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 (endometical) 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 said CpGs for a given nucleotide sequence are identifiable by a genome position for the cytosine (C) thereof, independently selected from the list of genome positions corresponding to said nucleotide sequence set forth in TABLE 1C.

4. The method of any one or claims 1 to 3, 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.

5. The method of any one of claims 1 to 4, wherein the presence in at least one of said cell-free DNA molecules of one or more pattern of methylation and/or un-methylation as set forth in TABLE 2B for the respective nucleotide sequence(s), indicates the presence of, or a reduced response to therapy against, the cancer in said human individual.

6. The method of any one of claims 1 to 5, wherein the methylation status at one or more CpGs located within a number of two, three, four or more of said nucleotide sequences is determined; 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, 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.

7. The method of any one of claims 1 to 6, wherein said nucleotide sequence(s) is/are associated with DMR(s) #228 and/or #144 and/or #205 and/or #141 and/or #204 (eg, SEQ ID NOs: 3, 4, 2 and/or 1), or an allelic variant and/or complementary sequence of said nucleotide sequence(s).

8. The method of claim 7, wherein the methylation status is determined at one or more of said CpGs located within each of DMR #228 and DMR #144, and optionally wherein the methylation status is also determined at one or more of said CpGs located within DMR #204 and/or DMR #141; wherein, the presence in at least one of said cell-free DNA molecules of one or more methylated CpGs, and/or of one or more pattern of methylation and/or un-methylation as set forth in TABLE 2B for the respective nucleotide sequence(s), located within any one of said nucleotide sequences indicates the presence of, or a reduced response to therapy against, the cancer in said human individual.

9. The method of claim 7 or 8, wherein the methylation status is determined at a number of between about 5 and about 18 of said CpGs located within said nucleotide sequence(s); wherein, the presence in at least one of said cell-free DNA molecules of at least said number of methylated CpGs, and/or of one or more pattern of methylation and/or un-methylation as set forth in TABLE 2B for the respective nucleotide sequence(s), located within any one of said nucleotide sequences 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 7 to 9, wherein the methylation status is determined at about 7 to 9 CpGs located within nucleotide sequence SEQ ID NO 3 and/or at about 11 CpGs located within nucleotide sequence SEQ ID NO 4 and/or at about 16 to 18 CpGs located within nucleotide sequence SEQ ID NO 2 and/or at about 7 CpGs located within nucleotide sequence SEQ ID NO 1.

11. The method of any one of claims 7 to 10, wherein the methylation status is determined at about 7 to 9 CpGs located within nucleotide sequence SEQ ID NO 3 and at about 11 CpGs located within nucleotide sequence SEQ ID NO 4, and optionally also at about 16 to 18 CpGs located within nucleotide sequence SEQ ID NO 2 and/or at about 7 CpGs located within nucleotide sequence SEQ ID NO 1; wherein, the presence in at least one of said cell-free DNA molecules of at least said number of methylated said CpGs, and/or of one or more pattern of methylation and/or un-methylation as set forth in TABLE 2B for the respective nucleotide sequence(s), located within any one of said nucleotide sequences indicates the presence of, or a reduced response to therapy against, the cancer in said human individual.

12. The method of any one of claims 1 to 11, comprising the step of isolating said cell-free DNA from said biological sample.

13. The method of any one of claims 1 to 12, 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.

14. The method of claim 13, wherein 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).

15. The method of claim 13 or 14, 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).

16. The method of any one of claims 1 to 15, comprising the step of amplifying one or more regions of said cell-free DNA to produce DNA prior to or as part of said determining step, and; preferably after said treating step.

17. The method of claim 16, wherein said amplified region(s) comprises at least one of said nucleotide sequences.

18. The method of claim 17, wherein said amplification comprises PCR using the primer-pair(s) for the respective nucleotide sequence(s) as independently selected from the group of primer-pairs set forth in each row of TABLE 3.

19. The method of any one of claims 1 to 18, wherein the methylation status of said CpGs is determined by a technology selected from the group consisting of: methylation specific PCR/MethylLight, Epityper, nucleic acid chip-hybridisation, nucleic acid mass-spectrometry, Methylated DNA immunoprecipitation (MeDIP), Raindance and nucleic acid sequencing, preferably, (single) strand sequencing, nanopore sequencing, bisulphite sequencing, such as targeted bisulphite sequencing; preferably wherein said determination step is conducted as a pool when in respect of two, three, four or more of said nucleotide sequences.

20. The method of any one of claims 1 to 19, 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.

21. The method of claim 20, wherein the presence in at least a plurality of said cell-free DNA molecules of one or more methylated and/or un-methylated CpGs (as applicable), and/or the presence in at least a plurality of said cell-free DNA molecules of 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 said nucleotide sequences, indicates the presence of, or a reduced response to therapy against, the cancer in said human individual.

22. The method of claim 20 or 21, wherein said plurality of cell-free DNA molecules with one or more of said methylated and/or un-methylated CpGs (as applicable), and/or the presence in at least a plurality of said cell-free DNA molecules of one or more pattern of methylation and/or un-methylation as set forth in TABLE 2B for the respective nucleotide sequence(s), located is at least 2, 3, 4, 5, 6, 7, 18, 9 or 10, or at least about 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 125, 150, 175 or 200, or a greater number such as greater than about 500, 1,000, 5,000, 7,500, 1,000, 2,500, 5,000 or greater than 5,000 molecules.

23. The method of any one of claims 20 to 22, wherein the methylation status of said CpG(s) is determined in a number of molecules of said cell-free DNA and/or amplified DNA representing each of said nucleotide sequences selected from the group consisting of at least about: 1,000, 5,000, 10,000, 50,000, 100,000, 200,000, 500,000, 1,000,000, 1,500,000, 2,000,000, 2,500,000, 3,000,000, 3,500,000, 4,000,000 and 5,000,000 molecules, or more than 5,000,000 molecules.

24. The method of any one of claims 20 to 23, 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.

25. The method of claim 24, 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.

26. The method of claim 25, wherein said standard or cut-off value is about 0.0008 for said methylated/un-methylated CpG or said pattern of methylation and/or un-methylation associated with nucleotide sequence SEQ ID NO 1 and/or about 0.00003 for said methylated/un-methylated CpG or said pattern of methylation and/or un-methylation associated with nucleotide sequence SEQ ID NO 2 and/or about 0.00001 for said methylated/un-methylated CpG or said pattern of methylation and/or un-methylation associated with nucleotide sequence SEQ ID NO 3.

27. The method of claim 25 or 26, wherein a fraction or ratio of cell-free DNA molecules with said methylated and/or un-methylated CpG(s) (as applicable) located within each of said nucleotide sequence(s), and/or with said pattern of methylation and/or un-methylation as set forth in TABLE 2B for the respective nucleotide sequence(s), is estimated and compared to a respective standard or cut-off value; wherein any one of such fraction or ratios being greater than its respective standard or cut-off value indicates the presence of, or a reduced response to therapy against, the cancer in said human individual.

28. The method of any one of claims 25 to 27, wherein said standard or cut-off value(s) is/are modified for a given sample based on:

- the amount or concentration of total cell-free DNA present in said sample; and/or
- a baseline value of said fraction or ratio previously determined for said human individual; and/or
- a value of said fraction or ratio determined from multiple samples from a population of women and/or men representative of said human individual; and/or
- the specificity and/or sensitivity desired for said method of determination.

29. The method of claim 28, wherein said standard or cut-off value is/are reduced for a given sample that has an amount or concentration of total cell-free DNA present in said sample that is greater than a standard or cut-off value.

30. The method of any one of claims 1 to 29, which is practiced on multiple samples; wherein each sample is collected from the same human individual at different time points.

31. The method of claim 30, wherein said multiple samples are collected from said human individual with an interval between them selected from the group consisting of: about: 2 days, 3 days, 4 days, 5 days, 7 days, 10, days, 14 days, 21 days, 24 days, 3weeks, 4 weeks, 5 weeks, 6 weeks, 6, weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, 8 months, 12 months, 18 months, 2 years, 3 years and 5 years.

32. The method of claim 30 or 31, wherein in comparison to a previous sample, the presence of, or an increase in the absolute number of, or an increase in the fraction or ratio 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), indicates the presence of, or a reduced response to therapy against, the cancer in said human individual.

33. The method of any one of claims 1 to 32, wherein said cancer is ovarian cancer and said human individual is a woman comprising the step of determining (in-vitro), from a blood sample from said woman, the amount present therein of one or more proteins independently selected from the group consisting of: CA-125, HE4, transthyretin, apolipoprotein A1, beta-2-microglobin and transferrin; wherein, either or both of:

- the presence in at least one of said cell-free DNA molecules of one or more methylated and/or un-methylated CpGs (as applicable) located within one or more of said nucleotide sequences, and/or the presence in at least one of said cell-free DNA molecules of one or more pattern of methylation and/or un-methylation as set forth in TABLE 2B for the respective nucleotide sequence(s);
- an amount of said protein(s) present in said blood sample is greater than a standard or cut-off value for such amount or protein,

indicates the presence of, or a reduced response to therapy against, an ovarian cancer in said woman.

34. The method of claim 33, wherein said protein is determined by a ROCA, a ROMA and/or an OVA1 diagnostic test.

35. The method of claim 33 or 34, wherein said ovarian cancer is an invasive ovarian cancer, such as an invasive epithelial ovarian cancer; in particular one selected from the group consisting of: high grade serious (HGS), endometroid, cell-cell and mucinous ovarian cancers; and/or is a peritoneal cancer or a Fallopian tube cancer.

36. The method of any one of claims 33 to 35, for distinguishing the presence of ovarian cancer from the presence of a benign pelvic mass.

37. The method of any one of claims 1 to 36, for determining the response of a human individual suffering from a cancer to a therapy comprising chemotherapeutic agent(s) against said cancer.

38. The method of claim 37, wherein the risk of death of said human individual is predicted.

39. The method of claim 37 or 38, practiced on said human individual after one, two, three, four and/or five cycles of said (chemo)therapy.

40. The method of any one of claims 37 to 39, wherein said sample is obtained from said human individual within a period after completion of said cycle or (chemo)therapy that is selected from the group consisting of: about: 2 hours, 4 hours, 6 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 3 days, 4 days, 5 days, 6, days, 7 days, 8 days, 10 days, 12 days, 14 days, 16, days, 18 days, 21 days, 24 days, 4 weeks, 5 weeks, 6 weeks, and 8 weeks.

41. The method of any one of claims 37 to 40, wherein said (chemo)therapy includes one or more chemotherapeutic agent(s) independently selected from the group consisting of: a platinum-based antineoplastic and a taxane.

42. The method of claim 41, wherein at least one of said chemotherapeutic agents is carboplatin, cisplatin, paclitaxel or docetaxel.

43. The method of any one of claims 37 to 42, wherein said therapy is a neoadjuvant (chemo)therapy.

44. The method of any one of claims 37 to 43, wherein if said human individual is determined to respond to said (chemo)therapy, then said human individual is designated as being eligible for tumour de-baulking surgery.

45. The method of any one of claims 37 to 43, wherein if said human individual is determined to not respond to said (chemo)therapy, then said human individual is designated as eligible for therapy with one or more second-line chemotherapeutic agent(s) against said cancer.

46. The method of claim 45, wherein said second-line (chemo)therapy includes one or more chemotherapeutic agent(s) independently selected from the list consisting of: paclitaxel, carboplatin, cisplatin, liposomal doxorubicin, gemcitabine, trabectedin, etoposide, cyclophosphamide, an angiogenesis inhibitor and a PARP inhibitor.

47. **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 any one of claims 37 to 43, to not respond to a therapy against the cancer.

48. **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.

49. The nucleic acid sequence of claim 48, 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.

50. The nucleic acid sequence of claim 48 or 49, which is comprised in a sequence as set forth in TABLE 2B (eg, a sequence selected from the group consisting of: 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.

51. **A nucleic acid probe** complementary to a nucleic acid sequence recited in any one of claims 48 to 50, preferably for detection of said nucleic acid.

52. The nucleic acid probe of claim 51, that differentially binds to said nucleic acid sequence depending on the methylation status of one or more CpGs within said nucleic acid sequence.

53. The nucleic acid probe of claim 51 or 52, comprising a label, preferably a label being a detectable fluorescent moiety.

54. **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).

55. The primer pair of claim 54, selected from the group of primer-pairs set forth in each row of TABLE 3.

56. **A plurality of nucleic acids** comprising at least two or three nucleic acid sequences of any one of claims 48 to 50 and/or at least two or three nucleic acid probes of any one of claims 51 to 53 and/or at least two or three primer pairs of claim 54 or 55.

57. The plurality of nucleic acids of claim 56, as an admixture or array of said nucleic acid sequences and/or nucleic acid probes and/or primer pairs.

58. **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 any one of claims 48 to 50 and/or nucleic acid probes of any one of claims 51 to 53 and/or primer pairs of claim 54 or 55 and/or the plurality of nucleic acids of claim 56 or 57; 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 46 and/or to produce or detect the nucleic acid sequence(s) of any one of any one of claims 48 to 50; 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 46 and and/or the production or detection of the nucleic acid sequence(s) of any one of claims 48 to 50, including any such item, component or reagent disclosed herein useful for such practice, production or detection.

59. The kit of claim 58, further comprising one or more of the following components.

- means to collect and/or store a biological sample, such as blood, to be taken from said human individual, preferably wherein said means is a blood collection tube; and/or
- means to extract DNA, preferably cell-free DNA, from the sample to be taken from said human individual, preferably wherein said means is a cell-free DNA extraction kit; and/or
- an agent to differentially modify DNA based on the methylation status of one or more CpGs located within said DNA, preferably wherein said agent is bisulphite; and/or
- one or more reagents to detect a nucleic acid sequence, preferably for detecting the sequence of a bisulphite-converted nucleotide sequence; and/or
- a printed manual or computer readable memory comprising instructions to identify, obtain and/or use one or more of said means, agent or reagent(s) in the context of a method of any one of claims 1 to 46.

60. **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 46; 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.

61. The computer program product of claim 60, wherein said operation further comprising the steps of:

- receiving a second signal representing the number of molecules of said cell-free DNA comprising said nucleotide sequence(s); and

- estimating a fraction or ratio of 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 or un-methylation, located within one or more of the nucleotide sequences within all of said nucleotide sequences.

62. The computer program product of claim 61, wherein said classification is determined by comparing said a fraction or ratio to a standard or cut-off value.

63. The computer program product of claim 62, wherein said operation further comprising the steps of:
- receiving a third signal representing: (i) the amount or concentration of total cell-free DNA present in said sample; and/or (ii) a baseline value of said fraction or ratio previously determined for said human individual; and
- modifying said standard or cut-off value for a given sample based on said third signal.

64. The computer program product of any one of claims 60 to 63, wherein said first signal, and optional second signal, is determined from nucleotide sequence and/or methylation status information of a plurality of said molecules of said cell-free DNA and/or amplified DNA representing each of said nucleotide sequences, preferably wherein said plurality is a number selected from the group consisting of at least about: 1,000, 5,000, 10,000, 50,000, 100,000, 200,000, 500,000, 1,000,000, 1,500,000, 2,000,000, 2,500,000, 3,000,000, 3,500,000, 4,000,000 and 5,000,000 molecules, or more than 5,000,000 molecules.

65. The computer program product of claim 64, wherein said operation further comprises the steps of:
- for each of said molecule's sequence and/or methylation status information, determining if said molecule comprises none, one or more methylated and/or un-methylated CpGs (as applicable), and/or comprises none, one or more pattern of methylation 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
- calculating said first signal, and optional second signal, based on said determination for all or a portion of said plurality of molecules.

66. The computer program product of any one of claims 60 to 65, wherein the cancer is ovarian cancer and said human individual is a womain, and said operation further comprises the steps of:
- receiving a signal representing the amount present, in a sample of blood taken from said women, of one or more proteins independently selected from the group consisting of: CA-125, HE4, transthyretin, apolipoprotein A1, beta-2-microglobin and transferrin; and
- comparing said a fraction or ratio to a standard or cut-off value for said protein; and
- determining a classification of the presence or absence of, or response to therapy against, an ovarian cancer in said woman based on their being either or both of: (i) 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 or un-methylation, located within one or more of said nucleotide sequences; and/or (ii) an amount of said protein(s) present in said blood sample is greater than said standard or cut-off value for such amount or protein.

67. **A use** of a nucleic acid sequences of any one of claims 48 to 50 and/or a nucleic acid probes of any one of claims 51 to 53 and/or a primer pair of claim 54 or 55 and/or a plurality of nucleic acids of claim 56 or 57 and/or a kit of claim 58 or 59 and/or a computer program product of any one of claims 60 to 66, in each case for determining the presence or absence of, or response to therapy against, a cancer in a human individual.

68. The method of anyone of claims 1 to 46, the chemotherapeutic agent of claim 47, the kit of claim 58 or 59, the computer program product of any one of claims 60 to 66 or the use of claim 67, wherein said cancer is one selected from the list consisting of: breast cancer, lung cancer, colon cancer, pancreatic cancer and ovarian cancer, and said human individual is a woman; preferably where said cancer is breast cancer or one selected from the list consisting of: lung cancer and pancreatic cancer.

69. The method of anyone of claims 1 to 46, the chemotherapeutic agent of claim 47, the kit of claim 58 or 59, the computer program product of any one of claims 60 to 66 or the use of claim 67, wherein said cancer is one selected from the list consisting of: lung cancer, colon cancer and pancreatic cancer, and said human individual is a man.

70. The method of anyone of claims 1 to 46, the chemotherapeutic agent of claim 47, the kit of claim 58 or 59, the computer program product of any one of claims 60 to 66 or the use of claim 67, wherein said cancer is ovarian cancer, and said human individual is a woman.