CLAIMS

1. **A method** of determining the presence or absence of, or response to therapy against, a cancer in a human individual, said method comprising the steps:
   - providing a biological sample from said human individual, said sample comprising cell-free DNA of said human individual; and
   - determining, in at least one molecule of said cell-free DNA, the methylation status at one or more CpGs located within one or more of the nucleotide sequences independently selected from the group consisting of: SEQ ID NOs: 3 (DMR #228), 4 (DMR #144), 2 (DMR #204), 1 (DMR #141), 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 and 31, or a nucleotide sequence present within about 2,000bp 5′ or 3′ thereof, or an allelic variant and/or complementary sequence of said nucleotide sequence(s),

   wherein, the presence in at least one of said cell-free DNA molecules of one or more: (i) methylated CpGs associated with one or more of said nucleotide sequences independently selected from: SEQ ID NOs: 3 (DMR #228), 4 (DMR #144), 2 (DMR #204), 1 (DMR #141), 10, 12, 14, 15, 18, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29 and 30; and/or (ii) un-methylated CpGs associated with one or more of said nucleotide sequences independently selected from: SEQ ID NOs: 5, 6, 7, 8, 9, 11, 13, 16, 17, 22 and 31, indicates the presence of, or a reduced response to therapy against, the cancer in said human individual; and

   wherein: (a) when the human individual is a woman the cancer is selected from the group consisting of: breast cancer, lung cancer, colon cancer, pancreatic cancer, uterine (endometrial) cancer, cervical cancer and ovarian cancer; or (b) when the human individual is a man the cancer is selected from the group consisting of: lung cancer, colon cancer, pancreatic cancer and prostate cancer.

2. The method of claim 1, wherein said biological sample is liquid biological sample selected from the group consisting of: a blood sample, a plasma sample and a serum sample.

3. The method of claim 1 or 2, wherein the methylation status is determined at a number being two, three, four, five, six, seven, eight, nine, ten, about 12, about 15, about 20, about 25 or more of said CpGs located within said nucleotide sequence; wherein, the presence in at least one of said cell-free DNA molecules of at least one, such as up to said number, of: (i) methylated CpGs associated with one or more of said nucleotide sequences independently selected from: SEQ ID NOs: 3, 4, 2, 1, 10, 12, 14, 15, 18, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29 and 30; and/or (ii) un-methylated CpGs associated with one or more of said nucleotide sequences independently selected from: SEQ ID NOs: 5, 6, 7, 8, 9, 11, 13,

16, 17, 22 and 31, indicates the presence of, or a reduced response to therapy against, the cancer in said human individual.

4. The method of any one of claims 1 to 3, wherein said nucleotide sequence(s) is/are associated with
DMR(s) #228 and/or #144 and/or #204 and/or #141 (eg, SEQ ID NOs: 3, 4, 2 and/or 1), or an allelic variant and/or complementary sequence of said nucleotide sequence(s).

5. The method of any one of claims 1 to 4, comprising the step of treating said cell-free DNA with an agent that differentially modifies said cell-free DNA based on the methylation status of one or more CpGs located within; preferably a methylation sensitive restriction enzyme and/or bisulphite.

6. The method of claim 5, wherein (a) said agent is bisulphite and said determining step comprises the detection of at least one bisulphite-converted un-methylated cytosine within one or more of the nucleotide sequences independently selected from those set forth in TABLE 2A (eg, independently selected the group consisting of: SEQ ID NOs 34, 35, 33, 32, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61 and 62), wherein one or more of the bases identified by "Y" therein is a U or T and, preferably, where one or more of the bases identified by "Y" in a CpG therein is a C, or an allelic variant and/or complementary sequence of said nucleotide sequence(s); and/or.
(b) wherein said agent is bisulphite and said determining step comprises the detection of at least one bisulphite-converted un-methylated cytosine within a nucleotide sequence having a length of at least 50bp comprised in SEQ ID NO 34 and/or SEQ ID NO 35 and/or SEQ ID NO 33 and/or SEQ ID NO 32, wherein one or more of the bases identified by "Y" therein is a U or T and, preferably, where one or more of the bases identified by "Y" in a CpG therein is a C, or an allelic variant and/or complementary sequence of said nucleotide sequence(s).

7. The method of any one of claims 1 to 6, wherein the methylation status of said CpG(s) is determined in multiple molecules of said cell-free DNA and/or amplified DNA representing each of said nucleotide sequences.

8. The method of claim 7, wherein a fraction or ratio of, or an absolute number of, cell-free DNA molecules in said sample having said methylated and/or un-methylated CpG(s) (as applicable) located within said nucleotide sequence(s), and/or having said pattern of

methylation and/or un-methylation as set forth in TABLE 2B for the respective nucleotide sequence(s), is estimated.

9. The method of claim 8, further comprising a step of comparing said fraction or ratio with a standard or cut-off value; wherein a fraction or ratio greater than the standard or cut-off value indicates the presence of or a reduced response to therapy against, the cancer in said human individual.

10. The method of any one of claims 1 to 9, for determining the response of a human individual suffering from a cancer to a therapy comprising chemotherapeutic agent(s) against said cancer.

11. **A chemotherapeutic agent**, such as one selected from the list consisting of: carboplatin, paclitaxel, docetaxel, cisplatin, liposomal doxorubicin, gemcitabine, trabectedin, etoposide, cyclophosphamide an angiogenesis inhibitor and a PARP inhibitor, for use in a method of therapy of a cancer in a human individual, wherein said chemotherapeutic agent is administered to a human individual within about 3 months of said human individualhaving been determined, using a method of claim 10, to not respond to a therapy against the cancer.

12. **A nucleic acid** comprising at least 10 (preferable at least about 15, such as at least 50, for any SEQ ID other than SEQ ID NO:58) contiguous bases comprised in a sequence selected from the group consisting of: SEQ ID NOs 34, 35, 33, 32, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61 and 62, wherein said nucleic acid sequence includes one or more of the bases identified by "Y" therein is a U or T and, preferably, where one or more of the bases identified by "Y" therein is a C, or an allelic variant and/or complementary sequence of said nucleotide sequence.

13. The nucleic acid sequence of claim 12, comprising at least 50 contiguous bases comprised in a sequence of SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 33 or SEQ ID NO 32, wherein said nucleic acid sequence includes one or more of the bases identified by "Y" therein is a U or T and, preferably, where one or more of the bases identified by "Y" therein is a C, or an allelic variant and/or complementary sequence of said nucleotide sequence.

14. **A nucleic acid probe** complementary to a nucleic acid sequence recited in any one of claims 12 to 13, preferably for detection of said nucleic acid.

15. **A nucleic acid primer pair** for amplifying a nucleic acid sequence consisting of at least 10 (preferable at least about 15, such as at least 50, for any SEQ ID other than SEQ ID NO:89) contiguous bases comprised in a sequence) selected from the group consisting of: SEQ ID NOs: SEQ ID NOs 65, 66, 64, 63, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92 and 93, or a nucleotide sequence present within about 2,000 bp 5' or 3' thereof, or an allelic variant and/or complementary sequence said nucleotide sequence(s), preferably wherein at least one primer of said pair includes a sequence corresponding to at least one bisulphite-converted CpG present in said nucleotide sequence(s).

16. The primer pair of claim 15, selected from the group of primer-pairs set forth in each row of TABLE 3.

17. **A kit**, preferably for determining the presence or absence of, or response to therapy against, a cancer in a human individual, said kit comprising:
    - one or more nucleic acid sequences of claim 12 or 13 and/or nucleic acid probes of claim 14 and/or primer pairs of claim 15 or 16; and
    - optionally, said kit further comprising:

    (i) a printed manual or computer readable memory comprising instructions to use said nucleic acid sequence(s), nucleic acid probe(s), primer pair(s) and/or plurality of nucleic acids to practice a method of any one of claims 1 to 10 and/or to produce or detect the nucleic acid sequence(s) of any one of claim 12 or 13; and/or

    (ii) one or more other claim, component or reagent useful for the practice of a method of any one of claims 1 to 10 and and/or the production or detection of the nucleic acid sequence(s) of claim 12 or 13, including any such item, component or reagent disclosed herein useful for such practice, production or detection.

18. **A computer program product** comprising: a computer readable medium encoded with a plurality of instructions for controlling a computing system to perform and/or manage an operation for determining the presence or absence of, or response to therapy against, a cancer in a human individual, from a biological sample from said human individual, said sample comprising cell-free DNA of said human individual, and determining, in at least one molecule of said cell-free DNA, the methylation status at one or more CpGs located within one or more nucleotide sequences in accordance with a method as set forth in any one of claims 1 to 10; said operation comprising the steps of:
    - receiving a first signal representing the number of molecules of said cell-free DNA comprising one or more methylated and/or un-methylated CpGs (as applicable), and/or

comprising one or more pattern of methylation and/or un-methylation as set forth in TABLE 2B for the respective nucleotide sequence(s), located within one or more of the nucleotide sequences independently selected from the group consisting of: SEQ ID NOs: 3, 4, 2, 1, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 and 31, or a nucleotide sequence present within about 2,000bp 5' or 3' thereof, or an allelic variant and/or complementary sequence of said nucleotide sequence(s); and

- determining a classification of the presence or absence of, or response to therapy against, the cancer in said human individual based on their being at least one molecules of said cell-free DNA comprising one or more said methylated and/or un-methylated CpGs (as applicable), and/or comprising one or more said pattern of methylation and/or un-methylation, located within one or more of said nucleotide sequences.

19. **A use** of a nucleic acid sequences of claim 12 or 13 and/or a nucleic acid probes of claim 14 and/or a primer pair of claim 15 or 16 and/or a kit of claim 17 and/or a computer program product of claim 18, in each case for determining the presence or absence of, or response to therapy against, a cancer in a human individual.