CLAIMS

1. A method for enriching for a nucleic acid sequence of interest in a sample comprising nucleic acids, the method comprising:

a. fragmenting nucleic acids in the sample comprising the nucleic acids, thereby generating nucleic acid fragments, wherein the nucleic acid fragments comprise the nucleic acid sequence of interest, wherein the nucleic acid fragments are single-stranded or double-stranded;

b. ligating a first adaptor sequence to 5' ends of the nucleic acid fragments, thereby generating nucleic acid fragments comprising the ligated first adaptor sequence on the 5' ends of the nucleic acid fragments;

c. denaturing the nucleic acid fragments, thereby generating single-stranded nucleic acid fragments with the first adaptor sequence at the 5' ends, if the nucleic acid fragments comprising the ligated first adaptor sequence are double-stranded;

d. annealing one or more oligonucleotides to the nucleic acid sequence of interest in the nucleic acid fragments comprising the ligated first adaptor sequence, wherein the one or more oligonucleotides comprise a 3' portion with at least 10 bases that are complementary to the nucleic acid sequence of interest and a 5' tail portion comprising a second adaptor sequence that is non-complementary to the nucleic acid sequence of interest;

e. extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragments comprising the ligated first adaptor sequence with a polymerase, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the ligated first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end; and

f. amplifying the one or more oligonucleotide extension products using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals to the complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest; and

g. sequencing the enriched nucleic acid sequence of interest by massively parallel sequencing.

2. The method of claim 1, further comprising adhering the amplified extension products generated in step f to a flow cell before step g.

3. The method of claim 1, wherein the nucleic acid sequence of interest comprises genomic DNA, RNA, or cDNA.

4. The method of claim 1, wherein the first adaptor sequence and the second adaptor sequence are distinct from each other.

5. The method of claim 1, wherein the first adaptor sequence and/or the second adaptor sequence comprise barcode sequence.

6. The method of claim 1, wherein the one or more oligonucleotides comprise a 3' portion that is complementary to a different nucleic acid sequence of interest in the nucleic acid fragments.

7. The method of claim 1, wherein the nucleic acid fragments are double stranded.

8. The method of claim 1, wherein the 3' portion of the one or more oligonucleotides comprises a random sequence.

9. The method of claim 1, wherein the first adaptor sequence is a partial duplex adaptor.

10. The method of claim 9, wherein the partial duplex adaptor comprises a long strand and wherein the partial duplex adaptor comprises a second strand, wherein the second strand is a short strand.

11. The method of claim 1, wherein the first adaptor sequence is in an adaptor, wherein the adaptor comprises a ligation strand and a non-ligation strand, and wherein the ligation strand ligates to the 5' ends of the nucleic acid fragments and the non-ligation strand does not ligate to a 3' end of the nucleic acid fragments.

12. The method of claim 1, wherein the 3' portion of each of the one or more oligonucleotides is designed to hybridize to the nucleic acid sequence of interest.

13. The method of claim 1, wherein the nucleic acid fragments are single-stranded.

14. The method of claim 1, wherein the sequencing comprises use of four labelled reversible terminators.

15. The method of claim 1, wherein the sequencing comprises semiconductor sequencing.