**What is claimed is:**

1. A method of detecting genomic alterations within a biological sample comprising nucleic acids, comprising the steps of:

(a) extracting nucleic acid from the biological sample;

(b) performing a plurality of multiplexed PCR reactions on the extracted nucleic acid using:

a plurality of target capture primer pairs specific to a plurality of target genes that are capable of undergoing genomic alteration,

wherein each target capture primer pair comprises a forward target capture primer and a reverse target capture primer specific to a target gene that is capable of undergoing genomic alteration,

wherein each forward target capture primer and each reverse target capture primer comprises a target-specific sequence at its 3' end that is specific to the target gene, a barcode sequence linker, and an adapter-specific sequence at its 5' end,

thereby generating a plurality of amplicons comprising a plurality of target gene sequences corresponding to the plurality of target genes that are capable of undergoing genomic alteration;

(c) removing target capture primers that have not been incorporated into the plurality of amplicons generated in step (b) using at least one nuclease, thereby generating a purified mixture of the plurality of amplicons comprising the plurality of target gene sequences;

(d) amplifying the plurality of amplicons in the purified mixture obtained from step (c) by using universal indexed adapter primers to generate a sequencing library, wherein each amplicon of the sequencing library comprises two barcode sequences;

(e) purifying the sequencing library obtained from step (d);

(f) subjecting the purified sequencing library from step (e) to multiplex sequencing on a next-generation sequencing platform to obtain a plurality of sequencing reads;

(g) mapping the plurality of sequencing reads obtained from step (f) to a first reference genome;

(h) grouping the sequencing reads where the barcode sequences of the sequencing reads are identical into a consensus cluster;

(i) performing a sequence alignment of each consensus cluster obtained from step (h) with all consensus clusters having at least one overlapping barcode sequence, then

determining the presence of a consensus base in each sequence alignment result to generate a consensus sequencing read;

(j) mapping each of the consensus sequencing read from step (i) with a second reference genome;

(k) identifying the differences between the sequencing read and the reference genome from step (j) to thereby determine the presence of genomic alteration in the nucleic acid present in the biological sample.

2. The method of claim 1, wherein the genomic alteration is selected from the group consisting of single-nucleotide variations, insertions, deletions, genomic copy number alterations, deletions of homopolymeric regions, total mutation (or variant) load, detection of microbial nucleic acid sequences, detection of polymorphisms or single-nucleotide variations in nucleic acid sequences, and DNA structural rearrangements giving rise to variant RNA molecules, wherein optionally the variant RNA molecules are selected from the group consisting of structural variants of RNA molecules and copy number alterations of RNA molecules.

3. The method of claim 1 or 2, wherein the nucleic acid is selected from the group consisting of DNA and RNA, wherein optionally the DNA is genomic DNA, tumor tissue DNA, circular DNA, circulating tumor DNA (ctDNA) or cell-free DNA (cfDNA), and wherein optionally the RNA is messenger RNA, circular RNA or non-coding RNA.

4. The method of any one of the preceding claims, wherein the biological sample is selected from the group consisting of a liquid sample, a tissue sample, and a cell sample, optionally wherein the liquid sample is a bodily fluid, wherein optionally the bodily fluid is selected from the group consisting of blood, bone marrow, cerebral spinal fluid, peritoneal fluid, pleural fluid, lymph fluid, ascites, serous fluid, sputum, lacrimal fluid, stool, urine, saliva, ductal fluid from breast, gastric juice and pancreatic juice, wherein further optionally the bodily fluid is blood, and wherein optionally the blood is plasma.

5. The method of any one of the preceding claims, wherein the at least one nuclease used to remove the target capture primers that have not been incorporated into amplicons in step (c) is selected from the group consisting of:

(i) an endonuclease, wherein optionally the endonuclease is selected from the group consisting of mung bean nuclease, nuclease P1, nuclease S1 and combinations thereof; and

(ii) an exonuclease, wherein optionally the exonuclease is selected from the group consisting of exonuclease I, exonuclease T, exonuclease VII and combinations thereof; wherein optionally the at least one nuclease comprises a combination of exonuclease I and exonuclease T.

6. The method of any one of the preceding claims, wherein the sequencing library generated in step (d) comprises at least 1 amplicon, or at least 50 amplicons, or at least 100 amplicons, or at least 200 amplicons, or at least 300 amplicons, or at least 400 amplicons, or at least 500 amplicons, or at least 600 amplicons, or at least 700 amplicons, or at least 800 amplicons, or at least 900 amplicons, or at least 1000 amplicons, or at least 1100 amplicons, or at least 1200 amplicons, or at least 1300 amplicons, or at least 1400 amplicons, or at least 1500 amplicons, or at least 1600 amplicons, or at least 1700 amplicons, or at least 1800 amplicons, or at least 1900 amplicons, or at least 2000 amplicons, or at least 2100 amplicons, or at least 2200 amplicons, or at least 2300 amplicons, or at least 2400 amplicons, or at least 2500 amplicons, or at least 2600 amplicons, or at least 2700 amplicons, or at least 2800 amplicons, or at least 2900 amplicons, or at least 3000 amplicons, wherein optionally the sequencing library generated in step (d) comprises at least 2600 amplicons.

7. The method of any one of the preceding claims, wherein only amplicons comprising barcode sequences and adapters on both their 5' and 3' ends from step (d) are subjected to multiplex sequencing on a next-generation sequencing platform as defined in step (f).

8. The method of any one of the preceding claims, wherein the length of the target-specific sequence is from 15 nucleotides to 70 nucleotides, or from 16 nucleotides to 69 nucleotides, or from 17 nucleotides to 68 nucleotides, or from 18 nucleotides to 67 nucleotides, or from 19 nucleotides to 66 nucleotides, or from 20 nucleotides to 65

nucleotides, or from 21 nucleotides to 64 nucleotides, or from 22 nucleotides to 63 nucleotides, or from 23 nucleotides to 62 nucleotides, or from 24 nucleotides to 61 nucleotides, or from 25 nucleotides to 60 nucleotides, or from 26 nucleotides to 59 nucleotides, or from 27 nucleotides to 58 nucleotides, or from 28 nucleotides to 57 nucleotides, or from 29 nucleotides to 56 nucleotides, or from 30 nucleotides to 55 nucleotides, or from 31 nucleotides to 54 nucleotides, or from 32 nucleotides to 53 nucleotides, or from 33 nucleotides to 52 nucleotides, or from 34 nucleotides to 51 nucleotides, or from 35 nucleotides to 50 nucleotides, or from 36 nucleotides to 49 nucleotides, or from 37 nucleotides to 48 nucleotides, or from 38 nucleotides to 47 nucleotides, or from 39 nucleotides to 46 nucleotides, or from 40 nucleotides to 45 nucleotides, or from 41 nucleotides to 44 nucleotides, or 15 nucleotides, or 16 nucleotides, or 17 nucleotides, or 18 nucleotides, or 19 nucleotides, or 20 nucleotides, or 21 nucleotides, or 22 nucleotides, or 23 nucleotides, or 24 nucleotides, or 25 nucleotides, or 26 nucleotides, or 27 nucleotides, or 28 nucleotides, or 29 nucleotides, or 30 nucleotides, or 31 nucleotides, or 32 nucleotides, or 33 nucleotides, or 34 nucleotides, or 35 nucleotides, or 36 nucleotides, or 37 nucleotides, or 38 nucleotides, or 39 nucleotides, or 40 nucleotides, or 41 nucleotides, or 42 nucleotides, or 43 nucleotides, or 44 nucleotides, or 45 nucleotides, or 46 nucleotides, or 47 nucleotides, or 48 nucleotides, or 49 nucleotides, or 50 nucleotides, or 51 nucleotides, or 52 nucleotides, or 53 nucleotides, or 54 nucleotides, or 55 nucleotides, or 56 nucleotides, or 57 nucleotides, or 58 nucleotides, or 59 nucleotides, or 60 nucleotides, or 61 nucleotides, or 62 nucleotides, or 63 nucleotides, or 64 nucleotides, or 65 nucleotides, or 66 nucleotides, or 67 nucleotides, or 68 nucleotides, or 69 nucleotides, or 70 nucleotides, wherein optionally the length of the target-specific sequence is from 17 nucleotides to 40 nucleotides.

9. The method of any one of the preceding claims, wherein the barcode sequence is an oligonucleotide comprising 8 to 30 random nucleotides or an oligonucleotide comprising 10 random nucleotides.

10. The method of any one of the preceding claims, wherein the amount of nucleic acid within the biological sample is from 1ng to 300ng, or from 10ng to 290ng, or from 20ng to 280ng, or from 30ng to 270ng, or from 40ng to 260ng, or from 50ng to 250ng, or from 60ng to 240ng, or from 70ng to 230ng, or from 80ng to 220ng, or from 90ng

to 210ng, or from 100ng to 200ng, or from 110ng to 190ng, or from 120ng to 180ng, or from 130ng to 170ng, or from 140ng to 160ng, or about 1ng, or about 2ng, or about 2.5ng, or about 5ng, or about 10ng, or about 20ng, or about 30ng, or about 40ng, or about 50ng, or about 60ng, or about 70ng, or about 80ng, or about 90ng, or about 100ng, or about 110ng, or about 120ng, or about 130ng, or about 140ng, or about 150ng, or about 160ng, or about 170ng, or about 180ng, or about 190ng, or about 200ng, or about 210ng, or about 220ng, or about 230ng, or about 240ng, or about 250ng, or about 260ng, or about 270ng, or about 280ng, or about 290ng, or about 300ng..

11. The method of any one of the preceding claims, wherein the plurality of multiplexed PCR reactions performed on the nucleic acid in step (b) comprises a first PCR step comprising 3 to 15 PCR cycles and the amplification of the plurality of amplicons in the purified mixture as defined in step (d) comprises a second PCR step comprising 4 to 32 PCR cycles; wherein optionally the first PCR step comprises 3 to 5 PCR cycles; wherein optionally the second PCR step comprises 14 to 16 PCR cycles; and wherein the number of PCR cycles in the first PCR step and the second PCR step are independent of each other.

12. The method of any one of the preceding claims, wherein the mapping in steps (g) and (j) and the sequence alignment in step (i) are performed using bioinformatic algorithms, wherein optionally the algorithm used for the mapping in steps (g) and (j) is bwa-mem, and wherein optionally the algorithm used for the sequence alignment in step (i) is MAFFT.

13. The method of any one of the preceding claims, wherein each consensus cluster as defined in step (h) comprises at least 1 family member.

14. The method of any one of the preceding claims, wherein prior to performing step (i), consensus clusters with fewer than 5 family members are removed from downstream analysis, wherein optionally consensus clusters with fewer than 4 family members are removed from downstream analysis, or consensus clusters with fewer than 3 family members are removed from downstream analysis, or consensus clusters with fewer than 2 family members are removed from downstream analysis.

15. The method of any one of the preceding claims, wherein the first reference genome as defined in step (g) and the second reference genome as defined in step (j) comprise identical gene sequences.

16. The method of any one of the preceding claims, wherein prior to performing step (g), (I) bases having poor quality scores are removed, and (II) universal indexed adapter primers and barcode sequences are trimmed.

17. The method of any one of the preceding claims, wherein the biological sample is obtained from a subject having and/or suspected of having a disease, and wherein optionally the disease is cancer or an infectious disease, optionally wherein the cancer is selected from the group consisting of leukemia, lung cancer, colorectal cancer, breast cancer, pancreatic cancer, prostate cancer, nasopharyngeal cancer, liver cancer, cholangiocarcinoma, esophageal cancer, urothelial cancer, and gastrointestinal cancer.

18. The method of claim 17, wherein the infectious disease is viral infection or bacterial infection.