embodiments, the thyroid cancer diagnostic system **600** can further process the reacted thyroid nodule DNA by desulphonating, cleansing, and/or amplifying the reacted thyroid nodule DNA.
(200) The thyroid cancer diagnostic system **600** (e.g., the detection module **616**) can detect methylation and/or unmethylation of the isolated thyroid nodule DNA by at least detecting a presence and/or absence of uracil in the reacted thyroid nodule DNA (**708**). In embodiments, the thyroid cancer diagnostic system **600** can be configured to detect a presence and/or absence of uracil at specific methylation sites (e.g., as set forth in Table 1). Moreover, the thyroid cancer diagnostic system **600** can be configured to detect a level of methylation and/or unmethylation at the methylation sites.
(201) The thyroid cancer diagnostic system **600** (e.g., the diagnostics module **618**) can generate a diagnosis for the subject based on the methylation and/or unmethylation of the isolated thyroid nodule DNA (**710**). For example, the thyroid cancer diagnostic system **600** can generate a diagnosis based on a level of methylation and/or unmethylation at a plurality of specific methylation sites. Each methylation site may be associated with a certain threshold unmethylation level (e.g., as set forth in Table 2). As such, the thyroid cancer diagnostic system **600** can determine that the thyroid nodule from the subject is malignant (e.g., cancerous) if the level of unmethylation at the plurality of methylation sites exceeds the corresponding thresholds.
(202) The thyroid cancer diagnostic system **600** (e.g., the treatment module **620**) can formulate, based on the diagnosis, a treatment plan for the subject (**712**). For example, when the diagnosis indicates that a presence and/or risk of malignant thyroid nodules in the subject, the thyroid cancer diagnostic system **600** can prescribe thyroid surgery, radiation therapy, radioactive iodine therapy, chemotherapy, thyroid hormone therapy, and/or administration of an active agent. The thyroid cancer diagnostic system **600** (e.g., the UI module **622**) can provide, via a UI (e.g., GUI at the device **630**), the diagnosis and/or the treatment plan for the subject (**714**).
(203) FIG. **6** depicts a flowchart illustrating an exemplary process **800** for diagnosing thyroid cancer. Referring to FIGS. **4** and **6**, the process **700** can be performed by the thyroid cancer diagnostic system **600**.
(204) The thyroid cancer diagnostic system **600** (e.g., the input module **610**) can receive a sample of a thyroid nodule from a subject (**802**). The thyroid cancer diagnostic system **600** (e.g., the isolation module **612**) can isolate thyroid nodule DNA from the thyroid nodule sample (**804**). The thyroid cancer diagnostic system **600** (e.g., the conversion module **614**) can treat the isolated thyroid nodule DNA with a bisulfite salt to generate reacted thyroid nodule DNA (**806**).
(205) As shown in FIG. **6**, the thyroid cancer diagnostic system **600** (e.g., the conversion module **614**) can amplify the reacted thyroid nodule DNA (**808**). For instance, the thyroid cancer diagnostic system **600** can amplify the reacted thyroid nodule DNA subsequent to treating the isolated thyroid nodule NA with the bisulfite salt to generate the reacted thyroid nodule DNA. The thyroid cancer diagnostic system **600** can detect methylation and/or unmethylation of the isolated thyroid nodule DNA by detecting a presence and/or absence of thymidine in the amplified reacted thyroid nodule DNA (**810**).

(206) The thyroid cancer diagnostic system **600** (e.g., the diagnostics module **618**) can generate a diagnosis for the subject based on the methylation and/or unmethylation of the isolated thyroid nodule DNA (**812**). Moreover, the thyroid cancer diagnostic system **600** (e.g., the treatment module **620**) can formulate, based on the diagnosis, a treatment plan for the subject (**814**). The thyroid cancer diagnostic system **600** (e.g., the UI module **622**) can provide, via a UI, the diagnosis and/or treatment plan for the subject.
(207) It should be appreciated that the process **700** and/or **800** can include different and/or additional operations without departing from the scope of the present subject matter. Moreover, one or more operations of the process **700** and/or **800** can be omitted and/or repeated without departing from the scope of the present subject matter.
(208) Implementations of the present subject matter can include, but are not limited to, methods consistent with the descriptions provided above as well as articles that comprise a tangibly embodied machine-readable medium operable to cause one or more machines (e.g., computers, etc.) to result in operations implementing one or more of the described features. Similarly, computer systems are also described that can include one or more processors and one or more memories coupled to the one or more processors. A memory, which can include a computer-readable storage medium, can include, encode, store, or the like one or more programs that cause one or more processors to perform one or more of the operations described herein. Computer implemented methods consistent with one or more implementations of the current subject matter can be implemented by one or more data processors residing in a single computing system or multiple computing systems. Such multiple computing systems can be connected and can exchange data and/or commands or other instructions or the like via one or more connections, including but not limited to a connection over a network (e.g. the Internet, a wireless wide area network, a local area network, a wide area network, a wired network, or the like), via a direct connection between one or more of the multiple computing systems, etc.
(209) One or more aspects or features of the subject matter described herein can be realized in digital electronic circuitry, integrated circuitry, specially designed ASICs, FPGAs, computer hardware, firmware, software, and/or combinations thereof. These various aspects or features can include implementation in one or more computer programs that are executable and/or interpretable on a programmable system including at least one programmable processor, which can be special or general purpose, coupled to receive data and instructions from, and to transmit data and instructions to, a storage system, at least one input device, and at least one output device. The programmable system or computing system can include clients and servers. A client and server are generally remote from each other and typically interact through a communication network. The relationship of client and server arises by virtue of computer programs running on the respective computers and having a client-server relationship to each other.
(210) These computer programs, which can also be referred to programs, software, software applications, applications, components, or code, include machine instructions for a programmable processor, and can be implemented in a high-level procedural language, an object-oriented programming language, a functional programming language, a logical programming language, and/or in assembly/machine language. As used herein, the term “machine-readable medium” refers to any computer program product, apparatus and/or device, such as for example magnetic discs, optical disks, memory, and Programmable Logic Devices (PLDs), used to provide machine instructions and/or data to a programmable processor, including a machine-readable medium that receives machine instructions as a machine-readable signal. The term “machine-readable signal” refers to any signal used to provide machine instructions and/or data to a programmable processor. The machine-readable medium can store such machine instructions non-transitorily, such as for example as would a non-transient solid-state memory or a magnetic hard drive or any equivalent storage medium. The machine-readable medium can alternatively or additionally store such machine instructions in a transient manner, such as for example as would a processor cache or other random access memory associated with one or more physical processor cores.
(211) To provide for interaction with a user, one or more aspects or features of the subject matter

described herein can be implemented on a computer having a display device, such as for example a cathode ray tube (CRT) or a liquid crystal display (LCD) or a light emitting diode (LED) monitor for displaying information to the user and a keyboard and a pointing device, such as for example a mouse or a trackball, by which the user may provide input to the computer. Other kinds of devices can be used to provide for interaction with a user as well. For example, feedback provided to the user can be any form of sensory feedback, such as for example visual feedback, auditory feedback, or tactile feedback; and input from the user can be received in any form, including, but not limited to, acoustic, speech, or tactile input. Other possible input devices include, but are not limited to, touch screens or other touch-sensitive devices such as single or multi-point resistive or capacitive trackpads, voice recognition hardware and software, optical scanners, optical pointers, digital MRI image capture devices and associated interpretation software, and the like.

(212) Examples are provided below to facilitate a more complete understanding of the invention. The following examples illustrate the exemplary modes of making and practicing the invention. However, the scope of the invention is not limited to specific embodiments disclosed in these Examples, which are for purposes of illustration only, since alternative methods can be utilized to obtain similar results.

EMBODIMENTS

(213) Embodiments include embodiments P1 to P41 following.

(214) Embodiment P1. A method of detecting methylation or unmethylation of a thyroid nodule DNA of a subject, the method comprising: (i) isolating DNA from a thyroid nodule of said subject thereby forming isolated thyroid nodule DNA, (ii) contacting said isolated thyroid nodule DNA with sodium bisulfite thereby forming a reacted thyroid nodule DNA, (iii) detecting the presence or absence of uracil in said reacted thyroid nodule DNA at a methylation site set forth in Table 1, thereby detecting methylation or unmethylation of said thyroid nodule DNA of said subject.

(215) Embodiment P2. The method of embodiment P1, further comprising determining alteration in methylation at a plurality of methylation sites set forth in Table 1.

(216) Embodiment P3. The method of embodiment P2, said alteration comprises increase or loss of uracil level at said plurality of methylation sites.

(217) Embodiment P4. The method of embodiment P3, wherein said uracil level is above a threshold as set forth in Table 2.

(218) Embodiment P5. The method of embodiment P3, wherein said uracil level is above a threshold as set forth in Table 3.

(219) Embodiment P6. The method of embodiment P3, wherein said uracil level is below a threshold as set forth in Table 4.

(220) Embodiment P7. The method of embodiment P3, wherein said subject is a candidate thyroid cancer patient.

(221) Embodiment P8. The method of embodiment P4, wherein said above threshold identifies said thyroid nodule as a cancerous thyroid nodule.

(222) Embodiment P9. The method of embodiment P5, wherein said above threshold identifies said thyroid nodule as a benign thyroid nodule.

(223) Embodiment P10. The method of embodiment P6, wherein said below threshold identifies said thyroid nodule as a benign thyroid nodule.

(224) Embodiment P11. The method of one of the above embodiments, wherein said thyroid nodule is a specimen obtained by biopsy or by surgical resection of said subject.

(225) Embodiment P12. The method of embodiment P11, wherein said subject has undergone thyroid surgery, radiation therapy, radioactive iodine therapy, chemotherapy, thyroid hormone therapy, and administration of an active agent.

(226) Embodiment P13. The method of embodiment P12, wherein said active agent is chosen from Cabozantinib-S-Malate, Caprelsa (Vandetanib), Cometriq (Cabozantinib-S-Malate), Doxorubicin Hydrochloride, Lenvatinib Mesylate, Lenvima (Lenvatinib Mesylate), Nexavar (Sorafenib Tosylate), Sorafenib Tosylate, and Vandetanib.

(227) Embodiment P14. A method of determining a thyroid cancer or risk of developing thyroid

cancer in a subject in need thereof, said method comprising: (i) isolating DNA from a thyroid nodule of said subject thereby forming isolated thyroid nodule DNA; (ii) contacting said isolated thyroid nodule DNA with sodium bisulfite thereby forming a reacted thyroid nodule DNA; and (iii) detecting the presence or absence of uracil in said reacted thyroid nodule DNA at a methylation site set forth in Table 1; thereby determining said thyroid cancer in said subject.
(228) Embodiment P15. The method of embodiment P14, further comprising selecting a subject that has or is at risk for developing thyroid cancer.
(229) Embodiment P16. The method of embodiment P14, further comprising determining alteration in methylation at a plurality of methylation sites set forth in Table 1.
(230) Embodiment P17. The method of embodiment P16, said alteration comprises increase or loss of uracil level at said plurality of methylation sites.
(231) Embodiment P18. The method of embodiment P17, wherein said uracil level is above a threshold as set forth in Table 2.
(232) Embodiment P19. The method of embodiment P17, wherein said uracil level is above a threshold as set forth in Table 3.
(233) Embodiment P20. The method of embodiment P17, wherein said uracil level is below a threshold as set forth in Table 4.
(234) Embodiment P21. The method of embodiment P17, wherein said subject is a candidate thyroid cancer patient.
(235) Embodiment P22. The method of embodiment P18, wherein said above threshold identifies said thyroid nodule as a cancerous thyroid nodule.
(236) Embodiment P23. The method embodiment P19, wherein said above threshold identifies said thyroid nodule as a benign thyroid nodule.
(237) Embodiment P24. The method of embodiment P20, wherein said below threshold identifies said thyroid nodule as a benign thyroid nodule.
(238) Embodiment P25. The method of embodiments P14-P24, wherein said thyroid nodule is a specimen obtained by biopsy or by surgical resection of said subject.
(239) Embodiment P26. The method of embodiment P25, wherein said subject has undergone thyroid surgery, radiation therapy, radioactive iodine therapy, chemotherapy, thyroid hormone therapy, and administration of an active agent, before said determination.
(240) Embodiment P27. The method of embodiment P26, wherein said active agent is chosen from Cabozantinib-S-Malate, Caprelsa (Vandetanib), Cometriq (Cabozantinib-S-Malate), Doxorubicin Hydrochloride, Lenvatinib Mesylate, Lenvima (Lenvatinib Mesylate), Nexavar
(241) (Sorafenib Tosylate), Sorafenib Tosylate, and Vandetanib.
(242) Embodiment P28. A method of treating thyroid cancer in a subject determined by the method as set forth in embodiment P22, comprising administering to said subject an active agent for treating thyroid cancer.
(243) Embodiment P29. The method of embodiment P28, wherein said subject has undergone surgery, radiation therapy, radioactive iodine therapy, chemotherapy, or thyroid hormone therapy, before said detection of embodiment 14 at (iii).
(244) Embodiment P30. The method of embodiment P29, wherein said active agent is chosen from Cabozantinib-S-Malate, Caprelsa (Vandetanib), Cometriq (Cabozantinib-S-Malate), Doxorubicin Hydrochloride, Lenvatinib Mesylate, Lenvima (Lenvatinib Mesylate), Nexavar
(245) (Sorafenib Tosylate), Sorafenib Tosylate, and Vandetanib.
(246) Embodiment P31. The method of one of above embodiments, wherein said subject has or is at risk of papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, or anaplastic thyroid cancer.
(247) Embodiment P32. A deoxyribonucleic acid 5 to 100 nucleotides in length comprising a uracil-containing sequence identical to at least a 5 contiguous nucleotide sequence within a sequence chosen from SEQ ID NO:1 to SEQ ID NO:550.
(248) Embodiment P33. The deoxyribonucleic acid of embodiment P32 identical to 5-10, 10-20, 20-

30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-100, 100-110, 110-120, 120-130, 130-140, 140-150, 150-160, 160-170, 170-180, 180-190, or 190-200 of contiguous nucleotide sequence of said sequence chosen from SEQ ID NO: 1 to SEQ ID NO:550.
(249) Embodiment P34. The deoxyribonucleic acid of embodiment P32 or P33, wherein said sequence comprises a methylation site set forth in Table 2.
(250) Embodiment P35. The deoxyribonucleic acid of embodiment P34, wherein a plurality of methylation sites set forth in Table 2 are methylated or unmethylated.
(251) Embodiment P36. A deoxyribonucleic acid chosen from SEQ ID NO:551 to SEQ ID NO: 782, wherein said nucleic acid is hybridized to a complementary DNA sequence comprising uridine or cytosine.
(252) Embodiment P37. The deoxyribonucleic acid of embodiment P36, further comprising an enzyme in a complex with said hybridized complementary DNA sequence.
(253) Embodiment P38. The deoxyribonucleic acid of embodiment P37, wherein said enzyme is Taq polymerase.
(254) Embodiment P39. A kit comprising 322 nucleic acids each independently comprising SEQ ID NO:551 to SEQ ID NO:782, wherein said nucleic acids do not simultaneously comprise the same SEQ ID NO:551 to SEQ ID NO:782.
(255) Embodiment P40. The kit according to embodiment P39, further comprising: enzymes, reagents for deamination of cytosine, buffers, vials, plasmid vectors, control DNA, devices for collecting thyroid tissue samples, reagents for isolating DNA, reagents for labeling DNA, or any combinations thereof.
(256) Embodiment P41. The kit according to embodiment P40, wherein the enzymes are selected from the group consisting of: thermostable DNA polymerase enzymes, restriction enzymes, and combination thereof.
(257) Further embodiments include embodiments 1-58 following.
(258) Embodiment 1. A method of detecting methylation or unmethylation of a thyroid nodule DNA molecule of a subject, the method comprising: (i) isolating a thyroid nodule DNA molecule from a thyroid nodule of said subject thereby forming an isolated thyroid nodule DNA molecule, (ii) contacting said isolated thyroid nodule DNA molecule with a bisulfite salt thereby forming a reacted thyroid nodule DNA molecule, (iii) detecting the presence or absence of uracil in said reacted thyroid nodule DNA molecule at a methylation site set forth in Table 1, thereby detecting methylation or unmethylation of said thyroid nodule DNA molecule of said subject.
(259) Embodiment 2. The method of embodiment 1, further comprising detecting the presence or absence of uracil in said reacted thyroid nodule DNA molecule at a plurality of methylation sites set forth in Table 1, wherein said methylation site forms a part of said plurality of methylation sites.
(260) Embodiment 3. The method of embodiment 1, the method further comprising: (i) isolating a plurality of thyroid nodule DNA molecules from said thyroid nodule of said subject thereby forming a plurality of isolated thyroid nodule DNA molecules, wherein said isolated thyroid nodule DNA molecule forms part of said plurality of isolated thyroid nodule DNA molecules, (ii) contacting said plurality of isolated thyroid nodule DNA molecules with said bisulfite salt thereby forming a plurality of reacted thyroid nodule DNA molecules, wherein said reacted thyroid nodule DNA molecule forms part of said plurality of reacted thyroid nodule DNA molecules, (iii) detecting the level of reacted thyroid nodule DNA molecules in said plurality of reacted thyroid nodule DNA molecules having a uracil at a methylation site set forth in Table 1, thereby detecting the level of methylation or unmethylation in said plurality of thyroid nodule DNA molecules of said subject.
(261) Embodiment 4. The method of embodiment 3, further comprising determining the level of uracil in said reacted thyroid nodule DNA molecule at a plurality methylation sites set forth in Table 1, wherein said methylation site forms a part of said plurality of methylation sites.
(262) Embodiment 5. The method of embodiment 4, wherein said uracil level is above a threshold as set forth in Table 2.
(263) Embodiment 6. The method of embodiment 4, wherein said uracil level is above a threshold as

set forth in Table 3.
(264) Embodiment 7. The method of embodiment 4, wherein said uracil level is below a threshold as set forth in Table 4.
(265) Embodiment 8. The method of one of the above embodiments, wherein said subject is suspected of having thyroid cancer.
(266) Embodiment 9. The method of one of the above embodiments, wherein said thyroid nodule is a specimen obtained by biopsy or by surgical resection of said subject.
(267) Embodiment 10. The method of one of the above embodiments, wherein said subject has undergone thyroid surgery, radiation therapy, radioactive iodine therapy, chemotherapy, thyroid hormone therapy, and/or administration of an active agent.
(268) Embodiment 11. The method of embodiment 10, wherein said active agent is chosen from Cabozantinib-S-Malate, Caprelsa (Vandetanib), Cometriq (Cabozantinib-S-Malate), Doxorubicin Hydrochloride, Lenvatinib Mesylate, Lenvima (Lenvatinib Mesylate), Nexavar (Sorafenib Tosylate), Sorafenib Tosylate, and/or Vandetanib.
(269) Embodiment 12. A method of detecting a thyroid cancer or risk of developing thyroid cancer in a subject in need thereof, said method comprising: (i) isolating a thyroid nodule DNA molecule from a thyroid nodule of said subject thereby forming an isolated thyroid nodule DNA molecule; (ii) contacting said isolated thyroid nodule DNA molecule with a bisulfite salt thereby forming a reacted thyroid nodule DNA molecule; and (iii) detecting the presence or absence of uracil in said reacted thyroid nodule DNA molecule at a methylation site set forth in Table 1; thereby detecting said thyroid cancer in said subject.
(270) Embodiment 13. The method of embodiment 12, wherein said subject (a) is a woman; (b) is about 20 to about 55 years old; (c) has a mutated Ret Proto-Oncogene; (d) has a grandparent, parent, or sibling who has been diagnosed with thyroid cancer; (e) self-identifies as being Caucasian or Asian; and/or (f) has or has had breast cancer.
(271) Embodiment 14. The method of embodiment 12, further comprising detecting the presence or absence of uracil in said reacted thyroid nodule DNA molecule at a plurality of methylation sites set forth in Table 1, wherein said methylation site forms a part of said plurality of methylation sites.
(272) Embodiment 15. The method of embodiment 12, the method further comprising: (i) isolating a plurality of thyroid nodule DNA molecules from said thyroid nodule of said subject thereby forming a plurality of isolated thyroid nodule DNA molecules, wherein said isolated thyroid nodule DNA molecule forms part of said plurality of isolated thyroid nodule DNA molecules, (ii) contacting said plurality of isolated thyroid nodule DNA molecules with said bisulfite salt thereby forming a plurality of reacted thyroid nodule DNA molecules, wherein said reacted thyroid nodule DNA molecule forms part of said plurality of reacted thyroid nodule DNA molecules, (iii) detecting the level of reacted thyroid nodule DNA molecules in said plurality of reacted thyroid nodule DNA molecules having a uracil at a methylation site set forth in Table 1; thereby detecting said thyroid cancer in said subject.
(273) Embodiment 16. The method of embodiment 15, further comprising determining the level of uracil in said reacted thyroid nodule DNA molecule at a plurality methylation sites set forth in Table 1, wherein said methylation site forms a part of said plurality of methylation sites.
(274) Embodiment 17. The method of embodiment 16, wherein said uracil level is above a threshold as set forth in Table 2.
(275) Embodiment 18. The method of embodiment 16, wherein said uracil level is above a threshold as set forth in Table 3.
(276) Embodiment 19. The method of embodiment 16, wherein said uracil level is below a threshold as set forth in Table 4.
(277) Embodiment 20. The method of one of the above embodiments, wherein said subject is suspected of having thyroid cancer.
(278) Embodiment 21. The method of one of the above embodiments, wherein said thyroid nodule is a specimen obtained by biopsy or by surgical resection of said subject.
(279) Embodiment 22. The method of one of the above embodiments, wherein said subject has

undergone thyroid surgery, radiation therapy, radioactive iodine therapy, chemotherapy, thyroid hormone therapy, and administration of an active agent, before said determination.
(280) Embodiment 23. The method of embodiment 22, wherein said active agent is chosen from Cabozantinib-S-Malate, Caprelsa (Vandetanib), Cometriq (Cabozantinib-S-Malate), Doxorubicin Hydrochloride, Lenvatinib Mesylate, Lenvima (Lenvatinib Mesylate), Nexavar (Sorafenib Tosylate), Sorafenib Tosylate, and.
(281) Embodiment 24. A method of treating thyroid cancer in a subject determined by the method as set forth in any of embodiments 12 to 23, comprising administering to said subject an active agent for treating thyroid cancer.
(282) Embodiment 25. The method of embodiment 24, wherein said subject has undergone surgery, radiation therapy, radioactive iodine therapy, chemotherapy, or thyroid hormone therapy, before said detection of claim **12** at (iii).
(283) Embodiment 26. The method of embodiment 25, wherein said active agent is chosen from Cabozantinib-S-Malate, Caprelsa (Vandetanib), Cometriq (Cabozantinib-S-Malate), Doxorubicin Hydrochloride, Lenvatinib Mesylate, Lenvima (Lenvatinib Mesylate), Nexavar (Sorafenib Tosylate), Sorafenib Tosylate, and Vandetanib.
(284) Embodiment 27. The method of one of the above embodiments, wherein said subject has or is at risk of papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, or anaplastic thyroid cancer.
(285) Embodiment 28. The method of one of the above embodiments, wherein said bisulfite salt is sodium bisulfite.
(286) Embodiment 29. The method of one of the above embodiments, further comprising determining a papillary thyroid carcinoma (PTC) methylation alteration score for said subject, wherein the PTC methylation alteration score is equal to: the number of methylation sites in Table I having a uracil level equal to or greater than the corresponding threshold level set forth in Table 2.
(287) Embodiment 30. The method of one of the above embodiments, further comprising determining a benign thyroid nodule (BTN) methylation alteration score for said subject, wherein the BTN methylation alteration score is equal to: (a) the number of methylation sites in Table 1 having a uracil level equal to or greater than the corresponding threshold level set forth in Table 3; (b) the number of methylation sites in Table 1 having a uracil level equal to or less than the corresponding threshold level set forth in Table 4; or (c) the number of methylation sites in Table 1 having a uracil level equal to or greater than the corresponding threshold level set forth in Table 3 plus the number of methylation sites in Table 1 having a uracil level equal to or less than the corresponding threshold level set forth in Table 4.
(288) Embodiment 31. The method of embodiment 29, further comprising calculating a Composite Cancer Risk Score for said subject.
(289) Embodiment 32. The method of embodiment 31, wherein said Composite Cancer Risk Score for said subject equals:
[the PTC methylation alteration score for said subject]/[BTN methylation alteration score for said subject].
(290) Embodiment 33. The method of embodiment 31, wherein said Composite Cancer Risk Score for said subject equals:
[(the PTC methylation alteration score for said subject)+1]/[(BTN methylation alteration score for said subject)+1].
(291) Embodiment 34. The method of one of embodiments 29 to 33, wherein said subject is identified as being at risk of developing thyroid cancer or diagnosed as having thyroid cancer if (a) the PTC methylation alteration score for said subject is at least 5, 6, 7, 8, 9, or 10; (b) the BTN methylation alteration score for said subject is at least 5, 6, 7, 8, 9, or 10; and/or (c) the Composite Cancer Risk Score for said subject is at least about 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0.
(292) Embodiment 35. The method of one of embodiments 29 to 33, wherein said subject is treated for thyroid cancer or directed to receive additional screening for thyroid cancer if (a) the PTC

methylation alteration score for said subject is at least 5, 6, 7, 8, 9, or 10; (b) the BTN methylation alteration score for said subject is at least 5, 6, 7, 8, 9, or 10; and/or (c) the Composite Cancer Risk Score for said subject is at least about 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0.
(293) Embodiment 36. A deoxyribonucleic acid at least 5 to 100 nucleotides in length comprising a uracil-containing sequence that is identical to a sequence of at least a 5 contiguous nucleotides within a sequence chosen from SEQ ID NO:1 to SEQ ID NO:550.
(294) Embodiment 37. The deoxyribonucleic acid of embodiment 36, comprising a uracil-containing sequence that is identical to a sequence of at least 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-100, 100-110, 110-120, 120-130, 130-140, 140-150, 150-160, 160-170, 170-180, 180-190, or 190-200 contiguous nucleotides within said sequence chosen from SEQ ID NO:1 to SEQ ID NO:550.
(295) Embodiment 38. The deoxyribonucleic acid of embodiment 36 or 37, wherein said sequence comprises a methylation site set forth in Table 1.
(296) Embodiment 39. The deoxyribonucleic acid of one of embodiments 36 to 38, wherein a plurality of methylation sites set forth in Table 1 contain a uracil or a cytosine.
(297) Embodiment 40. A deoxyribonucleic acid chosen from SEQ ID NO:551 to SEQ ID NO: 782, wherein said nucleic acid is hybridized to a complementary DNA sequence comprising uridine or cytosine.
(298) Embodiment 41. The deoxyribonucleic acid of embodiment 40, further comprising an enzyme in a complex with said hybridized complementary DNA sequence.
(299) Embodiment 42. The deoxyribonucleic acid of embodiment 41, wherein said enzyme is Taq polymerase.
(300) Embodiment 43. A kit comprising a plurality of nucleic acids each independently comprising SEQ ID NO:551 to SEQ ID NO:782, wherein each nucleic acid of said plurality is unique.
(301) Embodiment 44. The kit according to embodiment 43, further comprising: an enzyme, a reagent for deamination of cytosine, a buffer, a vial, a plasmid vector, a control DNA, a device for collecting a thyroid tissue sample, a reagent for isolating DNA, a reagent for labeling DNA, or any combination thereof.
(302) Embodiment 45. The kit according to embodiment 44, wherein the enzyme comprises a thermostable DNA polymerase enzyme and/or a restriction enzyme.
(303) Embodiment 46. A system for detecting methylation or unmethylation of a thyroid nodule deoxyribonucleic acid (DNA) of a subject, the system comprising: at least one processor; and at least one memory including program code which when executed by the at least one memory provides operations comprising: isolating a thyroid nodule DNA molecule from a thyroid nodule of said subject thereby forming an isolated thyroid nodule DNA molecule; contacting said isolated thyroid nodule DNA molecule with a bisulfite salt thereby forming a reacted thyroid nodule DNA molecule; detecting the presence or absence of uracil in said reacted thyroid nodule DNA molecule at a methylation site set forth in Table 1, thereby detecting methylation or unmethylation of said thyroid nodule DNA molecule of said subject; generating a diagnosis for said subject based at least in part on the presence or absence of uracil in said reacted thyroid nodule DNA molecule at the methylation site set forth in Table 1; and providing, via a user interface, the diagnosis for said subject.
(304) Embodiment 47. The system of embodiment 46, wherein the system is further configured to detect the presence or absence of uracil in said reacted thyroid nodule DNA molecule at a plurality of methylation sites set forth in Table 1, wherein said methylation site forms a part of said plurality of methylation sites.
(305) Embodiment 48. The system of embodiment 46, wherein the system is further configured to: (i) isolate a plurality of thyroid nodule DNA molecules from said thyroid nodule of said subject thereby forming a plurality of isolated thyroid nodule DNA molecules, wherein said isolated thyroid nodule DNA molecule forms part of said plurality of isolated thyroid nodule DNA molecules, (ii) contact said plurality of isolated thyroid nodule DNA molecules with said bisulfite salt thereby forming a plurality of reacted thyroid nodule DNA molecules, wherein said reacted thyroid nodule DNA

molecule forms part of said plurality of reacted thyroid nodule DNA molecules, (iii) detect the level of reacted thyroid nodule DNA molecules in said plurality of reacted thyroid nodule DNA molecules having a uracil at a methylation site set forth in Table 1, thereby detecting the level of methylation or unmethylation in said plurality of thyroid nodule DNA molecules of said subject.

(306) Embodiment 49. The system of embodiment 48, wherein the system is further configured to detect the level of uracil in said reacted thyroid nodule DNA molecule at a plurality methylation sites set forth in Table 1, wherein said methylation site forms a part of said plurality of methylation sites.

(307) Embodiment 50. The system of embodiment 49, wherein said uracil level is above a threshold as set forth in Table 2.

(308) Embodiment 51. The system of embodiment 49, wherein said uracil level is above a threshold as set forth in Table 3.

(309) Embodiment 52. The system of embodiment 49, wherein said uracil level is below a threshold as set forth in Table 4.

(310) Embodiment 53. The system of embodiment 49, wherein said subject is a candidate thyroid cancer patient.

(311) Embodiment 54. The system of one of embodiments 46 to 53, wherein said thyroid nodule is a specimen obtained by biopsy or by surgical resection of said subject.

(312) Embodiment 55. The system of one of embodiments 46 to 54, wherein said subject has undergone thyroid surgery, radiation therapy, radioactive iodine therapy, chemotherapy, thyroid hormone therapy, and/or administration of an active agent.

(313) Embodiment 56. The system of embodiment 55, wherein said active agent is chosen from Cabozantinib-S-Malate, Caprelsa (Vandetanib), Cometriq (Cabozantinib-S-Malate), Doxorubicin Hydrochloride, Lenvatinib Mesylate, Lenvima (Lenvatinib Mesylate), Nexavar (Sorafenib Tosylate), Sorafenib Tosylate, and Vandetanib.

(314) Embodiment 57. The system of one of embodiments 46 to 56, wherein the system is further configured to: formulate, based at least in part on the diagnosis, a treatment plan for said subject; and provide, via the user interface, the treatment plan.

(315) Embodiment 58. The system of embodiment 57, wherein the treatment plan includes one or more of thyroid surgery, radiation therapy, radioactive iodine therapy, chemotherapy, thyroid hormone therapy, and administration of an active agent.

EXAMPLES

Example 1

(316) Human frozen specimens were blindly evaluated by a pathologist. In the study, 28 benign nodules and 40 thyroid cancer specimens were analyzed.

(317) DNA Methylation Profiling

(318) Genomic DNA was isolated by using a standard phenol/chloroform extraction approach followed by ethanol precipitation. Further, genomic DNA underwent Reduced Representation Bisulfite Sequencing (RRBS) procedure. RRBS DNA amplicons were paired-end sequenced by using Hiseq 2500 (Illumina). For each sample, at least 15 million aligned reads were obtained. BTN and PTC specific signatures were determined based on cytosines which are characterized by at least 5 sequencing reads in each sample.

(319) Identification of BTN Specific and PTC Specific DNA Methylation Changes

(320) DNA methylation patterns were analyzed in 114 thyroid specimens including 28 benign nodules, 40 thyroid cancer, and 46 adjacent normal thyroid tissues, to identify the presence of thyroid cancer specific and benign nodule specific signatures. After genome alignment, a search was performed for DNA regions which have BTN or PTC specific alterations. For identification of a DNA region with a BTN specific loss of DNA methylation, DNA regions were identified which had a DNA methylation level in at least 6 out 28 that was at least 2-fold less than the level of methylation in the same DNA region any analyzed PTC specimen; where the lowest value of DNA methylation at this DNA region among all PTC specimens is 20% or higher (FIG. **1**A). For identification of DNA regions with BTN specific DNA methylation accumulation, the following criteria were used: a level

of DNA methylation in an individual BTN that is at least 2-fold higher than the level of DNA methylation in the same DNA region in any analyzed PTC; where the value of DNA methylation of analyzed BTN specimen is at least 20% or more greater (FIG. **1**B). The BTN signature includes DNA regions which were affected by DNA methylation loss in at least 6 out 28 analyzed BTN samples and regions which were affected by DNA methylation accumulation in at least 6 out 28 analyzed BTN samples.

(321) Further, regions were determined which undergo PTC specific DNA methylation alterations. The criteria for the identification of DNA regions with a PTC specific loss of DNA methylation, was: a level of DNA methylation in 6 out of 46 PTC that is 2-fold less than in any analyzed adenoma and any normal matching tissue, where the lowest value of DNA methylation in the region among all non-malignant specimens is 20% or higher. The criteria for the identification of DNA regions with PTC specific DNA methylation accumulation was a level of DNA methylation in an individual PTC that is at least 2-fold higher than the level of methylation in any analyzed adenoma and normal matching tissue, where the value of DNA methylation in analyzed PTC sample should be 20% or higher. There were no DNA regions that were affected by DNA methylation accumulation in at least 6 PTC out 46 analyzed PTC. Therefore, the PTC specific DNA methylation signatures contain only DNA regions which are affected by DNA methylation loss in at least 6 out 46 analyzed PTC.

(322) The total number of identified DNA regions which fall in PTC specific or BTN specific signature is 258, which comprises DNA methylation information for 364 cytosines (FIG. **2**A). There are 230 cytosines which characterize the PTC signature and 134 cytosines characterizing the BTN signature.

(323) Evaluation of the cancer specific and benign specific changes revealed that 10 out of 40 thyroid cancer specimens are characterized by few (less than 5) or no cancer specific changes, and 4 out 28 benign nodules indicated very few (less than 5) benign specific changes (FIG. **2**A). Since the approach described herein is based on the identification of the tissue specific alterations, these specimens were determined to be “epigenetically indeterminate.”

(324) For specimens with a determinate epigenetic state, clustering analysis revealed a strict separation of thyroid cancer from benign nodules based on DNA methylation levels of cytosines associated with benign and cancer scores (FIG. **2**B). Thus, the use of benign and cancer scores can provide a unique thyroid nodule diagnostic tool.

(325) Development of Diagnostic Panel Based on BTN/PTC Signature Scores.

(326) The data disclosed herein demonstrates that analysis of DNA methylation of one or more of 258 DNA regions can provide substantial information regarding a presence of malignancy in thyroid samples. Therefore, DNA methylation analysis within BTN and PTC signature can be used as a PTC diagnostic tool. According to the data, PTC diagnosis can be made by using both BTN and PTC signatures. Each signature can be a score based on the number of specific alterations within the signature for each individual sample. For example, the number of BTN specific alterations within BTN signature DNA regions reflects a BTN signature score. At the same time, the number of PTC specific alterations for DNA regions within PTC signature group indicates PTC signature score.

(327) In order to validate the approach disclosed herein and estimate an accuracy of the proposed signatures, a statistical analysis was performed based on the leave-one-out-cross-validation technique. Specifically, cancer and benign scores were determined for each individual nodule by using benign and cancer signatures which were developed based on DNA methylation patterns of the rest of samples excluding the testing sample. In order to predict benign and cancer scores for 68 nodules, 68 benign and cancer unique predictive signatures were developed.

(328) After cross-validation, DNA methylation signatures (score >=5) were observed in 80% (32 out 40) of thyroid cancers and 82% (23 out 28) of benign nodules (FIG. **3**A). These specimens with a determinate epigenetic state were used for the further analysis.

(329) According to the cross-validation observations, both, benign and malignant diagnostic scores provided accurate results for thyroid nodule diagnostics (FIG. **3**A). However, a combining of benign and malignant scores into a cancer risk score is associated with even higher diagnostic performance.

The cancer risk score was calculated using the following equation: Cancer Risk Score=(cancer score+1)/(benign score+1)
(330) According to the data herein, specimens with cancer risk score above 2.6 represent thyroid cancer and specimens with cancer score below 2.6 are benign nodules. Based on these criteria, all 23 nodules were correctly diagnosed as benign and 30 out 32 thyroid malignancies were diagnosed as a cancer (FIG. **3**B). Therefore, the test had a specificity of 100% and a sensitivity of 94%, with a 100% positive predictive value (PPV) and a 92% negative predictive value (NPV). These data suggest that DNA methylation analysis of 258 DNA regions in thyroid specimens can serve as a potential diagnostic tool for the determination of malignancy.
(331) An algorithm for performing a thyroid nodule diagnostic evaluation is shown in FIG. **3**C. Specimens with benign and malignant signatures are associated with indeterminate epigenetic state and were excluded from the study. Specimens with a cancer risk score above 2.6 are considered to be malignant, and thyroid nodules with a cancer risk score below 2.6 are considered to be benign.
(332) This scoring approach clearly differentiates benign from malignant specimens. These data suggest that DNA methylation analysis of 258 DNA regions in thyroid specimens, including potentially FNA specimens, can serve as a diagnostic tool for the determination of malignancy.
(333) The data indicates that malignancy of thyroid specimens can be determined by DNA methylation pattern analysis of one or more of 258 different DNA regions.

Claims

1. A method of treating papillary thyroid cancer in a subject in need thereof, the method comprising: (i) measuring decreased DNA methylation levels, relative to a control, at papillary thyroid carcinoma DNA methylation sites in an isolated DNA obtained from a thyroid nodule from the subject, wherein the papillary thyroid carcinoma DNA methylation sites, with respect to reference human genome assembly hg19, comprise: (a) chromosome 10, position 112259015, (b) chromosome 12, position 56115043, and (c) chromosome 15, position 85402496; and (ii) administering cabozantinib-S-malate, doxorubicin hydrochloride, lenvatinib mesylate, sorafenib tosylate, vandetanib, or a combination of two or more thereof to the subject having the decreased DNA methylation levels at the papillary thyroid carcinoma DNA methylation sites in step (i) to treat the papillary thyroid cancer.
2. The method of claim 1, further comprising measuring a decreased DNA methylation level, relative to a control, at a benign thyroid nodule DNA methylation site in an isolated DNA obtained from a thyroid nodule from the subject, wherein the benign thyroid nodule DNA methylation site, with respect to reference human genome assembly hg19, is chromosome 2, position 8793724.
3. The method of claim 1, further comprising measuring a decreased DNA methylation level, relative to a control, at a benign thyroid nodule DNA methylation site in an isolated DNA obtained from a thyroid nodule from the subject, wherein the benign thyroid nodule DNA methylation site, with respect to reference human genome assembly hg19, is chromosome 12, position 45610695.
4. The method of claim 1, wherein the papillary thyroid carcinoma DNA methylation sites are unmethylated.
5. The method of claim 1, wherein the control is a subject that does not have papillary thyroid cancer.
6. The method of claim 1, wherein the papillary thyroid carcinoma DNA methylation sites, with respect to human genome assembly hg19, consist of: (a) chromosome 10, position 112259015, (b) chromosome 12, position 56115043, and (c) chromosome 15, position 85402496.
7. The method of claim 1, wherein the isolated DNA is obtained from the thyroid nodule in the subject by a biopsy or a surgical resection.
8. The method of claim 1, wherein the subject: (a) is a woman; (b) is about 20 years old to about 55 years old; (c) has a mutated Ret proto-oncogene; (d) has a grandparent, parent, or sibling who has been diagnosed with thyroid cancer; (e) self-identifies as Caucasian or Asian; (f) has or has had breast cancer, or (g) any combination of two or more of (a)-(f).
9. A method of measuring DNA methylation levels at papillary thyroid carcinoma DNA methylation

sites in a human subject with thyroid carcinoma, the method comprising measuring decreased DNA methylation levels, relative to a control, at papillary thyroid carcinoma DNA methylation sites in an isolated DNA obtained from a thyroid nodule from the human subject, wherein the papillary thyroid carcinoma DNA methylation sites, with respect to reference human genome assembly hg19, comprise: (a) chromosome 10, position 112259015, (b) chromosome 12, position 56115043, and (c) chromosome 15, position 85402496 and measuring methylation levels comprises amplifying DNA by contacting the DNA with a primer complementary to a sequence at or within 1000 nucleotides of the chromosomal positions to produce amplicons thereof to measure methylation levels.

10. The method of claim 9, wherein the papillary thyroid carcinoma DNA methylation sites are unmethylated.

11. The method of claim 9, wherein the control is a subject that does not have papillary thyroid cancer.

12. The method of claim 9, further comprising measuring a decreased DNA methylation level, relative to a control, at a benign thyroid nodule DNA methylation site in an isolated DNA obtained from a thyroid nodule from the subject, wherein the benign thyroid nodule DNA methylation site, with respect to reference human genome assembly hg19, is chromosome 2, position 8793724.

13. The method of claim 9, further comprising measuring a decreased DNA methylation level, relative to a control, at a benign thyroid nodule DNA methylation site in an isolated DNA obtained from a thyroid nodule from the subject, wherein the benign thyroid nodule DNA methylation site, with respect to reference human genome assembly hg19, is chromosome 12, position 45610695.

14. The method of claim 9, wherein the isolated DNA is obtained from the thyroid nodule in the subject by a biopsy or a surgical resection.

15. The method of claim 9, wherein the papillary thyroid carcinoma DNA methylation sites are unmethylated.

16. A method of measuring DNA methylation levels at papillary thyroid carcinoma methylation sites in an isolated DNA obtained from a thyroid nodule in a human subject, the method comprising: (i) contacting the isolated DNA with a bisulfite salt, thereby forming a reacted thyroid nodule DNA, and (ii) measuring decreased DNA methylation levels, relative to a control, at papillary thyroid carcinoma DNA methylation sites by detecting the presence of uracil in the reacted thyroid nodule DNA; wherein the papillary thyroid carcinoma DNA methylation sites, with respect to reference human genome assembly hg19, comprise: (a) chromosome 10, position 112259015, (b) chromosome 12, position 56115043, and (c) chromosome 15, position 85402496 and measuring methylation levels comprises amplifying DNA by contacting the DNA with a primer complementary to a sequence at or within 1000 nucleotides of the chromosomal positions to produce amplicons thereof to measure methylation levels.

17. The method of claim 16, wherein the bisulfite salt is sodium bisulfite or ammonium bisulfite.

18. The method of claim 16, wherein the bisulfite salt is sodium bisulfite, potassium bisulfite, ammonium bisulfite, magnesium bisulfite, sodium metabisulfite, potassium metabisulfite, ammonium metabisulfite and magnesium metabisulfite.

19. The method of claim 16, wherein the control is a subject that does not have papillary thyroid cancer.

20. The method of claim 16, wherein the isolated DNA is obtained from the thyroid nodule in the subject by a biopsy or by a surgical resection.