pathology. The human genome project laid the groundwork for genome-wide analysis of cancers.

[0005] Changes in gene copy number are a fundamental driver of biological diversity. In the context of evolution, duplication of genes and divergence of function is a well-recognized driver of species diversity. In the context of human disease, gene loss and gene amplification within somatic cells are hallmarks of diseased tissues such as cancer. Certain therapeutic agents act specifically on cells with these genomic gain and/or loss mutations, however, the identification of these copy number variations is difficult because often such mutations are only present within the DNA of diseased or cancerous cells and are not found in other cells of the body. While the diseased tissue or cells is the major source of the mutated DNA, acquiring DNA through a biopsy is invasive, risky and often not possible. The observation that dying tumor or cancer cells release small pieces of their DNA into the bloodstream, termed cell free DNA or circulating DNA has allowed for the development of genetic tests that can be performed with less invasive techniques, such as a blood sample. However, only small amounts of DNA can be obtained from isolating cell free DNA from a sample, and only a portion of the total DNA will carry the mutation associated with the disease. For example, in the context of cancer genomics, diagnostically significant tumor mutations are often only found at minor allele frequencies that are significantly less than 50%. This is in contrast to conventional SNP genotyping where allele frequencies are generally ~100%, 50% or 0%.

[0006] Thus there is a need for genomic techniques capable of detecting genetic copy number changes in specific target loci.

SUMMARY

[0007] Methods of detecting rare mutations in cfDNA have been previously described in International PCT Publication No. WO 2016/028316. However, these techniques still lack the requisite sensitivity to detect the rarest copy number losses at very minor allele frequencies. Provided herein are compositions and methods for detection of target-specific copy number change that are applicable to several sample types, including direct tissue biopsies, peripheral blood, and in particular cfDNA, The compositions and methods described herein are sensitive enough to detect changes in copy number that are present only a tiny fraction of the total DNA.

[0008] The present disclosure includes, *inter alia*, compositions and methods that are useful for the detection of a mutational change, SNP, translocation, inversion, deletion, change in copy number, or other genetic variation within a sample of cellular genomic DNA (*e.g.*, from a tissue biopsy sample) or cfDNA (*e.g.*, from a blood sample). In particular, the compositions and methods of the present disclosure provide an extremely high level of resolution that is particularly useful in detecting copy number variations in a small fraction of the total cfDNA from a biological sample (*e.g.*, blood).

[0009] Particular examples are drawn to a method for performing a genetic analysis on a DNA target region from a test sample comprising: (a) generating a genomic DNA library comprising a plurality of DNA library fragments, wherein each of the DNA library fragments comprises a genomic DNA fragment from the test sample and an adaptor; (b) contacting the genomic DNA library with a plurality of capture probes that specifically bind to a DNA target region, thereby forming complexes between the capture probes and DNA library fragments comprising the DNA target region; and (c) performing a quantitative genetic analysis of the genomic DNA fragments comprising the DNA target region; wherein the adaptor is a DNA polynucleotide that comprises: an amplification region, a sample tag region, and an anchor region; wherein the amplification region comprises a polynucleotide sequence capable of serving as a primer recognition site for PCR amplification; wherein the sample tag comprises a polynucleotide sequence that encodes an identity of the unique library DNA fragment and encodes an identity of the test sample; wherein the anchor region comprises a polynucleotide sequence that encodes the identity of the test sample and wherein the anchor region is capable of attaching to the genomic DNA fragment; and wherein the genetic analysis is performed to detect a genetic change indicative of a disease state.

[0009a] In one aspect, the present disclosure refers to a method for performing a genetic analysis on a DNA target region from a test sample comprising a plurality of genomic DNA fragments, the method comprising: (a) generating a genomic DNA library by contacting the test sample with a set of adaptors, wherein each adaptor of the set of adaptors comprises a sample tag region selected from a pool of unique sample tag regions, wherein the pool is selected from a plurality of pools, and wherein the selected pool is unique to the test sample; wherein the genomic DNA library comprises a plurality of library DNA fragments and at least two unique sample tag regions; wherein each of the library DNA fragments comprises a genomic DNA fragment from the test sample attached to an adaptor; (b) contacting the genomic DNA library with a plurality of capture probes that specifically bind to the DNA target region, thereby forming complexes between the capture probes and library DNA fragments comprising the DNA target region; and (c) performing a quantitative genetic analysis of the genomic DNA fragments comprising the DNA target region; wherein the adaptor is a DNA polynucleotide that comprises: (i) an amplification region, (ii) a sample tag region, and (iii) an anchor region; wherein the amplification region comprises a polynucleotide sequence capable of serving as a primer recognition site for PCR amplification; wherein the sample tag region identifies the test sample; and wherein the anchor region comprises a polynucleotide sequence that is capable of attaching to the genomic DNA fragment.

[0010] In some examples, the genetic change indicative of a disease state is selected from a single nucleotide variant (SNV), an insertion less than 40 nucleotides in length, a deletion of a DNA region less than 40 nucleotides in length, and/or a change in copy number. In particular examples, the genetic change indicative of a disease state is a change in copy number. In some examples, the test sample is a tissue biopsy. In various examples, the tissue biopsy is taken from a tumor or a tissue suspected of being a tumor. In certain examples, the genomic DNA is cell free DNA (cfDNA) or cellular DNA. In particular examples, the genomic DNA is cfDNA is isolated from the test sample; and wherein the test sample is a biological sample selected from the group consisting of: amniotic

fluid, blood, plasma, serum, semen, lymphatic fluid, cerebral spinal fluid, ocular fluid, urine, saliva, stool, mucous, and sweat.

[0011] In certain examples, the genomic DNA fragments are obtained the steps comprising; (i) isolating cellular DNA from the test sample; and (ii) fragmenting the cellular DNA to obtain the genomic DNA fragments. In particular examples, step (ii) is performed by contacting the cellular DNA with at least one digestion enzyme. In some examples, step (ii) is performed by applying mechanical stress to the cellular DNA. In certain examples, the mechanical stress is applied by sonicating the cellular DNA.

[0012] In particular examples, the sample tag further comprises a unique molecule identifier (UMI) that facilitates the identification of the unique genomic DNA fragment.

[0013] In some examples, the amplification region is between 10 and 50 nucleotides in length. In particular examples, the amplification region is between 20 and 30 nucleotides in length. In certain examples, the amplification region is 25 nucleotides in length.

[0014] In some examples, the sample tag is between 5 and 50 nucleotides in length. In particular examples, the sample tag is between 5 and 15 nucleotides in length. In certain examples, the sample tag is 8 nucleotides in length. In some examples, the UMI multiplier is adjacent to or contained within the sample tag region.

[0015] In certain examples, the UMI multiplier is between 1 and 5 nucleotides in length. In particular examples, the UMI multiplier is 3 nucleotides in length, and comprises one of 64 possible nucleotide sequences.

[0016] In some examples, the anchor region is between 1 and 50 nucleotides in length. In particular examples, the anchor region is between 5 and 25 nucleotides in length. In certain examples, the anchor region is 10 nucleotides in length.

[0017] Particular examples of the present disclosure are drawn to methods where the step of (a) generating a genomic DNA library comprising a plurality of DNA library fragments, comprises attaching the genomic DNA fragments to a plurality of adaptors. In certain examples, the genomic DNA fragments are end repaired prior to attaching the genomic DNA fragments with a plurality of adaptors. In particular examples, the amplification regions of each adaptor of the plurality of adaptors comprises an identical nucleotide sequence.

[0018] In certain examples, the sample tag region of each adaptor of the plurality of adaptors comprise one of between 2 and 1,000 nucleotide sequences. In particular examples, the sample tag region of each adaptor of the plurality of adaptors comprise one of between 50 and 500 nucleotide sequences. In various examples, the sample tag region of each adaptor of the plurality of adaptors comprises one of between 100 and 400 nucleotide sequences. In some examples, the sample tag region of each adaptor of the plurality of adaptors comprises one of between 200 and 300 nucleotide sequences. In certain examples, the sample tag region of each adaptor of the plurality of adaptors is 8 nucleotides in length. In some examples, each sequence of the nucleotide sequences are discrete from any other sequence of the 240 nucleotide sequences by Hamming distance of at least two.

[0019] In particular examples, each of the plurality of adaptors comprises a UMI multiplier that is adjacent to or contained within the sample tag region. In some examples, each of the plurality of adaptors comprises a UMI multiplier that is adjacent to the sample tag region. In certain examples, the UMI multiplier of each adaptor of the plurality of adaptors is between 1 and 5 nucleotides in length. In some examples, the UMI multiplier of each adaptor of the plurality of adaptors is three nucleotides in length.

[0020] In particular examples, the anchor tag region of each adaptor of the plurality of adaptors comprises one of four nucleotide sequences, and each sample region of a given sequence is paired to only one of the four anchor regions of a given sequence.

[0021] In some examples, the amplification regions of each adaptor of the plurality of adaptors comprises an identical nucleotide sequence; the sample tag region of each adaptor of the plurality of adaptors is 8 nucleotides in length; the nucleotide sequence of each sample tag is discrete from any other nucleotide sequence of the sample tags of the plurality of adaptors by Hamming distance of at least two; each of the plurality of adaptors comprises a UMI multiplier that is adjacent to or contained within the sample tag region; the UMI multiplier of each adaptor of the plurality of adaptors is three nucleotides in length; and the UMI multiplier of each of the possible nucleotide sequences is paired to each sample tag region of the plurality of adaptors; the anchor tag region of each adaptor of the plurality of adaptors comprises one of four nucleotide sequences; and each sample region of a given sequence is paired to only one of the four anchor regions of a given sequence.

[0022] Particular examples of the present disclosure are drawn to a method where the step of attaching the genomic DNA fragments with a plurality of adaptors

comprises: (i) attaching an oligonucleotide comprising least a portion of an anchor region to each genomic DNA fragment, wherein the oligonucleotide comprising least a portion of an anchor region is a DNA duplex comprising a 5' phosphorylated attachment strand duplexed with a partner strand, wherein the partner strand is blocked from attachment by chemical modification at its 3' end, and wherein the attachment strand is attached to the genomic DNA fragment; (ii) contacting the genomic DNA fragments attached to the oligonucleotides comprising at least a portion of the anchor region with DNA oligonucleotides encoding full length adaptor sequences for each adaptor nucleotide sequence of the plurality of adaptors; and (iii) contacting the genomic DNA fragments and the DNA oligonucleotides encoding the full length adaptor sequence with T4 polynucleotide kinase, Taq DNA ligase and full-length Bst polymerase under conditions suitable for DNA ligation; thereby attaching the plurality of adaptors to the genomic DNA fragments. In some examples, the genomic DNA fragments are cfDNA. In certain examples, the DNA target region is analyzed for a change in copy number.

[0023] In particular examples, step (c) performing a quantitative genetic analysis of the genomic DNA fragments comprising the DNA target region comprises purification of the complexes formed between the capture probes and DNA library fragments comprising the DNA target region. In certain examples, step (c) comprises purification of the complexes formed between the capture probes and DNA library fragments comprising the DNA target region, preforming primer extension and/or amplification of the DNA library fragments comprising the region of interest from the genomic DNA library. In some examples, step (c) comprises purification of the complexes formed between the capture probes and DNA library fragments comprising the DNA target region, preforming primer extension and amplification of the DNA library fragments comprising the region of interest from the genomic DNA library. In certain examples, step (c) comprises DNA sequencing of the DNA library fragments comprising the DNA target region to generate a plurality of sequencing reads.

[0024] In some examples, the present disclosure is drawn to a method wherein the genomic analysis comprises determining a change of copy number in a DNA region of interest, and wherein step (c), performing a quantitative genetic analysis of the genomic DNA fragments comprising the DNA target region, comprises determining a copy number of the region of interest present in the genomic DNA library derived from the test sample, and comparing it to a copy number of the region of interest present in the genomic

DNA library derived from a reference sample, wherein the reference sample comprises a known copy number of the DNA target region.

[0025] In some examples, determining the copy number in the region of interest comprises DNA sequencing of the DNA library fragments comprising the DNA target region to generate a plurality of sequencing reads, wherein each sequencing read comprises a unique molecular identification element (UMIE). In some examples, the UMIE comprises sequencing information from the adaptor and at least a portion of the genomic DNA sequence. In some examples, sequencing reads comprising identical UMIEs are identified as a unique genomic sequence (UGS).

[0026] In some examples, methods of determining the copy number further comprise determining a raw genomic depth (RGD) for each of the capture probes contacted with the genomic DNA library. In some examples, determining the RGD comprises determining the average number of UGSs associated with each capture probe sequence within a group of sample replicates. In some examples, capture probes associated with a highly variable number of UGSs are identified as noisy probes and are removed from further calculations. In some examples, determining the RGD further comprises calculating an RGD for a sample, comprising calculating a numerical average of all RGDs for all capture probes in the sample. In some examples, the RGD values for noisy probes are not included in calculating an RGD for a sample.

[0027] In some examples, the RGDs for the capture probes are normalized across all samples in an experimental group by converting the RGD for each capture probe into a probe-specific, normalized read count comprising (i) multiplying each capture probe RGD in a sample by a normalization constant, wherein the normalization constant comprises any real number; and (ii) dividing the product of (i) by the RGD calculated for the corresponding sample; or (iii) dividing the product of (i) by an average RGD calculated from a subset of probes. In some examples, the subset of probes is a set of control probes.

[0028] In some examples, the probe-specific, normalized read counts are converted in to a copy number value comprising (i) multiplying the probe-specific, normalized read counts of probes directed to autosomal and/or X-linked regions by 2 in samples derived from females; (ii) multiplying the probe-specific, normalized read counts of probes directed to Y-linked and/or X-linked regions by 1 in samples derived from males; (iii) averaging the products of (i) and/or (ii) across all samples in an experiment; and (iv) dividing

the product of (i) and/or (ii) by the average of (iii). In some examples, the approximate copy number values for all probes that target a specific gene are averaged.

[0029] In some examples, the present disclosure is drawn to a method for highly sensitive detection of copy number gain and copy number loss comprising (i) determining an RGD for a capture probe; (ii) normalizing the RGD for the capture probe across all samples in an experimental group by converting the RGD for the capture probe into a probe-specific, normalized read count; (iii) calculating an approximate copy number value for each probe-specific, normalized read count; and (iv) averaging the approximate copy number values for all probes that target a specific gene.

[0030] In some examples, the present disclosure is drawn to a method for measuring chromosome stability comprising (i) designing and validating a set of one or more chromosomal stability probes, wherein the chromosomal stability probes are uniformly distributed across human chromosomes; (ii) performing targeted sequencing on patient samples using the one or more chromosomal stability probes; (iii) determining an approximate copy number value for each chromosomal probe; (iv) determining a genomic phenotype of a patient sample, wherein fluctuations in the copy number values for one or more chromosomal probes in the patient sample indicate genomic instability.

[0031] In some examples, the present disclosure is drawn to a method of treating a cancer in a subject in need thereof, wherein the subject has been identified as having a destabilized genome according to the method claim 62, wherein the method of treating the cancer comprises administering a pharmaceutically effective amount of a PARP inhibitor.

[0032] In some examples, the present disclosure is drawn to a method wherein the genomic analysis comprises determining a change of copy number in a DNA region of interest, and wherein step (c), performing a quantitative genetic analysis of the genomic DNA fragments comprising the DNA target region, comprises determining a copy number of the region of interest present in the genomic DNA library derived from the test sample, and comparing it to a copy number of the region of interest present in the genomic DNA library derived from a reference sample, wherein the reference sample comprises a known copy number of the DNA target region. In some examples, the region of interest is a gene or a portion of the gene. In particular examples, the gene is associated with a disease. In certain examples, the disease is a cancer. In various examples, the gene is BRCA2, ATM, BRCA1, BRIP1, CHEK2, FANCA, HDAC2, and/or PALB2.

[0033] Particular examples are drawn to a genomic DNA library comprising a plurality of DNA library fragments, wherein each of the DNA library fragments comprises an adaptor and a genomic DNA fragment; wherein the adaptor is a DNA polynucleotide that comprises: an amplification region, a sample tag region, and an anchor region; wherein the amplification region comprises a polynucleotide sequence capable of serving as a primer recognition site for PCR amplification; wherein the sample tag comprises a polynucleotide sequence that encodes an identity of the unique library DNA fragment and encodes an identity of the test sample; and wherein the anchor region comprises a polynucleotide sequence that encodes the identity of the test sample, and wherein the anchor region is capable of attaching to the genomic DNA fragment. In some examples, the sample tag further comprises a unique molecule identifier (UMI), wherein the UMI facilitates the identification of the unique genomic DNA fragment. In particular examples, the amplification region is between 10 and 50 nucleotides in length. In particular examples, the amplification region is 25 nucleotides in length. In particular examples, the sample tag is between 5 and 50 nucleotides in length. In certain examples, the sample tag is 8 nucleotides in length. In some examples, the UMI multiplier is adjacent to or contained within the sample tag region. In particular examples, the UMI multiplier is between 1 and 5 nucleotides in length. In certain examples, the anchor region is between 1 and 50 nucleotides in length. In some examples, the anchor region is 10 nucleotides in length. In particular examples, the amplification regions of each adaptor of the plurality of adaptors comprises an identical nucleotide sequence. In some examples, each nucleotide sequence of the sample tags are discrete from any other sequence of the nucleotide sequences of the sample by Hamming distance of at least two. In certain examples, each of the plurality of adaptors comprises a UMI multiplier that is adjacent to or contained within the sample tag region. In particular examples, each of the plurality of adaptors comprises a UMI multiplier that is adjacent to the sample tag region. In some examples, the anchor tag region of each adaptor of the plurality of adaptors comprises one of four nucleotide sequences, and wherein each sample region of a given sequence is paired to only one of the four anchor regions of a given sequence. In some examples, the genomic DNA fragment is cfDNA.

[0034] In certain examples, the amplification regions of each adaptor of the plurality of adaptors comprises an identical nucleotide sequence; the sample tag region of each adaptor of the plurality of adaptors is 8 nucleotides in length, the sample tag region of

each adaptor of the plurality of adaptors comprises a nucleotide sequence that is discrete from any other nucleotide sequence of the sample tags of the plurality of adaptors by Hamming distance of at least two, the each of the plurality of adaptors comprises a UMI multiplier that is adjacent to or contained within the sample tag region, the UMI multiplier of each adaptor of the plurality of adaptors is three nucleotides in length, and the UMI multiplier of each of the possible nucleotide sequences is paired to each of the sample tag regions of the plurality of adaptors, the anchor tag region of each adaptor of the plurality of adaptors comprises one of four nucleotide sequences, and each sample region of a given sequence is paired to only one of the four anchor regions of a given sequence. In some examples, the genomic DNA fragment is cfDNA.

[0035] Certain examples are drawn to a plurality of genomic DNA libraries, comprising more than one genomic library described herein. In some examples, the nucleic acid sequences of the sample tag regions of a genomic DNA library belonging to the plurality of genomic DNA libraries are different from the nucleic acid sequences of the sample tag regions of other genomic DNA libraries belonging to the plurality of genomic DNA libraries. In particular examples, the nucleic acid sequences of the amplification regions of a genomic DNA library belonging to the plurality of genomic DNA libraries are identical to the nucleic acid sequences of the amplification regions of other genomic DNA libraries belonging to the plurality of genomic DNA libraries.

[0036] Certain examples are drawn to a method for genetic analysis of a DNA target region of cell free DNA (cfDNA) comprising: (a) generating a DNA library as described herein; (b) contacting the cfDNA library with a plurality of capture probes that specifically bind to a DNA target region, thereby forming complexes between the capture probes and DNA library fragments comprising the DNA target region; and (c) performing a quantitative genetic analysis of the cfDNA fragments comprising the DNA target region; thereby performing genetic analysis of the DNA target region.

[0037] Certain examples are directed to a method of predicting, diagnosing, or monitoring a genetic disease in a subject comprising: (a) obtaining a test sample from the subject; (b) isolating genomic DNA from the test sample; (c) generating a DNA library comprising a plurality of DNA library fragments, wherein each of the DNA library fragments comprises a genomic DNA fragment from the test sample and an adaptor; (d) contacting the cfDNA library with a plurality of capture probes that specifically bind to a DNA target region, thereby forming complexes between the capture probes and DNA library

fragments comprising the DNA target region; and (e) performing a quantitative genetic analysis of one or more target genetic loci associated with the genetic disease in the cfDNA clone library, wherein the identification or detection of one or more genetic lesions in the one or more target genetic loci is prognostic for, diagnostic of, or monitors the progression of the genetic disease. In particular examples, the quantitative genetic analysis comprises DNA sequencing to generate a plurality of sequencing reads.

[0038] Particular examples are drawn to a set of adaptors that encode an identify of a unique genomic DNA fragment and an identity of a test sample, for use in generating a genomic DNA library, wherein each adaptor in said set of adapters is a DNA polynucleotide that comprises: an amplification region, a sample tag region, and an anchor region; wherein the amplification region comprises a polynucleotide sequence capable of serving as a primer recognition site for PCR amplification; wherein the sample tag comprises a polynucleotide sequence that encodes the identity of the unique library DNA fragment and encodes the identity of the test sample; and wherein the anchor region comprises a polynucleotide sequence that encodes the identity of the test sample, and wherein the anchor region is capable of attaching to the genomic DNA fragment. In some examples, the sample tag further comprises a unique molecule identifier (UMI), wherein the UMI facilitates the identification of the unique genomic DNA fragment. In various examples, the amplification region is between 10 and 50 nucleotides in length. In certain examples, the amplification region is 25 nucleotides in length. In particular examples, the sample tag is between 5 and 50 nucleotides in length. In some examples, the sample tag is 8 nucleotides in length. In particular examples, the UMI multiplier is adjacent to or contained within the sample tag region. In some examples, the UMI multiplier is between 1 and 5 nucleotides in length. In particular examples, the anchor region is between 1 and 50 nucleotides in length. In some examples, the anchor region is 10 nucleotides in length. In certain examples, the amplification regions of each adaptor of the plurality of adaptors comprises an identical nucleotide sequence.

[0039] In some examples, each nucleotide sequence of the sample tags is discrete from any other nucleotide sequence of the sample tags of the set of adaptors by Hamming distance of at least two. In various examples, each of the plurality of adaptors comprises a UMI multiplier that is adjacent to or contained within the sample tag region. In particular examples, each of the plurality of adaptors comprises a UMI multiplier that is adjacent to the sample tag region.

[0040] In some examples, the anchor tag region of each adaptor of the plurality of adaptors comprises one of four nucleotide sequences, and wherein each sample region of a given sequence is paired to only one of the four anchor regions of a given sequence. The set of adaptors claim 75, wherein the amplification regions of each adaptor of the plurality of adaptors comprises an identical nucleotide sequence; wherein the sample tag region of each adaptor is 8 nucleotides in length, wherein each nucleotide sequence of the sample tags is discrete from any other nucleotide sequence of the sample tags of the set of adaptors by Hamming distance of at least two, wherein each of the plurality of adaptors comprises a UMI multiplier that is adjacent to or contained within the sample tag region, wherein the UMI multiplier of each adaptor of the plurality of adaptors is three nucleotides in length, wherein the UMI multiplier comprises one of 64 possible nucleotide sequences, and wherein the UMI multiplier of each of the 64 possible nucleotide sequences is paired to each of the sample tag region of the plurality of adaptors, wherein the anchor tag region of each adaptor of the plurality of adaptors comprises one of four nucleotide sequences, and wherein each sample region of a given sequence is paired to only one of the four anchor regions of a given sequence.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0041] FIG. 1 shows the framework of the copy number loss (CNL) assay. Each gene (rows) exhibits a characteristic unique read value that is represented here by a shade. Each sample (columns) is interrogated across the same panel of genes.

[0042] FIG. 2 shows a diagram illustrating the drivers of the CNL assay signal.

[0043] FIG. 3 shows a diagram illustrating steps of an illustrative CNL assay performed on cell free DNA (cfDNA).

[0044] FIG. 4A – 4E shows diagrams of an illustrative first generation adaptor (FIG. 4A and 4B) and an adaptor of the present invention (FIGs. 4C-4E). FIG. 4A shows the first generation adaptor design. FIG. 4B shows that in the first generation adaptors, there were a collection of 249 possible sequence tags, each 5 nucleotides (nt) in length that attached to a single anchor sequence. FIG. 4C shows a diagram of a second generation adaptor. FIG. 4D shows an illustrative set of adaptors that are applied to a single sample that consists of four sets of 8mer tag sequences with each set having 60 members. Each set of 60

CLAIMS

1. A method for performing a genetic analysis on a DNA target region from a test sample comprising a plurality of genomic DNA fragments, the method comprising:

(a) generating a genomic DNA library by contacting the test sample with a set of adaptors, wherein each adaptor of the set of adaptors comprises a sample tag region selected from a pool of unique sample tag regions, wherein the pool is selected from a plurality of pools, and wherein the selected pool is unique to the test sample; wherein the genomic DNA library comprises a plurality of library DNA fragments and at least two unique sample tag regions; wherein each of the library DNA fragments comprises a genomic DNA fragment from the test sample attached to an adaptor;

(b) contacting the genomic DNA library with a plurality of capture probes that specifically bind to the DNA target region, thereby forming complexes between the capture probes and library DNA fragments comprising the DNA target region; and

(c) performing a quantitative genetic analysis of the genomic DNA fragments comprising the DNA target region;

wherein the adaptor is a DNA polynucleotide that comprises: (i) an amplification region, (ii) a sample tag region, and (iii) an anchor region;

wherein the amplification region comprises a polynucleotide sequence capable of serving as a primer recognition site for PCR amplification; wherein the sample tag region identifies the test sample;

and wherein the anchor region comprises a polynucleotide sequence that is capable of attaching to the genomic DNA fragment.

2. The method of claim 1, wherein the method identifies a genetic change indicative of a disease state selected from a single nucleotide variant (SNV), an insertion less than 40 nucleotides in length, a deletion of a DNA region less than 40 nucleotides in length, and/or a change in copy number.

3. The method of claim 2, wherein the genetic change indicative of a disease state is a change in copy number.

4. The method of claim 1, wherein the test sample is a tissue biopsy.

5. The method of claim 4, wherein the tissue biopsy is taken from a tumor or a tissue suspected of being a tumor.

6. The method of claim 1, wherein the genomic DNA fragments are cell free DNA (cfDNA) or cellular DNA.

7. The method of claim 6, wherein the genomic DNA fragments are isolated from the test sample; and wherein the test sample is a biological sample selected from the group consisting of: amniotic fluid, blood, plasma, serum, semen, lymphatic fluid, cerebral spinal fluid, ocular fluid, urine, saliva, stool, mucous, and sweat.

8. The method of claim 1, wherein the genomic DNA fragments are obtained by the steps comprising;

(i) isolating cellular DNA from the test sample;

(ii) fragmenting the cellular DNA to obtain the genomic DNA fragments.

9. The method of claim 8, wherein step (ii) is performed by contacting the cellular DNA with at least one digestion enzyme.

10. The method of claim 8, wherein step (ii) is performed by applying mechanical stress to the cellular DNA.

11. The method of claim 10, where the mechanical stress is applied by sonicating the cellular DNA.

12. The method of claim 1, wherein the amplification region is between 10 and 50 nucleotides in length.

13. The method of claim 1, wherein the amplification region is between 20 and 30 nucleotides in length.

14. The method of claim 1, wherein the amplification region is 25 nucleotides in length.

15. The method of claim 1, wherein the sample tag region is between 5 and 50 nucleotides in length.

16. The method of claim 15, wherein the sample tag region is between 5 and 15 nucleotides in length.

17. The method of claim 15, wherein the sample tag region is 8 nucleotides in length.

18. The method of claim 1, wherein the adaptor further comprises a unique molecule identifier multiplier (UMI multiplier) that is adjacent to or contained within the sample tag region.

19. The method of claim 18, wherein the UMI multiplier is between 1 and 5 nucleotides in length.

20. The method of claim 18, wherein the UMI multiplier is 3 nucleotides in length, and comprises one of 64 possible nucleotide sequences.

21. The method of claim 1, wherein the anchor region is between 1 and 50 nucleotides in length.

22. The method of claim 21, wherein the anchor region is between 5 and 25 nucleotides in length.

23. The method of claim 21, wherein the anchor region is 10 nucleotides in length.

24. The method of claim 1, wherein step (a) comprises attaching a first adaptor to one end of a genomic DNA fragment of the test sample and attaching a second adaptor to the other end of the genomic DNA fragment.

25. The method of claim 24, wherein the genomic DNA fragment is end repaired prior to attaching the first and second adaptors.

26. The method of claim 1, wherein the amplification region of each adaptor of the set of adaptors is identical to the amplification region of every other adaptor of the set of adaptors.

27. The method of claim 1, wherein the pool of sample tag regions comprises between 2 and 1,000 unique sample tag region sequences.

28. The method of claim 27, wherein the pool of sample tag regions comprises between 50 and 500 unique sample tag region sequences.

29. The method of claim 27, wherein the pool of sample tag regions comprises between 100 and 400 unique sample tag region sequences.

30. The method of claim 27, wherein the pool of sample tag regions comprises between 200 and 300 unique sample tag region sequences.

31. The method of claim 27, wherein each sample tag region of the pool of sample tag regions is 8 nucleotides in length.

32. The method of claim 27, wherein the pool of sample tag regions comprises 240 unique sample tag region sequences.

33. The method of claim 27, wherein each unique sample tag region sequence is discrete from any other unique sample tag region sequence by Hamming distance of at least two.

34. The method of claim 1, wherein the sample tag region identifies the genomic DNA fragment attached thereto.

35. The method of claim 34, wherein the adaptor further comprises a UMI multiplier which increases the number of unique sequences for identifying the genomic fragments.

36. The method of claim 1, wherein the anchor region of each adaptor of the set of adaptors comprises one of four sequences, and wherein each sample tag region of a given sequence is paired to only one of the four anchor regions of a given sequence.

37. The method of claim 1, wherein the amplification region of each adaptor of the set of adaptors comprises an identical nucleotide sequence;

wherein each sample tag region of the pool of sample tag regions is 8 nucleotides in length, wherein each unique sample tag region sequence is discrete from any other unique sample tag region sequence by Hamming distance of at least two,

wherein each adaptor of the set of adaptors comprises a UMI multiplier that is adjacent to or contained within the sample tag region, wherein the UMI multiplier of each adaptor of the set of adaptors is three nucleotides in length, and wherein the UMI multiplier of a given sequence is paired to one sample tag region of a given sequence,

wherein the anchor region of each adaptor of the set of adaptors comprises one of four nucleotide sequences, and wherein each sample tag region of a given sequence is paired to only one of the four anchor regions of a given sequence.

38. The method of claim 24, wherein the step of attaching each of the first and second adaptors to the genomic DNA fragment comprises:

(i) attaching an oligonucleotide comprising at least a portion of an anchor region to the genomic DNA fragment, wherein the oligonucleotide is part of a DNA duplex comprising a 5’ phosphorylated attachment strand duplexed with a partner strand, wherein the partner strand is blocked from attachment to the genomic DNA fragment by chemical modification at its 3’ end, and wherein the attachment strand is attached to the genomic DNA fragment; and

(ii) contacting the genomic DNA fragment attached to the attachment strand with a DNA oligonucleotide encoding a full-length adaptor sequence, a T4 polynucleotide kinase, a Taq DNA ligase, and a full-length Bst polymerase under conditions suitable for DNA ligation;

thereby attaching each of the first and second adaptors to the genomic DNA fragment.

39. The method of claim 1, wherein the DNA target region is analyzed for a change in copy number.

40. The method of claim 1, wherein step (c) comprises purification of the complexes formed between the capture probes and DNA library fragments comprising the DNA target region.

41. The method of claim 1, wherein step (c) comprises purification of the complexes formed between the capture probes and DNA library fragments comprising the DNA target region and performing primer extension and/or amplification of the DNA library fragments comprising the DNA target region.

42. The method of claim 1, wherein step (c) comprises purification of the complexes formed between the capture probes and DNA library fragments comprising the DNA target region and performing primer extension and amplification of the DNA library fragments comprising the DNA target region.

43. The method of claim 1, wherein step (c) comprises DNA sequencing of the DNA library fragments comprising the DNA target region to generate a plurality of sequencing reads.

44. The method of claim 1, wherein the genomic analysis comprises determining a change of a copy number in a DNA region of interest, and wherein step (c) comprises:

(i) determining a copy number of the region of interest present in the genomic DNA library derived from the test sample, and

(ii) comparing the copy number determined in step (i) to a copy number of the region of interest present in a genomic DNA library derived from a reference sample, wherein the reference sample comprises a known copy number of the DNA target region.

45. The method of claim 44, wherein determining the copy number in the region of interest comprises DNA sequencing of the DNA library fragments comprising the DNA target region to generate a plurality of sequencing reads, wherein each sequencing read comprises a unique molecular identification element (UMIE).

46. The method of claim 45, wherein the UMIE comprises sequencing information from the adaptor and at least a portion of the genomic DNA fragment sequence.

47. The method of claim 46, wherein sequencing reads comprising identical UMIEs are identified as a unique genomic sequence (UGS).

48. The method of claim 44, further comprising determining a raw genomic depth (RGD) for each of the capture probes contacted with the genomic DNA library.

49. The method of claim 48, wherein determining the RGD comprises determining the average number of UGSs associated with each capture probe sequence within a group of sample replicates.

50. The method of claim 49, wherein capture probes associated with a highly variable number of UGSs are identified as noisy probes and are removed from further calculations.

51. The method of claim 49, further comprising calculating an RGD for a sample, comprising calculating a numerical average of all RGDs for all capture probes in the sample.

52. The method of claim 49, wherein the RGD values for noisy probes are not included in calculating an RGD for a sample.

53. The method of claim 48, wherein the RGDs for the capture probes are normalized across all samples in an experimental group by converting the RGD for each capture probe into a probe-specific, normalized read count comprising:

(i) multiplying each capture probe RGD in a sample by a normalization constant, wherein the normalization constant comprises any real number; and

(ii) dividing the product of (i) by the RGD calculated for the corresponding sample; or

(iii) dividing the product of (i) by an average RGD calculated from a subset of probes.

54. The method of claim 53, wherein the subset of probes is a set of control probes.

55. The method of claim 54, wherein the probe-specific, normalized read counts are converted to a copy number value comprising:

(i) multiplying the probe-specific, normalized read counts of probes directed to autosomal and/or X-linked regions by 2 in samples derived from females;

(ii) multiplying the probe-specific, normalized read counts of probes directed to Y-linked and/or X-linked regions by 1 in samples derived from males;

(iii) averaging the products of (i) and/or (ii) across all samples in an experiment; and

(iv) dividing the product of (i) and/or (ii) by the average of (iii).

56. The method of claim 55, wherein the approximate copy number values for all probes that target a specific gene are averaged.