of polynucleotides collectively comprising a single exon sequence. Further provided herein are methods wherein the at least 700,000 polynucleotides comprises at least 150,000 sets.

[0009a] Provided herein are polynucleotide libraries, the polynucleotide library with controlled stoichiometry comprising at least 5000 polynucleotides, wherein the controlled stoichiometry comprises at least 30 percent of the at least 5000 polynucleotides have a GC percentage from 10 percent to 30 percent or 70 percent to 90 percent such that, following hybridization with genomic fragments and sequencing of the hybridized genomic fragments, the polynucleotide library provides for at least 30 fold read depth of at least 90 percent of the bases of the genomic fragments under conditions for up to a 55 fold theoretical read depth for the bases of the genomic fragments.

[0009b] Provided herein are polynucleotide libraries with controlled stoichiometry, the polynucleotide library comprising at least 5000 polynucleotides, wherein each of the polynucleotides is about 20 to 200 bases in length, wherein the plurality of polynucleotides encode sequences from each exon for at least 1000 preselected genes, wherein each polynucleotide comprises a molecular tag, wherein the controlled stoichiometry comprises at least 30 percent of the at least 5000 polynucleotides have a GC percentage from 10 percent to 30 percent or 70 percent to 90 percent such that, following hybridization with genomic fragments and sequencing of the hybridized genomic fragments, the polynucleotide library provides for at least 30 fold read depth of at least 90 percent of the bases of the genomic fragments under conditions for up to a 55 fold theoretical read depth for the bases of the genomic fragments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **Figure 1A** depicts a schematic workflow, including application of a first polynucleotide library, measuring bias from the application output, designing and synthesizing a second controlled stoichiometry polynucleotide library, and application of the second polynucleotide library to produce a desired representation output.

[0011] **Figure 1B** depicts a schematic for enriching target polynucleotides with a target binding polynucleotide library.

[0012] **Figure 1C** depicts an exemplary workflow for enrichment and sequencing of a nucleic acid sample.

[0013] **Figure 2** depicts a schematic for generation of polynucleotide libraries from cluster amplification.

[0014] **Figure 3A** depicts a pair of polynucleotides for targeting and enrichment. The polynucleotides comprise complementary target binding (insert) sequences, as well as primer binding sites.

[0015] **Figure 3B** depicts a pair of polynucleotides for targeting and enrichment. The polynucleotides comprise complementary target sequence binding (insert) sequences, primer binding sites, and non-target sequences**.**

[0016] **Figure 4A** depicts a polynucleotide binding configuration to a target sequence of a larger polynucleotide. The target sequence is shorter than the polynucleotide binding region, and the polynucleotide binding region (or insert sequence) is offset relative to the target sequence, and also binds to a portion of adjacent sequence.

[0017] **Figure 4B** depicts a polynucleotide binding configuration to a target sequence of a larger polynucleotide. The target sequence length is less than or equal to the polynucleotide binding region, and the polynucleotide binding region is centered with the target sequence, and also binds to a portion of adjacent sequence**.**

[0018] **Figure 4C** depicts a polynucleotide binding configuration to a target sequence of a larger polynucleotide. The target sequence is slightly longer than the polynucleotide binding region, and the polynucleotide binding region is centered on the target sequence with a buffer region on each side.

CLAIMS

WHAT IS CLAIMED IS:

1. A polynucleotide library, the polynucleotide library with controlled stoichiometry comprising at least 5000 polynucleotides, wherein the controlled stoichiometry comprises at least 30 percent of the at least 5000 polynucleotides have a GC percentage from 10 percent to 30 percent or 70 percent to 90 percent such that, following hybridization with genomic fragments and sequencing of the hybridized genomic fragments, the polynucleotide library provides for at least 30 fold read depth of at least 90 percent of the bases of the genomic fragments under conditions for up to a 55 fold theoretical read depth for the bases of the genomic fragments.
2. The polynucleotide library of claim 1, wherein the polynucleotide library provides for at least 30 fold read depth of at least 95 percent of the bases of the genomic fragments under conditions for up to a 55 fold theoretical read depth for the bases of the genomic fragments.
3. The polynucleotide library of claim 1, wherein the polynucleotide library provides for at least 30 fold read depth of at least 98 percent of the bases of the genomic fragments under conditions for up to a 55 fold theoretical read depth for the bases of the genomic fragments.
4. The polynucleotide library of claim 1, wherein the polynucleotide library provides for at least 90 percent unique reads for the bases of the genomic fragments.
5. The polynucleotide library of claim 1, wherein the polynucleotide library provides for at least 95 percent unique reads for the bases of the genomic fragments.
6. The polynucleotide library of claim 1, wherein the polynucleotide library provides for at least 90 percent of the bases of the genomic fragments having a read depth within about 1.5 times the mean read depth.
7. The polynucleotide library of claim 1, wherein the polynucleotide library provides for at least 95 percent of the bases of the genomic fragments having a read depth within about 1.5 times the mean read depth.
8. The polynucleotide library of claim 1, wherein the polynucleotide library provides for at least 90 percent of the genomic fragments having a GC percentage from 10 percent to 30 percent or 70 percent to 90 percent having a read depth within about 1.5x of the mean read depth.

9. The polynucleotide library of claim 1, wherein the polynucleotide library provides for at least about 80 percent of the genomic fragments having a repeating or secondary structure sequence percentage from 10 percent to 30 percent or 70 percent to 90 percent having a read depth within about 1.5x of the mean read depth.

10. The polynucleotide library of claim 1, wherein each of the genomic fragments are about 100 bases to about 500 bases in length.

11. The polynucleotide library of claim 1, wherein at least about 80 percent of the at least 5000 polynucleotides are represented in an amount within at least about 1.5 times the mean representation for the polynucleotide library.

12. The polynucleotide library of claim 1, wherein at least about 15 percent of the at least 5000 polynucleotides comprise polynucleotides having a repeating or secondary structure sequence percentage from 10 percent to 30 percent or 70 percent to 90 percent.

13. The polynucleotide library of claim 1, wherein the at least 5000 polynucleotides encode for at least 1000 genes.

14. The polynucleotide library of claim 1, wherein the polynucleotide library comprises at least 100,000 polynucleotides.

15. The polynucleotide library of claim 1, wherein the polynucleotide library comprises at least 700,000 polynucleotides.

16. The polynucleotide library of claim 1, wherein the at least 5000 polynucleotides comprise at least one exon sequence.

17. The polynucleotide library of claim 15, wherein the at least 700,000 polynucleotides comprise at least one set of polynucleotides collectively comprising a single exon sequence.

18. The polynucleotide library of claim 17, wherein the at least 700,000 polynucleotides comprises at least 150,000 sets.

19. A polynucleotide library with controlled stoichiometry, the polynucleotide library comprising at least 5000 polynucleotides, wherein each of the polynucleotides is about 20 to 200 bases in length, wherein the plurality of polynucleotides encode sequences from each exon for at least 1000 preselected genes, wherein each polynucleotide comprises a molecular tag, wherein the controlled stoichiometry comprises at least 30 percent of the at least 5000 polynucleotides have a GC percentage from 10 percent to 30 percent or 70 percent to 90 percent such that, following hybridization with genomic fragments and

sequencing of the hybridized genomic fragments, the polynucleotide library provides for at least 30 fold read depth of at least 90 percent of the bases of the genomic fragments under conditions for up to a 55 fold theoretical read depth for the bases of the genomic fragments.

20. The polynucleotide library of claim 19, wherein the polynucleotide library provides for at least 30 fold read depth of at least 95 percent of the bases of the genomic fragments under conditions for up to a 55 fold theoretical read depth for the bases of the genomic fragments.

21. The polynucleotide library of claim 19, wherein the polynucleotide library provides for at least 30 fold read depth of at least 98 percent of the bases of the genomic fragments under conditions for up to a 55 fold theoretical read depth for the bases of the genomic fragments.

22. The polynucleotide library of claim 19, wherein the polynucleotide library provides for at least 90 percent unique reads for the bases of the genomic fragments.

23. The polynucleotide library of claim 1, wherein the fragments are sequenced by a method comprising sequencing by synthesis.

24. The polynucleotide library of claim 23, wherein the fragments are sequenced on an Illumina Miseq sequencing instrument.

25. The polynucleotide library of claim 1, wherein the total number of sequencing reads is at least 49.3 million.

26. The polynucleotide library of claim 1, wherein the polynucleotides are configured to hybridize to genomic fragments comprising at least 33.2 million bases.

27. The polynucleotide library of claim 1, wherein the at least 5000 polynucleotides comprise sequences encoding for multiple exons.