

CLAIMS

WHAT IS CLAIMED IS:

1. A method for nucleic acid analysis, comprising: (a) preparing a first single-stranded deoxynucleic acid (DNA) library from a first plurality of nucleic acid molecules, said first plurality of nucleic acid molecules comprising single-stranded DNA and double-stranded DNA derived from a subject; (b) preparing a second single-stranded DNA library from a second plurality of nucleic acid molecules, said second plurality of nucleic acid molecules comprising single-stranded DNA and double-stranded DNA derived from a control; (c) using said first single-stranded DNA library to measure a first size distribution for at least a subset of said first plurality of nucleic acid molecules; (d) using said second single-stranded DNA library to measure a second size distribution for at least a subset of said second plurality of nucleic acid molecules; (e) using said first size distribution and said second size distribution to determine a difference in size between said first size distribution and said second size distribution.

2. The method of claim 1, wherein (a) comprises denaturing said first plurality of nucleic acid molecules and/or (b) comprises denaturing said second plurality of nucleic acid molecules.

3. The method of claim 1 or claim 2, wherein (a) comprises ligating an adapter to 5' ends, 3' ends or 5' and 3' ends of individual single stranded DNA molecules of said first plurality of nucleic acid molecules using a DNA ligase specific for single stranded DNA and/or (b) comprises ligating an adapter to 5' ends, 3' ends or 5' and 3' ends of individual single stranded DNA molecules of said second plurality of nucleic acid molecules using a DNA ligase specific for single stranded DNA.

4. The method of any one of claims 1 to 3, wherein (a) comprises (i) circularizing individual single stranded DNA molecules of said first plurality of nucleic acid molecules or a derivative thereof to form a first plurality of circular nucleic acid molecules; and (ii) amplifying said first plurality of circular nucleic acid molecules to yield a first plurality of amplified nucleic acid molecules and/ or (b) comprises (i) circularizing individual single stranded DNA molecules of said second plurality of nucleic acid molecules or a derivative thereof to form a second plurality of circular nucleic acid molecules; and (ii) amplifying said second plurality of circular nucleic acid molecules to yield a second plurality of amplified nucleic acid molecules.

5. The method of claim 1, further comprising enriching said first plurality of nucleic acid molecules or said second plurality of nucleic acid molecules for one or more target sequences.

6. The method of claim 5, wherein said enriching is performed with one or more primers or capture probes.

7. The method of claim 5, wherein said enriching is performed with one or more antibodies or fragments thereof.

8. The method of claim 1, wherein measuring said size distribution for said first single-stranded DNA library or said second single-stranded DNA library comprises sequencing said first single-stranded DNA library or said second single-stranded DNA library.

9. The method of claim 1, further comprising identifying an individual nucleic acid molecule of said single-stranded DNA library or said second single stranded library as having a genomic feature.

10. The method of claim 9, wherein said genomic feature comprises an epigenetic modification selected from the group consisting of methylation, phosphorylation, ubiquitination, sumoylation, acetylation, ribosylation, citrullination, and fragmentation.

11. The method of claim 9, said genomic feature comprises a copy number variation (CNV), a single nucleotide variant (SNV), an insertion, a deletion, a translocation, or a combination thereof.

12. The method of claim 1, wherein said first plurality of nucleic acids comprises tumor nucleic acids and/or wherein said second plurality of nucleic acids is derived from a healthy control.

13. The method of claim 1, wherein said subject is determined to be at risk of or to have a disease when said difference is greater than a predetermined threshold and/or wherein said subject is determined to be at risk of or to have a disease when an average of said first size distribution is less than an average of said second size distribution..

14. The method of claim 13, wherein said disease is cancer.

15. A method for nucleic acid analysis, comprising: (a) preparing a single-stranded deoxynucleic acid (DNA) library from a plurality of nucleic acid molecules said plurality comprising single-stranded DNA and double-stranded DNA derived from a subject; (b) identifying an individual nucleic acid molecule of said single-stranded DNA library as having a genomic feature; (c) measuring a size for said individual nucleic acid molecule; (d) associating said genomic feature with a disease based on said size of said individual nucleic acid molecule.

16. The method of claim 15, wherein (a) comprises denaturing said plurality of nucleic acid molecules and/or wherein (a) comprises ligating an adapter to 5' ends, 3' ends or 5' and 3' ends of individual single stranded DNA molecules of said plurality of nucleic acid molecules using a DNA ligase specific for single stranded DNA.

17. The method of claim 15 or claim 16, wherein (a) comprises (i) circularizing individual single stranded DNA molecules of said plurality of nucleic acid molecules to form a

plurality of circular nucleic acid molecules; and (ii) amplifying said plurality of circular nucleic acid molecules to yield a plurality of amplified nucleic acid molecules.

18. The method of claim 15, wherein said genomic feature comprises an epigenetic modification selected from the group consisting of methylation, phosphorylation, ubiquitination, sumoylation, acetylation, ribosylation, citrullination, and fragmentation.

19. The method of claim 15, wherein said genomic feature comprises a copy number variation (CNV), a single nucleotide variant (SNV), an insertion, a deletion, a translocation, or a combination thereof.

20. A method for nucleic acid analysis, comprising: (a) preparing a single-stranded deoxynucleic acid (DNA) library from a plurality of nucleic acid molecules said plurality comprising single-stranded DNA and double-stranded DNA derived from a subject; (b) identifying an individual nucleic acid molecule of said single-stranded DNA library as having a genomic feature; (c) identifying at least a 5' end or a 3' end for said individual nucleic acid molecule; (d) associating said genomic feature with a disease based on said 5' end or said 3' end of said individual nucleic acid molecule.