system, first sequence reads for cell-free DNA molecules from a biological sample of a subject having cancer, the first sequence reads comprised of first sequences; obtaining, by the computer system, second sequence reads for DNA molecules from a plurality of blood cells of the subject, the second sequence reads comprised of second sequences; and detecting, by the computer system, the tumor-derived mutations in the cell-free DNA molecules by filtering out a portion of the first sequences of the cell-free DNA molecules, that are also present in the second sequences from the plurality of blood cells of the subject.

[007b] In another aspect, the present disclosure refers to a method of detecting tumor-derived single-nucleotide variants (SNVs) in cell-free DNA molecules from a biological sample, the method comprising: (a) receiving first sequence reads of cell-free DNA molecules from a biological sample of a subject having cancer; (b) receiving second sequence reads of DNA molecules from a buffy coat sample of the subject; and (c) determining single-nucleotide variants present in the cell-free DNA molecules, but not in the DNA molecules from the buffy coat sample of the subject, as being tumor-derived by comparing the first sequence reads to the second sequence reads to detect a plurality of loci having single-nucleotide variants, wherein at each of the plurality of loci, a number of the first sequence reads having a single-nucleotide sequence variant relative to the second sequence reads is above a cutoff value, the cutoff value being greater than one.

[007c] In another aspect, the present disclosure refers to a method of identifying one or more tumor-derived mutations in a subject having cancer, the method comprising: determining a constitutional genome from a plurality of sequence reads obtained from sequencing DNA molecules from a constitutional sample from the subject; identifying one or more potential sequence variants from a cell-free DNA sample obtained from the subject, wherein identifying the one or more potential sequence variants comprises: obtaining a plurality of sequence reads from the cell-free DNA sample; determining genomic positions for the plurality of sequence reads obtained from the cell-free DNA sample; and detecting the one or more potential sequence variants in one or more sequence reads positioned at one or more loci; and identifying the one or more tumor-derived mutations in the subject based on a comparison of the one or more sequence reads of the one or more potential sequence variants to the constitutional genome at the one or more loci, wherein at each of the one or more loci, a number of the one or more sequence reads having a sequence variant relative to the constitutional genome is above a cutoff value, the cutoff value being greater than one.

[0007d] In another aspect, the present disclosure refers to a computer program product comprising a computer readable medium storing a plurality of instructions for controlling a processor to perform an operation for the method as disclosed herein.

[0007e] In another aspect, the present disclosure refers to a computer system including processors that are programmed to implement the method as disclosed herein.

[0008] In one example, the parameter can be compared with the same parameter derived from a group of subjects without cancer, or with a low risk of cancer. A significant

WHAT IS CLAIMED IS:

1. A method for detecting tumor-derived mutations in cell-free DNA molecules, the method comprising:

obtaining, by a computer system, first sequence reads for cell-free DNA molecules from a biological sample of a subject having cancer, the first sequence reads comprised of first sequences;

obtaining, by the computer system, second sequence reads for DNA molecules from a plurality of blood cells of the subject, the second sequence reads comprised of second sequences; and

detecting, by the computer system, the tumor-derived mutations in the cell-free DNA molecules by filtering out a portion of the first sequences of the cell-free DNA molecules, that are also present in the second sequences from the plurality of blood cells of the subject.

2. The method of claim 1, wherein the blood cells comprise white blood cells.

3. The method of any one of claims 1 to 2, wherein the biological sample of the subject comprises blood plasma.

4. The method of any one of claims 1 to 2, wherein the biological sample of the subject comprises one or more of a group consisting of urine, ascetic fluid, peritoneal fluid, saliva, cerebrospinal fluid, and a stool sample.

5. The method of any one of claims 1 to 4, further comprising sequencing the cell-free DNA molecules from the biological sample of the subject to obtain the first sequence reads.

6. The method of claim 5, wherein sequencing the cell-free DNA molecules from the biological sample comprises targeted sequencing.

7. The method of claim 6, wherein the targeted sequencing is performed using a solid-phase capture technique.

8. The method of claim 6, wherein the targeted sequencing comprises a solution hybridization technique.

9. The method of claim 6, wherein the targeted sequencing comprises amplification via PCR.

10. The method of claim 6, wherein the targeted sequencing comprises target-enriching a whole exome.

11. The method of claim 6, wherein the targeted sequencing comprises target-enriching exons.

12. The method of claim 6, wherein the targeted sequencing enriches 5' and 3' untranslated regions.

13. The method of claim 6, wherein the targeted sequencing targets specific tumor-associated mutations.

14. The method of claim 5, wherein sequencing the cell-free DNA molecules from the biological sample of the subject comprises paired-end sequencing.

15. The method of claim 5, wherein sequencing the cell-free DNA molecules from the biological sample of the subject comprises random sequencing.

16. The method of claim 5, wherein the sequencing the cell-free DNA molecules from the biological sample of the subject comprises massively parallel sequencing.

17. The method of any one of claims 1 to 16, further comprising sequencing the DNA molecules from the plurality of blood cells of the subject to obtain the second sequence reads.

18. The method of claim 17, wherein sequencing the DNA molecules from the plurality of blood cells comprises paired-end sequencing.

19. The method of claim 18, wherein the sequencing the DNA molecules from the plurality of blood cells comprises random sequencing.

20. The method of claim 17, wherein the sequencing the DNA molecules from the plurality of blood cells comprises massively parallel sequencing.

21. A method of detecting tumor-derived single-nucleotide variants (SNVs) in cell-free DNA molecules from a biological sample, the method comprising:

(a) receiving first sequence reads of cell-free DNA molecules from a biological sample of a subject having cancer;

(b) receiving second sequence reads of DNA molecules from a buffy coat sample of the subject; and

(c) determining single-nucleotide variants present in the cell-free DNA molecules, but not in the DNA molecules from the buffy coat sample of the subject, as being tumor-derived by comparing the first sequence reads to the second sequence reads to detect a plurality of loci having single-nucleotide variants, wherein at each of the plurality of loci, a number of the first sequence reads having a single-nucleotide sequence variant relative to the second sequence reads is above a cutoff value, the cutoff value being greater than one.

22. The method of claim 21, further comprising identifying the subject as having a cancer based on the tumor-derived single-nucleotide variants present in the cell-free DNA molecules.

23. The method of any one of claims 21 to 22, further comprising identifying a level of cancer in the subject based, at least in part, on the tumor-derived single-nucleotide variants present in the cell-free DNA molecules.

24. The method of any one of claims 21 to 23, further comprising determining a fractional concentration of tumor DNA based, at least in part, on the tumor-derived single-nucleotide variants present in the cell-free DNA molecules.

25. A method of identifying one or more tumor-derived mutations in a subject having cancer, the method comprising:

determining a constitutional genome from a plurality of sequence reads obtained from sequencing DNA molecules from a constitutional sample from the subject;

identifying one or more potential sequence variants from a cell-free DNA sample obtained from the subject, wherein identifying the one or more potential sequence variants comprises:

obtaining a plurality of sequence reads from the cell-free DNA sample;

determining genomic positions for the plurality of sequence reads obtained from the cell-free DNA sample; and

detecting the one or more potential sequence variants in one or more sequence reads positioned at one or more loci; and

identifying the one or more tumor-derived mutations in the subject based on a comparison of the one or more sequence reads of the one or more potential sequence variants to the constitutional genome at the one or more loci, wherein at each of the one or more loci, a number of the one or more sequence reads having a sequence variant relative to the constitutional genome is above a cutoff value, the cutoff value being greater than one.

26. The method of claim 25, wherein the one or more potential sequence variants at the one or more loci are detected in the one or more sequence reads relative to a reference genome.

27. The method of claim 26, wherein the one or more potential sequence variants comprise single-nucleotide variants.

28. The method of any one of claims 25 to 27, wherein the constitutional sample comprises blood cells, white blood cells, buccal cells, hair follicles, or any combination thereof.

29. The method of any one of claims 25 to 28, wherein the constitutional genome comprises one or more germline mutations, de novo variants, and non-cancer derived variants.

30. The method according to claim 29, wherein the one or more non-cancer derived variants are derived from different hematopoietic stem cells.

31. The method of any one of claims 25 to 30, further comprising detecting one or more constitutional variants, wherein identifying the one or more constitutional variants comprises:

determining genomic positions for the plurality of sequence reads obtained from the constitutional sample; and

detecting one or more constitutional variants at one or more loci relative to a reference genome.

32. The method of any one of claims 25 to 31, further comprising identifying the one or more tumor-derived mutations as associated with a non-synonymous change.

33. The method of any one of claims 25 to 32, wherein the constitutional genome is only a part of a genome of the subject.

34. The method of any one of claims 25 to 33, wherein the constitutional genome is part of a human genome.

35. The method of any one of claims 25 to 34, wherein the cell-free DNA sample is a cell-free DNA sample from blood plasma.

36. The method of any one of claims 25 to 35, wherein identifying the one or more tumor-derived mutations in the subject based on the comparison of the one or more potential sequence variants to the constitutional genome comprises subtracting constitutional variants of the constitutional genome from the one or more potential sequence variants.

37. The method of any one of claims 25 to 36, wherein the constitutional sample from the subject contains more than 90% constitutional DNA.

38. The method of any one of claims 25 to 37, wherein determining the constitutional genome from the plurality of sequence reads obtained from sequencing DNA molecules from the constitutional sample of the subject comprises determining a consensus sequence that includes a determination of a homozygous locus or a heterozygous locus having two alleles.

39. A computer program product comprising a computer readable medium storing a plurality of instructions for controlling a processor to perform an operation for the method of any one of claims 1-38.

40. A computer system including processors that are programmed to implement the method of any one of claims 1-38.