We claim:

1. A method for making a biallelic modification to a genomic target locus in a genome within a cell, comprising:

(I) introducing into a population of cells:

(a) a Cas protein;

(b) a first guide RNA that hybridizes to a first CRISPR RNA recognition sequence within the genomic target locus;

(c) a second guide RNA that hybridizes to a second CRISPR RNA recognition sequence within the genomic target locus; and

(d) a targeting vector comprising a nucleic acid insert flanked by a 5' homology arm that hybridizes to a 5' target sequence within the genomic target locus and a 3' homology arm that hybridizes to a 3' target sequence within the genomic target locus, wherein if the cell is a one-cell stage embryo the targeting vector is no more than 5 kb in length;

wherein the genome comprises a pair of first and second homologous chromosomes comprising the genomic target locus, optionally wherein the first and second CRISPR RNA recognition sequences flank all or part of a coding sequence for a gene; and

wherein the Cas protein cleaves at least one of the first and second CRISPR RNA recognition sequences to generate at least one double-strand break in each of the first and second homologous chromosomes, optionally wherein introducing both the first and second guide RNAs results in increased biallelic modification efficiency compared to introducing either the first guide RNA or second guide RNA alone; and

(II) identifying a cell comprising a modified genomic target locus comprising a deletion and/or an insertion, wherein the identifying comprises performing a quantitative modification-of-allele assay and a retention assay,

wherein the modification-of-allele assay comprises:

(a) a gain-of-allele assay to determine copy number of a nucleic acid insert DNA template in a genomic DNA sample from the cell; and/or

(b) a loss-of-allele assay to determine copy number in the genomic DNA sample of a DNA template within a region of the genomic target locus targeted for deletion, and

wherein the retention assay determines copy number in the genomic DNA sample of a 5’ target sequence DNA template intended to be retained in the modified genomic target locus and/or a 3’ target sequence DNA template intended to be retained in the modified genomic target locus,

wherein the cell is not produced using a process which involves modifying the germ line genetic identity of human beings or which involves use of a human embryo for industrial or commercial purposes, and

wherein the method is not a method for treatment of the human or animal body by therapy or surgery.

2. The method of claim 1, wherein the retention assay determines copy number of the 5’ target sequence DNA template in the genomic DNA sample and the 3’ target sequence DNA template in the genomic DNA sample, and optionally wherein the modification-of-allele assay comprises the loss-of-allele assay and the gain-of-allele assay.

3. The method of claim 2, wherein the nucleic acid insert comprises a selection cassette adjacent to a first homology arm that hybridizes to a first target sequence,

wherein the first homology arm is the 5’ homology arm and the first target sequence is the 5’ target sequence, or wherein the first homology arm is the 3’ homology arm and the first target sequence is the 3’ target sequence,

wherein the identifying comprises:

(a) obtaining DNA from the cell;

(b) exposing the DNA of the cell to a probe that binds within the first target sequence, a probe that binds within the nucleic acid insert, and a probe that binds within a reference gene having a known copy number, wherein each probe generates a detectable signal upon binding;

(c) detecting the signals from the binding of each of the probes; and

(d) comparing the signal from the reference gene probe to the signal from the first target sequence probe to determine a copy number for the first target sequence, and comparing the signal from the reference gene probe to the signal from the nucleic acid insert probe to determine a copy number for the nucleic acid insert,

wherein a nucleic acid insert copy number of one or two and a first target sequence copy number of two indicates targeted insertion of the nucleic acid insert at the genomic target locus, and

wherein a nucleic acid insert copy number of one or more and a first target sequence copy number of three or more indicates a random insertion of the nucleic acid insert at a genomic locus other than the genomic target locus.

4. The method of any preceding claim, wherein:

(a) the Cas protein cleaves the first and second CRISPR RNA recognition sequences in each of the first and second homologous chromosomes to generate at least two double-strand breaks in each of the first and second homologous chromosomes; or

(b) the Cas protein cleaves the first and second CRISPR RNA recognition sequences in at least one of the first and second homologous chromosomes to generate at least two double-strand breaks in at least one of the first and second homologous chromosomes.

5. The method of any preceding claim, wherein step (I) further comprises introducing into the population of cells:

(e) a third guide RNA that hybridizes to a third CRISPR RNA recognition sequence within the genomic target locus; and

(f) a fourth guide RNA that hybridizes to a fourth CRISPR RNA recognition sequence within the genomic target locus,

optionally wherein the first CRISPR RNA recognition sequence is adjacent to the third CRISPR RNA recognition sequence, and the second CRISPR RNA recognition sequence is adjacent to the fourth CRISPR RNA recognition sequence, and

optionally wherein the first and third CRISPR RNA recognition sequences are located near the 5’ end of the genomic target locus and the second and fourth CRISPR RNA recognition sequences are located near the 3’ end of the genomic target locus.

6. The method of claim 5, wherein:

(a) the first CRISPR RNA recognition sequence and the third CRISPR RNA recognition sequence are separated by about 25 bp to about 50 bp, about 50 bp to about 100 bp, about 100 bp to about 150 bp, about 150 bp to about 200 bp, about 200 bp to about 250 bp, about

250 bp to about 300 bp, about 300 bp to about 350 bp, about 350 bp to about 400 bp, about 400 bp to about 450 bp, about 450 bp to about 500 bp, about 500 bp to about 600 bp, about 600 bp to about 700 bp, about 700 bp to about 800 bp, about 800 bp to about 900 bp, about 900 bp to about 1 kb, about 1 kb to about 2 kb, about 2 kb to about 3 kb, about 3 kb to about 4 kb, about 4 kb to about 5 kb, about 5 kb to about 6 kb, about 6 kb to about 7 kb, about 7 kb to about 8 kb, about 8 kb to about 9 kb, about 9 kb to about 10 kb, about 10 kb to about 20 kb, about 20 kb to about 30 kb, about 30 kb to about 40 kb, about 40 kb to about 50 kb, about 50 kb to about 60 kb, about 60 kb to about 70 kb, about 70 kb to about 80 kb, about 80 kb to about 90 kb, or about 90 kb to about 100 kb; and/or

(b) the second CRISPR RNA recognition sequence and the fourth CRISPR RNA recognition sequence are separated by about 25 bp to about 50 bp, about 50 bp to about 100 bp, about 100 bp to about 150 bp, about 150 bp to about 200 bp, about 200 bp to about 250 bp, about 250 bp to about 300 bp, about 300 bp to about 350 bp, about 350 bp to about 400 bp, about 400 bp to about 450 bp, about 450 bp to about 500 bp, about 500 bp to about 600 bp, about 600 bp to about 700 bp, about 700 bp to about 800 bp, about 800 bp to about 900 bp, about 900 bp to about 1 kb, about 1 kb to about 2 kb, about 2 kb to about 3 kb, about 3 kb to about 4 kb, about 4 kb to about 5 kb, about 5 kb to about 6 kb, about 6 kb to about 7 kb, about 7 kb to about 8 kb, about 8 kb to about 9 kb, about 9 kb to about 10 kb, about 10 kb to about 20 kb, about 20 kb to about 30 kb, about 30 kb to about 40 kb, about 40 kb to about 50 kb, about 50 kb to about 60 kb, about 60 kb to about 70 kb, about 70 kb to about 80 kb, about 80 kb to about 90 kb, or about 90 kb to about 100 kb; and/or

(c) the first and third CRISPR RNA recognition sequences are located near the 5’ end of the genomic target locus and the second and fourth CRISPR RNA recognition sequences are located near the 3’ end of the genomic target locus, wherein the first and third CRISPR RNA recognition sequences are separated from the second and fourth CRISPR RNA recognition sequences by about 25 bp to about 50 bp, about 50 bp to about 100 bp, about 100 bp to about 150 bp, about 150 bp to about 200 bp, about 200 bp to about 250 bp, about 250 bp to about 300 bp, about 300 bp to about 350 bp, about 350 bp to about 400 bp, about 400 bp to about 450 bp, about 450 bp to about 500 bp, about 500 bp to about 600 bp, about 600 bp to about 700 bp, about 700 bp to about 800 bp, about 800 bp to about 900 bp, about 900 bp to about 1 kb, about 1 kb to about 5 kb, about 5 kb to about 10 kb, about 10 kb to about 20 kb, about 20 kb to

about 40 kb, about 40 kb to about 60 kb, about 60 kb to about 80 kb, about 80 kb to about 100 kb, about 100 kb to about 150 kb, about 150 kb to about 200 kb, about 200 kb to about 300 kb, about 300 kb to about 400 kb, about 400 kb to about 500 kb, about 500 kb to about 1 Mb, about 1 Mb to about 1.5 Mb, about 1.5 Mb to about 2 Mb, about 2 Mb to about 2.5 Mb, about 2.5 Mb to about 3 Mb, about 3 Mb to about 4 Mb, about 4 Mb to about 5 Mb, about 5 Mb to about 10 Mb, about 10 Mb to about 20 Mb, about 20 Mb to about 30 Mb, about 30 Mb to about 40 Mb, about 40 Mb to about 50 Mb, about 50 Mb to about 60 Mb, about 60 Mb to about 70 Mb, about 70 Mb to about 80 Mb, about 80 Mb to about 90 Mb, or about 90 Mb to about 100 Mb,

optionally wherein the Cas protein cleaves at least two of the first, second, third and fourth CRISPR RNA recognition sequences to generate at least two double-strand breaks in at least one of the first and second homologous chromosomes, optionally wherein the Cas protein cleaves at least two of the first, second, third and fourth CRISPR RNA recognition sequences to generate at least two double-strand breaks in both the first and second homologous chromosomes.

7. The method of any preceding claim, wherein the nucleic acid insert is inserted between the 5’ and 3’ target sequences.

8. The method of any preceding claim, wherein the cell is diploid, and the biallelic modification results in homozygosity, compound heterozygosity, or hemizygosity at the genomic target locus.

9. The method of any preceding claim, wherein the biallelic modification comprises a deletion between the first and second CRISPR RNA recognition sequences in the first homologous chromosome, optionally wherein:

(a) the biallelic modification comprises the deletion between the first and second CRISPR RNA recognition sequences in both the first and second homologous chromosomes; optionally wherein the biallelic modification further comprises insertion of the nucleic acid insert between the 5’ and 3’ target sequences in both the first and second homologous chromosomes;

(b) the deletion between the first and second CRISPR RNA recognition sequences in both the first and second homologous chromosomes, and insertion of the nucleic

acid insert between the 5’ and 3’ target sequences in the first homologous chromosome but not in the second homologous chromosome;

(c) the deletion between the first and second CRISPR RNA recognition sequences in the first homologous chromosome, and disruption of the genomic target locus in the second homologous chromosome, wherein the disruption is from non-homologous end joining (NHEJ)-mediated repair of the at least one double-strand break;

(d) the deletion between the first and second CRISPR RNA recognition sequences in the first homologous chromosome, an insertion of the nucleic acid insert between the 5’ and 3’ target sequences in the first homologous chromosome, and disruption of the genomic target locus in the second homologous chromosome, wherein the disruption is from non-homologous end joining (NHEJ)-mediated repair of the at least one double-strand break;

(e) the deletion between the first and second CRISPR RNA recognition sequences in the first homologous chromosome, and an insertion of the nucleic acid insert between the 5’ and 3’ target sequences in the first homologous chromosome, wherein the nucleic acid insert sequence is homologous or orthologous to the deleted sequence;

(f) the deleted nucleic acid is from about 5 kb to about 10 kb, from about 10 kb to about 20 kb, from about 20 kb to about 40 kb, from about 40 kb to about 60 kb, from about 60 kb to about 80 kb, from about 80 kb to about 100 kb, from about 100 kb to about 150 kb, from about 150 kb to about 200 kb, from about 200 kb to about 300 kb, from about 300 kb to about 400 kb, from about 400 kb to about 500 kb, from about 500 kb to about 1 Mb, from about 1 Mb to about 1.5 Mb, from about 1.5 Mb to about 2 Mb, from about 2 Mb to about 2.5 Mb, or from about 2.5 Mb to about 3 Mb; or

(g) the deleted nucleic acid is at least 20 kb, at least 30 kb, at least 40 kb, at least 50 kb, at least 60 kb, at least 70 kb, at least 80 kb, at least 90 kb, at least 100 kb, at least 110 kb, at least 120 kb, at least 130 kb, at least 140 kb, at least 150 kb, at least 160 kb, at least 170 kb, at least 180 kb, at least 190 kb, at least 200 kb, at least 250 kb, at least 300 kb, at least 350 kb, at least 400 kb, at least 450 kb, or at least 500 kb, at least 550 kb, at least 600 kb, at least 650 kb, at least 700 kb, at least 750 kb, at least 800 kb, at least 850 kb, at least 900 kb, at least 950 kb, at least 1 Mb, at least 1.5 Mb, or at least 2 Mb.

10. The method of any preceding claim, wherein:

(a) the first and second CRISPR RNA recognition sequences are each located

at least 50 bp, at least 100 bp, at least 200 bp, at least 300 bp, at least 400 bp, at least 500 bp, at least 600 bp, at least 700 bp, at least 800 bp, at least 900 bp, at least 1 kb, at least 2 kb, at least 3 kb, at least 4 kb, at least 5 kb, at least 6 kb, at least 7 kb, at least 8 kb, at least 9 kb, at least 10 kb, at least 20 kb, at least 30 kb, at least 40 kb, at least 50 kb, at least 60 kb, at least 70 kb, at least 80 kb, at least 90 kb, or at least 100 kb from both the 5' and 3' target sequences;

(b) the first and second CRISPR RNA recognition sequences are each located more than 50 bp, more than 100 bp, more than 200 bp, more than 300 bp, more than 400 bp, more than 500 bp, more than 600 bp, more than 700 bp, more than 800 bp, more than 900 bp, more than 1 kb, more than 2 kb, more than 3 kb, more than 4 kb, more than 5 kb, more than 6 kb, more than 7 kb, more than 8 kb, more than 9 kb, more than 10 kb, more than 20 kb, more than 30 kb, more than 40 kb, more than 50 kb, more than 60 kb, more than 70 kb, more than 80 kb, more than 90 kb, or more than 100 kb from both the 5' and 3' target sequences; or

(c) the first and second CRISPR RNA recognition sequences are each located between about 50 bp to about 100 bp, about 200 bp to about 300 bp, about 300 bp to about 400 bp, about 400 bp to about 500 bp, about 500 bp to about 600 bp, about 600 bp to about 700 bp, about 700 bp to about 800 bp, about 800 bp to about 900 bp, about 900 bp to about 1 kb, about 1 kb to about 2 kb, about 2 kb to about 3 kb, about 3 kb to about 4 kb, about 4 kb to about 5 kb, about 5 kb to about 10 kb, about 10 kb to about 20 kb, about 20 kb to about 30 kb, about 30 kb to about 40 kb, about 40 kb to about 50 kb, or about 50 kb to about 100 kb from both the 5' and 3' target sequences;

(d) the first and second CRISPR RNA recognition sequences are separated by about 1 kb to about 5 kb, about 5 kb to about 10 kb, about 10 kb to about 20 kb, about 20 kb to about 40 kb, about 40 kb to about 60 kb, about 60 kb to about 80 kb, about 80 kb to about 100 kb, about 100 kb to about 150 kb, about 150 kb to about 200 kb, about 200 kb to about 300 kb, about 300 kb to about 400 kb, about 400 kb to about 500 kb, about 500 kb to about 1 Mb, about 1 Mb to about 1.5 Mb, about 1.5 Mb to about 2 Mb, about 2 Mb to about 2.5 Mb, or about 2.5 Mb to about 3 Mb;

(e) the first and second CRISPR RNA recognition sequences are separated by at least 1 kb, at least 2 kb, at least 3 kb, at least 4 kb, at least 5 kb, at least 10 kb, at least 20 kb, at least 30 kb, at least 40 kb, at least 50 kb, at least 60 kb, at least 70 kb, at least 80 kb, at least 90 kb, at least 100 kb, at least 110 kb, at least 120 kb, at least 130 kb, at least 140 kb, at least 150

kb, at least 160 kb, at least 170 kb, at least 180 kb, at least 190 kb, at least 200 kb, at least 250 kb, at least 300 kb, at least 350 kb, at least 400 kb, at least 450 kb, or at least 500 kb;

(f) the first and second CRISP RNA recognition sequences are separated by about 25 bp to about 50 bp, about 50 bp to about 100 bp, about 100 bp to about 150 bp, about 150 bp to about 200 bp, about 200 bp to about 250 bp, about 250 bp to about 300 bp, about 300 bp to about 350 bp, about 350 bp to about 400 bp, about 400 bp to about 450 bp, about 450 bp to about 500 bp, about 500 bp to about 600 bp, about 600 bp to about 700 bp, about 700 bp to about 800 bp, about 800 bp to about 900 bp, or about 900 bp to about 1 kb; or

(g) the first and second CRISPR RNA recognition sequences are separated by less than 25 bp, less than 50 bp, less than 100 bp, less than 150 bp, less than 200 bp, less than 250 bp, less than 300 bp, less than 350 bp, less than 400 bp, less than 450 bp, less than 500 bp, less than 600 bp, less than 700 bp, less than 800 bp, less than 900 bp, less than 1 kb, less than 2 kb, less than 3 kb, less than 4 kb, less than 5 kb, or less than 10 kb.

11. The method of any preceding claim, wherein the targeting vector is in linear form, and/or wherein the targeting vector is single-stranded or double-stranded.

12. The method of any preceding claim, wherein the cell is a eukaryotic cell, optionally wherein the eukaryotic cell is a mammalian cell, a human cell, a non-human cell, a rodent cell, a mouse cell, a rat cell, a pluripotent cell, a non-pluripotent cell, a non-human pluripotent cell, a human pluripotent cell, a rodent pluripotent cell, a mouse pluripotent cell, a rat pluripotent cell, a mouse embryonic stem (ES) cell, a rat ES cell, a human ES cell, a human adult stem cell, a developmentally restricted human progenitor cell, a human induced pluripotent stem (iPS) cell, or a non-human one-cell stage embryo, or a mouse one-cell stage embryo.

13. The method of claim 12, wherein the cell is a non-human one-cell stage embryo, and wherein:

(a) the targeting vector is between about 50 nucleotides to about 5 kb in length;

(b) the targeting vector is single-stranded DNA and is between about 60 to about 200 nucleotides in length;

(c) the Cas protein, the first guide RNA, and the second guide RNA are each

introduced into the one-cell stage embryo by microinjection; or

(d) the Cas protein, the first guide RNA, and the second guide RNA are each introduced into the one-cell stage embryo in the form of RNA by microinjection into the cytoplasm.

14. The method of claim 12, wherein the cell is not a one-cell stage embryo, and wherein:

(a) the targeting vector is a large targeting vector (LTVEC) that is at least 10 kb, optionally wherein the LTVEC is from about 50 kb to about 75 kb, from about 75 kb to about 100 kb, from about 100 kb to 125 kb, from about 125 kb to about 150 kb, from about 150 kb to about 175 kb, about 175 kb to about 200 kb, from about 200 kb to about 225 kb, from about 225 kb to about 250 kb, from about 250 kb to about 275 kb or from about 275 kb to about 300 kb; or

(b) the targeting vector is a large targeting vector (LTVEC), wherein the sum total of the 5' and 3' homology arms of the LTVEC is at least 10 kb, optionally wherein the sum total of the 5' and 3' homology arms of the LTVEC is from about 10 kb to about 20 kb, from about 20 kb to about 30 kb, from about 30 kb to about 40 kb, from about 40 kb to about 50 kb, from about 50 kb to about 60 kb, from about 60 kb to about 70 kb, from about 70 kb to about 80 kb, from about 80 kb to about 90 kb, from about 90 kb to about 100 kb, from about 100 kb to about 110 kb, from about 110 kb to about 120 kb, from about 120 kb to about 130 kb, from about 130 kb to about 140 kb, from about 140 kb to about 150 kb, from about 150 kb to about 160 kb, from about 160 kb to about 170 kb, from about 170 kb to about 180 kb, from about 180 kb to about 190 kb, or from about 190 kb to about 200 kb.

15. The method of any one of claims 1-12 and 14, wherein the cell is not a one-cell stage embryo,

wherein the targeting vector is a large targeting vector (LTVEC), wherein the 5' and 3' homology arms have a sum total of at least 10 kb;

wherein the first and second CRISPR RNA recognition sequences are each located more than 200 bp, more than 300 bp, more than 400 bp, more than 500 bp, more than 600 bp, more than 700 bp, more than 800 bp, more than 900 bp, more than 1 kb, more than 2 kb, more than 3 kb, more than 4 kb, more than 5 kb, more than 6 kb, more than 7 kb, more than 8 kb, more than 9 kb, more than 10 kb, more than 20 kb, more than 30 kb, more than 40 kb, more than

50 kb, more than 60 kb, more than 70 kb, more than 80 kb, more than 90 kb, or more than 100 kb from both the 5’ and 3’ target sequences;

wherein the Cas protein cleaves the first and second CRISPR RNA recognition sequences in at least one of the first and second homologous chromosomes to generate at least two double-strand breaks in at least one of the first and second homologous chromosomes; and

wherein the biallelic modification comprises the deletion between the first and second CRISPR RNA recognition sequences in the first homologous chromosome and an insertion of the nucleic acid insert between the 5’ and 3’ target sequences in the first homologous chromosome, wherein the nucleic acid insert sequence is homologous or orthologous to the deleted sequence.

16. The method of any preceding claim, wherein the Cas protein is Cas9,

optionally wherein the Cas protein has nuclease activity on both strands of double-stranded DNA,

or optionally wherein the Cas protein is a nickase, and wherein the method further comprises introducing into the cell:

(e) a third guide RNA that hybridizes to a third CRISPR RNA recognition sequence; and

(f) a fourth guide RNA that hybridizes to a fourth CRISPR RNA recognition sequence;

wherein the Cas protein nicks a first strand of genomic DNA within the first and second CRISPR RNA recognition sequences, and the Cas protein nicks a second strand of genomic DNA within the third and fourth CRISPR RNA recognition sequences, wherein the nicks within the first and third CRISPR RNA recognition sequences are offset nicks to create a first double-strand break having staggered ends, and the nicks within the second and fourth CRISPR RNA recognition sequences are offset nicks to create a second double-strand break having staggered ends.

17. The method of any preceding claim, wherein:

(a) the first guide RNA comprises a first CRISPR RNA and a first tracrRNA fused together, and/or the second guide RNA comprises a second CRISPR RNA and a second tracrRNA fused together;

(b) the first guide RNA comprises a first CRISPR RNA and a first tracrRNA, wherein the first CRISPR RNA and the first tracrRNA are separate RNA molecules, and/or the second guide RNA comprises a second CRISPR RNA and a second tracrRNA, wherein the second CRISPR RNA and the second tracrRNA are separate RNA molecules;

(c) the Cas protein is introduced into the cell in the form of a protein, a messenger RNA (mRNA) encoding the Cas protein, or a DNA encoding the Cas protein;

(d) the first guide RNA is introduced into the cell in the form of an RNA or in the form of a DNA encoding the first guide RNA;

(e) the second guide RNA is introduced into the cell in the form of an RNA or in the form of a DNA encoding the second guide RNA;

(f) the Cas protein and the first guide RNA are introduced into the cell as a first protein-RNA complex, and/or the Cas protein and the second guide RNA are introduced into the cell as a second protein-RNA complex;

(g) the Cas protein, the first guide RNA, and the second guide RNA are each introduced into the cell in the form of DNA; or

(h) the Cas protein, the first guide RNA, and the second guide RNA are each introduced into the cell in the form of RNA.

18. The method of any preceding claim, wherein the cell has been modified to decrease non-homologous end joining (NHEJ) and/or to increase gene conversion or homology-directed repair (HDR), optionally wherein the cell has been modified to decrease the expression or activity of one or more of DNA-PK, PARP1, and ligase IV, and optionally wherein the decrease in expression or activity is inducible, reversible, temporally specific, and/or spatially specific.

19. The method of any preceding claim, wherein the method produces:

(a) a first subpopulation of cells comprising a deletion between the first and second CRISPR RNA recognition sequences in both the first and second homologous chromosomes, and insertion of the nucleic acid insert between the 5’ and 3’ target sequences in the first homologous chromosome but not in the second homologous chromosome;

(b) a second subpopulation of cells comprising a deletion between the first and second CRISPR RNA recognition sequences and insertion of the nucleic acid insert between

the 5’ and 3’ target sequences in both the first and second homologous chromosomes;

(c) a third subpopulation of cells comprising a deletion between the first and second CRISPR RNA recognition sequences in both the first and second homologous chromosomes but no insertion of the nucleic acid insert between the 5’ and 3’ target sequences;

(d) a fourth subpopulation of cells comprising a deletion between the first and second CRISPR RNA recognition sequences in the first homologous chromosome, and disruption of the genomic target locus in the second homologous chromosome, wherein the disruption is from non-homologous end joining (NHEJ)-mediated repair of the at least one double-strand break; or

(e) a fifth subpopulation of cells comprising a deletion between the first and second CRISPR RNA recognition sequences in the first homologous chromosome, an insertion of the nucleic acid insert between the 5’ and 3’ target sequences in the first homologous chromosome, and disruption of the genomic target locus in the second homologous chromosome, wherein the disruption is from non-homologous end joining (NHEJ)-mediated repair of the at least one double-strand break,

optionally wherein the method produces the first subpopulation of cells, the second subpopulation of cells, the third subpopulation of cells, the fourth subpopulation of cells, and the fifth subpopulation of cells.

20. The method of any preceding claim, wherein the cell is a mouse or rat embryonic stem (ES) cell, and the method further comprises introducing the mouse or rat ES cell into a host embryo.