

What is claimed is:

1. A method for enriching for multiple genomic regions, comprising:
 - (a) bringing a predetermined amount of nucleic acid from a sample in contact with a bait mixture comprising:
 - (i) a first bait set that selectively hybridizes to a first set of genomic regions of the nucleic acid from the sample, which first bait set is provided at a first concentration that is less than a saturation point of the first bait set, and
 - (ii) a second bait set that selectively hybridizes to a second set of genomic regions of the nucleic acid from the sample, which second bait set is provided at a second concentration that is at or above a saturation point of the second bait set; and
 - (b) enriching the nucleic acid from the sample for the first set of genomic regions and the second set of genomic regions, thereby producing an enriched nucleic acid.
2. The method of claim 1, wherein the second bait set has a saturation point that is larger than substantially all of the saturation points associated with baits in the second bait set when a bait of the second bait set is subjected to a titration curve generated by
 - (i) measuring capture efficiency of a bait of the second bait set as a function of the concentration of the bait, and
 - (ii) identifying an inflection point within the titration curve, thereby identifying a saturation point associated with the bait.
3. The method of claim 1, wherein the saturation point of the first bait set is selected such that an observed capture efficiency increases by less than 10% at a concentration of the bait twice that of the first concentration.
4. The method of claim 1, wherein the first bait set or the second bait set selectively enrich for one or more nucleosome-associated regions of a genome, the nucleosome-associated regions comprising genomic regions having one or more genomic base positions with differential nucleosomal occupancy, wherein the differential nucleosomal occupancy is characteristic of a cell or tissue type of origin or disease state.
5. The method of claim 1, further comprising:
 - (c) sequencing the enriched nucleic acid to produce a plurality of sequence reads.
6. The method of claim 5, further comprising:

(d) producing an output comprising nucleic acid sequences representative of the nucleic acid from the sample.

7. The method of claim 1, wherein the saturation point of the second bait set is selected such that an observed capture efficiency increases by less than 10% at a concentration of the bait twice that of the second concentration.

8. A method comprising:

(a) providing a plurality of bait mixtures, wherein each of the plurality of bait mixtures comprises a first bait set that selectively hybridizes to a first set of genomic regions and a second bait set that selectively hybridizes to a second set of genomic regions, wherein the first bait set is at different concentrations across the plurality of bait mixtures and the second bait set is at the same concentration across the plurality of bait mixtures;

(b) contacting each of the plurality of bait mixtures with a nucleic acid sample to capture nucleic acids from the nucleic acid sample with the first bait set and the second bait set, wherein the second bait set in each bait mixture is provided at a first concentration that is at or above a saturation point of the second bait set, wherein nucleic acids from the nucleic acid sample are captured by the first bait set and the second bait set;

(c) sequencing a portion of the nucleic acids captured with each bait mixture to produce sets of sequence reads within an allocated number of sequence reads;

(d) determining the read depth of sequence reads for the first bait set and the second bait set for each bait mixture; and

(e) identifying at least one bait mixture that provides read depths for the second set of genomic regions; wherein the read depths for the second set of genomic regions provides a sensitivity of detecting of a genetic variant of at least 0.0001% minor allele frequency (MAF).

9. The method of claim 8, wherein the second bait set has a saturation point when subjected to titration, which titration comprises generating a titration curve comprising:

(i) measuring capture efficiency of the second bait set as a function of the concentration of the baits; and

(ii) identifying an inflection point within the titration curve, thereby identifying a saturation point associated with the second bait set.

10. The method of claim 9, wherein the saturation point is selected such that an observed capture efficiency increases by less than 10% at a concentration of the bait set twice that of the first concentration.

11. The method of claim 8, wherein the first bait set or the second bait set selectively enrich for one or more nucleosome-associated regions of a genome, the nucleosome-associated regions comprising genomic regions having one or more genomic base positions with differential nucleosomal occupancy, wherein the differential nucleosomal occupancy is characteristic of a cell or tissue type of origin or disease state.

12. The method of claim 8, wherein the first set of genomic regions comprises one or more actionable mutations, wherein the one or more actionable mutations comprise one or more of:

- (i) druggable mutations,
- (ii) mutations for therapeutic monitoring,
- (iii) disease specific mutations,
- (iv) tissue specific mutations,
- (v) cell type specific mutations,
- (vi) resistance mutations, and
- (vii) diagnostic mutations.

13. The method of claim 8, wherein the first genomic regions comprise at least a portion of each of at least 5 genes selected from the following: Point Mutations (SNVs) AKT1, ALK, APC, AR, ARAF, ARID1A, ATM, BRAF, BRCA1, BRCA2, CCND1, CCND2, CCNE1, CDH1, CDK4, CDK6, CDKN2A, CDKN2B, CTNNB1, EGFR, ERBB2, ESR1, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, GATA3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KIT, KRAS, MAP2K1, MAP2K2, MET, MLH1, MPL, MYC, NF1, NFE2L2, NOTCH1, NPM1, NRAS, NTRK1, PDGFRA, PIK3CA, PTEN, PTPN11, RAF1, RB1, RET, RHEB, RHOA, RIT1, ROS1, SMAD4, SMO, SRC, STK11, TERT, TP53, TSC1, VHL; Amplifications (CNVs) AR, BRAF, CCND1, CCND2, CCNE1, CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, KIT, KRAS, MET, MYC, PDGFRA, PIK3CA, RAF1; Fusions ALK, FGFR2, FGFR3, NTRK1, RET, ROS1; Indels EGFR (exons 19 & 20), ERBB2 (exons 19 & 20), MET (exon 14 skipping), Point Mutations (SNVs) AKT1, ALK, APC, AR, ARAF, ARID1A, ATM, BRAF, BRCA1, BRCA2, CCND1, CCND2, CCNE1, CDH1, CDK4, CDK6, CDKN2A, DDR2, CTNNB1, EGFR, ERBB2, ESR1, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, GATA3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KIT, KRAS, MAP2K1, MAP2K2, MET, MLH1, MPL, MYC, NF1, NFE2L2, NOTCH1, NPM1, NRAS, NTRK1, PDGFRA, PIK3CA, PTEN, PTPN11, RAF1, RB1, RET, RHEB, RHOA, RIT1, ROS1, SMAD4, SMO, MAPK1, STK11, TERT, TP53, TSC1, VHL, MAPK3, MTOR, NTRK3; Amplifications (CNVs) AR, BRAF, CCND1, CCND2, CCNE1, CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, KIT, KRAS, MET, MYC, PDGFRA, PIK3CA, RAF1; Fusions ALK, FGFR2, FGFR3, NTRK1, RET, ROS1; Indels EGFR (exons 19 & 20), ERBB2 (exons 19 & 20), MET (exon 14 skipping), ATM, APC, ARID1A, BRCA1, BRCA2, CDH1, CDKN2A, GATA3, KIT, MLH1, MTOR, NF1, PDGFRA, PTEN, RB1, SMAD4, STK11, TP53, TSC1, VHL.

14. The method of claim 8, wherein the first genomic regions have a size between about 25 kilobases to 1,000 kilobases and a read depth of between 1,000 counts/base and 50,000 counts/base.

15. The method of claim 8, wherein the second set of genomic regions comprises one or more actionable mutations, wherein the one or more actionable mutations comprise one or more of:

- (i) druggable mutations,
- (ii) mutations for therapeutic monitoring,
- (iii) disease specific mutations,
- (iv) tissue specific mutations,
- (v) cell type specific mutations,
- (vi) resistance mutations, and
- (vii) diagnostic mutations.

16. The method of claim 8, wherein the second genomic regions comprise at least a portion of each of at least 5 genes selected from the following: Point Mutations (SNVs) AKT1, ALK, APC, AR, ARAF, ARID1A, ATM, BRAF, BRCA1, BRCA2, CCND1, CCND2, CCNE1, CDH1, CDK4, CDK6, CDKN2A, CDKN2B, CTNNB1, EGFR, ERBB2, ESR1, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, GATA3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KIT, KRAS, MAP2K1, MAP2K2, MET, MLH1, MPL, MYC, NF1, NFE2L2, NOTCH1, NPM1, NRAS, NTRK1, PDGFRA, PIK3CA, PTEN, PTPN11, RAF1, RB1, RET, RHEB, RHOA, RIT1, ROS1, SMAD4, SMO, SRC, STK11, TERT, TP53, TSC1, VHL; Amplifications (CNVs) AR, BRAF, CCND1, CCND2, CCNE1, CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, KIT, KRAS, MET, MYC, PDGFRA, PIK3CA, RAF1; Fusions ALK, FGFR2, FGFR3, NTRK1, RET, ROS1; Indels EGFR (exons 19 & 20), ERBB2 (exons 19 & 20), MET (exon 14 skipping), Point Mutations (SNVs) AKT1, ALK, APC, AR, ARAF, ARID1A, ATM, BRAF, BRCA1, BRCA2, CCND1, CCND2, CCNE1, CDH1, CDK4, CDK6, CDKN2A, DDR2, CTNNB1, EGFR, ERBB2, ESR1, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, GATA3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KIT, KRAS, MAP2K1, MAP2K2, MET, MLH1, MPL, MYC, NF1, NFE2L2, NOTCH1, NPM1, NRAS, NTRK1, PDGFRA, PIK3CA, PTEN, PTPN11, RAF1, RB1, RET, RHEB, RHOA, RIT1, ROS1, SMAD4, SMO, MAPK1, STK11, TERT, TP53, TSC1, VHL, MAPK3, MTOR, NTRK3; Amplifications (CNVs) AR, BRAF, CCND1, CCND2, CCNE1, CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, KIT, KRAS, MET, MYC, PDGFRA, PIK3CA, RAF1; Fusions ALK, FGFR2, FGFR3, NTRK1, RET, ROS1; Indels EGFR (exons 19 & 20), ERBB2 (exons 19 & 20), MET (exon 14 skipping), ATM, APC, ARID1A, BRCA1, BRCA2, CDH1, CDKN2A, GATA3, KIT, MLH1, MTOR, NF1, PDGFRA, PTEN, RB1, SMAD4, STK11, TP53, TSC1, VHL.

17. The method of claim 8, wherein the second genomic regions have a size between about 25 kilobases to 1,000 kilobases and a read depth of between 1,000 counts/base and 50,000 counts/base.