WHAT IS CLAIMED IS:

1. A method of analyzing a biological sample comprising a plurality of nucleic acid molecules that are cell-free, the method comprising:

for each nucleic acid molecule of the plurality of nucleic acid molecules:

ligating a first hairpin adapter to a first strand of the nucleic acid molecule and a second strand of the nucleic acid molecule at a first end of the nucleic acid molecule, wherein the first hairpin adapter comprises a first sequence identifier that identifies a first length of zero or more nucleotides at a first terminus of the first hairpin adapter having no complementary portion at a second terminus of the first hairpin adapter, and

ligating a second hairpin adapter to the first strand and the second strand at a second end of the nucleic acid molecule, wherein the second hairpin adapter comprises a second sequence identifier that identifies a second length of zero or more nucleotides at a first terminus of the second hairpin adapter having no complementary portion at a second terminus of the first hairpin adapter, thereby generating a plurality of ligated nucleic acid molecules;

performing rolling circle amplification on a first subset of the plurality of ligated nucleic acid molecules to form a plurality of concatemers; and

sequencing each concatemer of the plurality of concatemers to identify the respective first sequence identifier and the respective second sequence identifier.

2. The method of claim 1, wherein sequencing occurs simultaneously with performing rolling circle amplification.

3. The method of claim 1, further comprising:

determining first lengths of overhangs present at the first ends of nucleic acid molecules of the first subset of the plurality of nucleic acid molecules using the first sequence identifiers, and

determining second overhangs present at the second ends of nucleic acid molecules of the first subset of the plurality of nucleic acid molecules using the second sequence identifiers.

4. The method of claim 1, further comprising:

adding exonucleases to the plurality of ligated nucleic acid molecules to remove a second subset of the plurality of ligated nucleic acid molecules, wherein:

the first subset of the plurality of nucleic acid molecules does not include any of the nucleic acid molecules in the second subset,

for each nucleic acid molecule of the second subset, either:

the respective nucleic acid molecule is not completely hybridized to the respective first hairpin adapter or the respective second hairpin adapter, or

the respective first hairpin adapter or the respective second hairpin adapter is not completely hybridized to the respective nucleic acid molecule.

5. The method of claim 1, further comprising:

determining first sequence end motifs present at the first ends of nucleic acid molecules of the first subset of the plurality of nucleic acid molecules using the first sequence identifiers; and

determining second sequence end motifs present at the second ends of nucleic acid molecules of the first subset of the plurality of nucleic acid molecules using the second sequence identifiers.

6. The method of claim 1, further comprising:

determining whether a 5' strand or a 3' strand overhangs the other for each nucleic acid molecule having an overhang at the first end of the first subset using the respective first sequence identifier, and

determining whether a 5' strand or a 3' strand overhangs the other for each nucleic acid molecule having an overhang at the second end of the first subset using the respective second sequence identifier.

7. The method of any one of claims 1 to 6, wherein:

the biological sample is obtained from a female subject pregnant with a fetus,

the method further comprising:

selecting reads corresponding to a subset of the plurality of nucleic acid molecules having the 5’ strand or the 3’ strand overhanging the other end, and

analyzing the subset of nucleic acid molecules for a characteristic of the fetus.

8. The method of claim 1, wherein:

each first hairpin adapter of a plurality of first hairpin adapters comprises a first cleavage site, and

each second hairpin adapter of a plurality of second hairpin adapters comprises a second cleavage site,

the method further comprising:

cleaving each concatemer of the plurality of concatemers at a respective first cleavage site and at a respective second cleavage site.

9. The method of claim 1, wherein each nucleic acid molecule of a second portion of the first subset has the respective first strand even with the respective second strand at the respective first end.

10. The method of claim 1, wherein:

each nucleic acid molecule of a second portion of the first subset has the respective second strand overhanging the respective first strand at the respective first end,

the respective first strand is the 5’ strand, and

the respective second strand is the 3’ strand.

11. A method of analyzing a biological sample comprising a plurality of nucleic acid molecules that are cell-free, the method comprising:

for each nucleic acid molecule of the plurality of nucleic acid molecules:

ligating a first hairpin adapter to a first strand of the nucleic acid molecule and a second strand of the nucleic acid molecule at a first end of the nucleic acid molecule, wherein the first hairpin adapter comprises a first sequence identifier that identifies a first length of zero or more nucleotides at a first terminus of the first hairpin adapter having no complementary portion at a second terminus of the first hairpin adapter, and

ligating a second hairpin adapter to the first strand and the second strand at a second end of the nucleic acid molecule, wherein the second hairpin adapter comprises a second sequence identifier that identifies a first length of zero or more nucleotides at a first terminus of the second hairpin adapter having no complementary portion at a second terminus of the first hairpin adapter, thereby generating a plurality of ligated nucleic acid molecules;

adding exonucleases to the plurality of ligated nucleic acid molecules to remove a first subset of the plurality of ligated nucleic acid molecules, wherein:

for each nucleic acid molecule of the first subset, either:

the respective nucleic acid molecule is not completely hybridized to the respective first hairpin adapter or the respective second hairpin adapter, or

the respective first hairpin adapter or the respective second hairpin adapter is not completely hybridized to the respective nucleic acid molecule,

sequencing each ligated nucleic acid molecule of a second subset of the plurality of ligated nucleic acid molecules to identify the respective first sequence identifier and the respective second sequence identifier, wherein the second subset remains in the biological sample after removing the first subset.

12. The method of claim 11, further comprising:

determining first lengths of overhangs present at the first ends of nucleic acid molecules of the second subset of the plurality of nucleic acid molecules using the first sequence identifiers, and

determining second overhangs present at the second ends of nucleic acid molecules of the second subset of the plurality of nucleic acid molecules using the second sequence identifiers.

13. The method of claim 11, further comprising:

determining first sequence end motifs of overhangs present at the first ends of nucleic acid molecules of the second subset of the plurality of nucleic acid molecules using the first sequence identifiers; and

determining second sequence end motifs of overhangs present at the second ends of nucleic acid molecules of the second subset of the plurality of nucleic acid molecules using the second sequence identifiers.

14. The method of claim 11, further comprising:

determining whether a 5' strand or a 3' strand overhangs the other for each nucleic acid molecule having an overhang at the first end of the second subset using the respective first sequence identifier, and

determining whether a 5' strand or a 3' strand overhangs the other for each nucleic acid molecule having an overhang at the second end of the second subset using the respective second sequence identifier.

15. The method of any one of claims 11 to 14, wherein:

the biological sample is obtained from a female subject pregnant with a fetus,

the method further comprising:

selecting reads corresponding to a subset of a plurality of nucleic acid molecules having the 5' strand or the 3' strand overhanging the other end, and

analyzing the subset of nucleic acid molecules for a characteristic of the fetus.

16. A method of analyzing a biological sample comprising a plurality of nucleic acid molecules that are cell-free, the biological sample being obtained from an individual, each nucleic acid molecule of the plurality of nucleic acid molecules being double-stranded with a first strand and a second strand, at least some of the nucleic acid molecules of the plurality of nucleic acid molecules have nucleotides on one strand that having no complementary portion on the other strand, the method comprising:

for each nucleic acid molecule of the plurality of nucleic acid molecules:

determining a first sequence end motif of a strand at a first end of the nucleic acid molecule, wherein the first end is the 3' end for the strand;

determining a first amount of nucleic acid molecules having the first sequence end motif at the first end;

generating a value of the end motif parameter using the first amount;

comparing the value of the end motif parameter to a reference value; and

determining a level of a condition of the individual using the comparison.

17. The method of claim 16, further comprising:

for each nucleic acid molecule of the plurality of nucleic acid molecules:

determining a second sequence end motif of the strand at a second end of the nucleic acid molecule,

wherein:

the first amount is of nucleic acid molecules having the first sequence end motif at the first end and the second sequence end motif at the second end.

18. The method of claim 16, wherein:

the strand is a first strand,

the end motif parameter is a first end motif parameter, and

the reference value is a first reference value,

the method further comprising:

for each nucleic acid molecule of the plurality of nucleic acid molecules:

determining a second sequence end motif of a second strand at a second end of the nucleic acid molecule,

determining a second amount of nucleic acid molecules having the second sequence end motif at the second end,

generating a value of a second end motif parameter using the second amount,

comparing the value of the second end motif parameter to a second reference value, and

determining the level of the condition using the comparison.

19. The method of any one of claims 16 to 18, further comprising:

for each nucleic acid molecule of the plurality of nucleic acid molecules:

measuring a first strand-specific classification of the first end of the nucleic acid molecule, the strand-specific classification indicating whether the first strand or the second strand overhangs the other;

wherein determining the first amount comprises determining the first amount of nucleic acid molecules having the first combination and the first strand-specific classification.

20. The method of claim 19, wherein the first strand-specific classification is that the 3' strand overhangs the 5' strand.

21. The method of claim 19, further comprising:

for each nucleic acid molecule of the plurality of nucleic acid molecules:

measuring a second strand-specific classification of the second end of the nucleic acid molecule;

wherein determining the first amount comprises determining the first amount of nucleic acid molecules having the first combination, the first strand-specific classification, and the second strand-specific classification.

22. A method of enriching a biological sample for clinically-relevant DNA, the biological sample comprising a plurality of nucleic acid molecules that are cell-free, the plurality of nucleic acid molecules including the clinically-relevant DNA and other DNA, each nucleic acid molecule of the plurality of nucleic acid molecules being double-stranded with a first strand and a second strand, the method comprising:

for each nucleic acid molecule of the plurality of nucleic acid molecules:

measuring a first strand-specific classification of a first end of the nucleic acid molecule, a strand-specific classification indicating whether the first strand or the second strand overhangs the other strand; and

selecting reads corresponding to a subset of nucleic acid molecules having the first strand-specific classification to form an enriched sample.

23. The method of claim 22, wherein the subset of nucleic acid molecules has the first strand-specific classification of the first strand overhanging the second strand.

24. The method of claim 23, wherein the first strand is the 3' strand.

25. The method of claim 22, wherein the first strand-specific classification comprises the first strand overhanging the second strand and the second strand overhanging the first strand.

26. The method of claim 22, further comprising:

for each nucleic acid molecule of the plurality of nucleic acid molecules:

measuring a second strand-specific classification of the second end of the nucleic acid molecule,

wherein the subset of nucleic acid molecules has the second strand-specific classification.

27. The method of claim 26, wherein:

the first strand-specific classification of the subset of nucleic acid molecules indicates the first strand of the nucleic acid molecule overhangs the second strand, and

the second strand-specific classification of the subset of nucleic acid molecules indicates the second strand of the nucleic acid molecule overhangs the first strand.

28. The method of claim 22, wherein the clinically-relevant DNA is tumor DNA.

29. The method of claim 22, wherein the biological sample is obtained from a female subject pregnant with a fetus, and the clinically-relevant DNA is fetal DNA.

30. The method of claim 28 or 29, further comprising analyzing the subset of nucleic acid molecules to determine a classification of a level of a disorder.

31. The method of claim 22, further comprising analyzing the subset of nucleic acid molecules to determine a chromosomal aberration or a fetal haplotype.

32. The method of any one of claims 22 to 31, further comprising:

for each nucleic acid molecule of the plurality of nucleic acid molecules:

determining a first sequence end motif at the first end of the nucleic acid molecule,

wherein selecting the reads corresponding to the subset of nucleic acid molecules comprises selecting reads corresponding to nucleic acid molecules having the first sequence end motif.

33. The method of claim 32, further comprising:

for each nucleic acid molecule of the plurality of nucleic acid molecules:

determining a second sequence end motif at the second end of the nucleic acid molecule,

wherein selecting the reads corresponding to the subset of nucleic acid molecules comprises selecting reads corresponding to nucleic acid molecules having the second sequence end motif.

34. The method of claim 32 or 33, further comprising:

determining a first amount of the reads;

determining a first parameter using the first amount of the reads; and

determining a characteristic of the biological sample using the first parameter.

35. The method of claim 34, wherein the characteristic of the biological sample is a fractional concentration of clinically-relevant DNA molecules in the biological sample.

36. The method of claim 34, wherein the first parameter is determined using the first amount and another amount of sequence reads.

37. The method of claim 34, wherein the characteristic of the biological sample is a level of abnormality in the biological sample.

38. The method of any one of the above claims, wherein each nucleic acid molecule of the plurality of nucleic acid molecules has a size greater than a cutoff size.

39. The method of any one of the above claims, wherein each nucleic acid molecule of the plurality of nucleic acid molecules has a size less than a cutoff size.

40. The method of claim 38 or 39, further comprising measuring the size of each nucleic acid molecule by aligning subsequences corresponding to the ends of the respective nucleic acid molecule with a reference genome.

41. The method of any one of the above claims, wherein the condition is cancer, HCC, an autoimmune disease, or a pregnancy-associated disorder.

42. The method of any one of the above claims, wherein the reference value is determined from one or more subjects having a certain level of the condition or one or more healthy subjects.

43. A computer product comprising a non-transitory computer readable medium storing a plurality of instructions that when executed control a computer system to perform the method of any of the above claims.

44. A system comprising:

the computer product of claim 43; and

one or more processors for executing instructions stored on the computer readable medium.