[0005] Besides screening for an existence of cancer, current techniques are also lacking for providing a prognosis of a patient with cancer and for monitoring the effects of treatment (e.g. recovery after surgery or chemotherapy or immunotherapy or targeted therapy). Such techniques are often expensive (e.g. imaging techniques), inaccurate, ineffective, insensitive or may subject the patient to the radiation used for imaging techniques.

[0006] Accordingly, it is desirable to provide new techniques for screening, prognosticating, and monitoring a patient for cancer.

BRIEF SUMMARY

[0007] Disclosed are~~Embodiments provide~~ systems, apparatus, and methods for determining genetic aberrations associated with cancer. Biological samples including cell-free DNA fragments are analyzed to identify imbalances in chromosomal regions, e.g., due to deletions and/or amplifications in a tumor. Using a chromosomal region with multiple loci can allow for greater efficiency and/or accuracy. Such imbalances can then be used to diagnose or screen a patient for cancer, as well as prognosticate a patient with cancer. The severity of an imbalance as well as the number of regions exhibiting an imbalance can be used. Additionally, a patient can be tested over time to track severity of each of one or more chromosomal regions and a number of chromosomal regions to enable screening and prognosticating, as well as monitoring of progress (e.g. after treatment).

[0007a] In one aspect, there is provided a method of analyzing a biological sample of an organism for chromosomal deletions or amplifications associated with cancer, the biological sample including nucleic acid molecules originating from normal cells and potentially from cells associated with cancer, wherein at least some of the nucleic acid molecules are cell-free in the biological sample, the method comprising: determining first and second haplotypes for normal cells of the organism at a first chromosomal region, the first chromosomal region including a first plurality of loci, wherein the first and second haplotypes are heterozygous at each of the first plurality of loci; for each of a plurality of the nucleic acid molecules in the biological sample: identifying a location of the nucleic acid molecule in a reference genome of the organism; and determining a respective allele of the nucleic acid molecule; identifying a first group of nucleic acid molecules as being from the first haplotype based on the identified locations and determined alleles, the first group including at least one nucleic acid molecule located at each of the first plurality of loci; identifying a second group of nucleic acid molecules as being from the second haplotype based on the identified locations and determined alleles, the second group including at least one nucleic acid molecule located at each of the first plurality of loci; calculating, with a computer system, a first value of the first group of nucleic acid molecules, the first value defining a property of the nucleic acid molecules of the first group; calculating, with the computer system, a second value of the second group of nucleic acid molecules, the second value defining a property of the nucleic acid molecules of the second group; and comparing the first value to the second value to determine a classification of whether the first chromosomal region exhibits a deletion or an amplification in any cells associated with cancer.

[0008] According to one example~~embodiment~~, a method of analyzing a biological sample of an organism for chromosomal deletions or amplifications associated with cancer is provided. The biological sample includes nucleic acid molecules originating from normal cells and potentially from cells associated with cancer. At least some of the nucleic acid molecules are cell-free in the sample. First and second haplotypes are determined for normal cells of the organism at a first chromosomal region. The first chromosomal region including a first plurality of heterozygous loci. Each of a plurality of the nucleic acid molecules in the sample have a location in a reference genome of the organism identified and have a respective allele determined. The locations and determined alleles are used to determine a first group of nucleic acid molecules from the first haplotype and a second group from the second haplotype. A computer system calculates a first value of the first group and a second value of the second group. Each value defined a property of the respective group of nucleic acid molecules (e.g. an average size or number of molecules in the group). The first value is compared to the second value to determine

a classification of whether the first chromosomal region exhibits a deletion or an amplification in any cells associated with cancer.

[0008a] In another aspect, there is provided a method of analyzing a biological sample of an organism, the biological sample including nucleic acid molecules originating from normal cells and potentially from cells associated with cancer, wherein at least some of the nucleic acid molecules are cell-free in the biological sample, the method comprising: identifying a plurality of non-overlapping chromosomal regions of the organism, each chromosomal region including a plurality of loci; for each of a plurality of nucleic acid molecules in a biological sample of the organism: identifying a location of the nucleic acid molecule in a reference genome of the organism; for each of the plurality of non-overlapping chromosomal regions: identifying a respective group of nucleic acid molecules as being from the chromosomal region based on the identified locations, the respective group including at least one nucleic acid molecule located at each of the plurality of loci of the chromosomal region; calculating, with a computer system, a respective value of the respective group of nucleic acid molecules, the respective value defining a property of the nucleic acid molecules of the respective group; and comparing the respective value to a reference value to determine a classification of whether the chromosomal region exhibits a deletion or an amplification; determining an amount of chromosomal regions classified as exhibiting a deletion or amplification; and comparing the amount to a threshold value to determine a classification of whether the organism has cancer.

[0009] According to another example~~embodiment~~, a method of analyzing a biological sample of an organism is provided. The biological sample includes nucleic acid molecules originating from normal cells and potentially from cells associated with cancer. At least some of the nucleic acid molecules are cell-free in the sample. A plurality of non-overlapping chromosomal regions of the organism are identified. Each chromosomal region includes a plurality of loci. Each of a plurality of the nucleic acid molecules in the sample have a location in a reference genome of the organism identified. For each chromosomal region, a respective group of nucleic acid molecules are identified as being from the chromosomal region based on the identified locations. Each respective group includes at least one nucleic acid molecule located at each of the plurality of loci of the chromosomal region. A computer system calculates a respective value of the respective group, where the respective value defines a property of the nucleic acid molecules of the respective group. The respective value is compared to a reference value to determine a classification of whether the chromosomal region exhibits a deletion or an amplification. An amount of chromosomal regions classified as exhibiting a deletion or amplification is then determined.

[0009a] In yet another aspect, there is provided a method of determining a progress of chromosomal aberrations in an organism using biological samples including nucleic acid molecules originating from normal cells and potentially from cells associated with cancer, wherein at least some of the nucleic acid molecules are cell-free in the biological samples, the method comprising identifying one or more non-overlapping chromosomal regions of a reference genome of the organism, each chromosomal region including a plurality of loci; at each of a plurality of times: for each of a plurality of nucleic acid molecules in a biological sample of the organism: identifying a location of the nucleic acid molecule in the reference genome; for each of the one or more non-overlapping chromosomal regions, identifying a respective group of nucleic acid molecules as being from the chromosomal region based on the identified location, the respective group including at least one nucleic acid molecule located at each of the plurality of loci of the chromosomal region; calculating, with a computer system, a respective value of the respective group of nucleic acid molecules, the respective value of defining a property of the nucleic acid molecules of the respective group; comparing the respective value to a reference value to determine a classification of whether the first chromosomal region exhibits a deletion or an amplification; and using the one or more classifications of the one or more chromosomal regions at the plurality of times to determine the progress of the chromosomal aberrations in the organism by: calculating a numerical change in classifications from one time to another time; and comparing the numerical change to a threshold value.

[0010] According to another example~~mbodiment~~, a method is provided for determining a progress of chromosomal aberrations in an organism using biological samples including nucleic acid molecules originating from normal cells and potentially from cells associated with cancer. At least some of the nucleic acid molecules are cell-free in the biological samples. One or more non-overlapping chromosomal regions are identified for a reference genome of the organism. Each chromosomal region includes a plurality of loci. Samples taken from the organism at different times are analyzed to determine the progress. For a sample, each of a plurality of the nucleic acid molecules in the sample have a location in a reference genome of the organism identified. For each chromosomal region, a respective group of nucleic acid molecules are identified as being from the chromosomal region based on the identified locations. The respective group including at least one nucleic acid molecule located at each of the plurality of loci of the chromosomal region. A computer system calculates a respective value of the respective group of nucleic acid molecules. The respective value defines a property of the nucleic acid molecules of the respective group. The respective value is compared to a reference value to determine a classification of whether the first chromosomal region exhibits a deletion or

an amplification. Then, the classifications of each of the chromosomal regions at the plurality of times are used to determine the progress of the chromosomal aberrations in the organism.

[0010a] In yet another aspect, there is provided a computer program product comprising a computer readable medium storing a plurality of instructions for controlling a processor to perform an operation for methods described herein, the instructions comprising the steps as defined herein.

[0010b] In yet another aspect, there is provided a computer system including processors that are programmed to implement any of the methods as defined herein.

[0011] Other example~~embodiments~~ of the disclosure~~invention~~ are directed to systems, portable consumer devices, and computer readable media associated with methods described herein.

[0012] A better understanding of the nature and advantages of the present invention may be gained with reference to the following detailed description and the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 illustrates a chromosomal region of a cancer cell exhibiting an aberration of a deletion.

[0014] FIG. 2 illustrates a chromosomal region of a cancer cell exhibiting an aberration of an amplification.

[0015] FIG. 3 shows a table 300 illustrating different types of cancers and associated regions and their corresponding aberrations.

[0016] FIG. 4 illustrates chromosomal regions within a cancer cell that do not exhibit an aberration along with measurements made in plasma according to embodiments of the present invention.

[0017] FIG. 5 illustrates the deletion of chromosomal region 510 within a cancer cell along with measurements made in plasma to determine the deleted region according to embodiments of the present invention.

[0018] FIG. 6 illustrates the amplification of chromosomal region 610 within a cancer cell along with measurements made in plasma to determine the amplified region according to embodiments of the present invention.

[0019] FIG. 7 shows an RHDO analysis of the plasma DNA of an hepatocellular carcinoma (HCC) patient for a segment located at chromosome 1p which showed mono-allelic amplification in the tumor tissue according to embodiments of the present invention.

[0020] FIG. 8 shows the change in size distribution of fragments for two haplotypes of a chromosomal region when a tumor containing a deletion is present according to embodiments of the present invention.