What is Claimed is:

1. ~~A method of treating a subject having obesity comprising administering to the subject~~ Use of an agonist of the leptin-melanocortin signaling pathway in the manufacture of a medicament for treating a subject having obesity in a subject.

2. ~~A method of treating a subject having elevated BMI comprising administering to the subject~~ Use of an agonist of the leptin-melanocortin signaling pathway in the manufacture of a medicament for treating a subject having elevated BMI.

3. The use~~method~~ according to claim 1 or claim 2, wherein the agonist of the leptin-melanocortin signaling pathway is a melanocortin-4 receptor (MC4R) agonist or a proprotein convertase subtilisin/kexin type 1 (PCSK1) agonist.

4. The use~~method~~ according to claim 3, wherein the MC4R agonist comprises a protein, a peptide, a nucleic acid molecule, or a small molecule.

5. The use~~method~~ according to claim 4, wherein the protein is a peptide analog of MC4R.

6. The use~~method~~ according to claim 4, wherein the peptide is setmelanotide.

7. The use~~method~~ according to claim 4, wherein the MC4R agonist is peptide comprising the amino acid sequence His-Phe-Arg-Trp (SEQ ID NO:32).

8. The use~~method~~ according to claim 4, wherein the MC4R agonist is 1,2,3R,4-tetrahydroisoquinoline-3-carboxylic acid.

9. The use~~method~~ according to claim 4, wherein the MC4R agonist is ALB-127158(a).

10. The use~~method~~ according to any one of claims 1 to 9, further comprising detecting the presence or absence of a PCSK1 variant nucleic acid molecule or PCSK1 variant polypeptide associated with an increased risk of developing obesity and/or elevated BMI in a biological sample from the subject.

11. The use~~method~~ according to claim 10, wherein the PCSK1 variant nucleic acid molecule associated with an increased risk of developing obesity and/or elevated BMI is a PCSK1 predicted loss-of-function variant or PCSK1 missense variant, or an mRNA molecule produced therefrom, or a cDNA molecule produced from the mRNA molecule.

12. The use~~method~~ according to claim 10 or claim 11, wherein detecting the presence or absence of the PCSK1 variant nucleic acid molecule or variant polypeptide associated with an increased risk of developing obesity and/or elevated BMI comprises:

determining whether the subject is heterozygous for a PCSK1 variant genomic nucleic acid molecule associated with an increased risk of developing obesity and/or elevated BMI, a

PCSK1 variant mRNA molecule associated with an increased risk of developing obesity and/or elevated BMI, a PCSK1 variant cDNA molecule produced from the mRNA molecule, and/or a PCSK1 variant polypeptide associated with an increased risk of developing obesity and/or elevated BMI, by:

obtaining or having obtained a biological sample from the subject; and

performing or having performed an assay on the biological sample to determine whether the subject is heterozygous for a PCSK1 variant nucleic acid molecule or variant polypeptide associated with an increased risk of developing obesity and/or elevated BMI.

13. The use~~method~~ according to claim 12, further comprising determining the subject's aggregate burden of having: a PCSK1 variant genomic nucleic acid molecule associated with an increased risk of developing obesity and/or elevated BMI, a PCSK1 variant mRNA molecule associated with an increased risk of developing obesity and/or elevated BMI, a PCSK1 variant cDNA molecule produced from the mRNA molecule, and/or a PCSK1 variant polypeptide associated with an increased risk of developing obesity and/or elevated BMI.

14. The use~~method~~ according to claim 13, wherein the subject is heterozygous for at least one PCSK1 loss-of-function variant.

15. The use~~method~~ according to claim 14, wherein the PSCK1 loss-of-function variant is a protein truncating variant.

~~16. The method according to any one of claims 10 to 15, wherein the assay is a genotyping assay or sequence analysis for nucleic acid molecules.~~

~~17. The method according any one of claims 10 to 15, wherein the assay is an immunoassay for polypeptides.~~

~~18. The method according to any one of claims 10 to 17, wherein the detecting step, determining step, or assay is carried out *in vitro*.~~

~~19. The method according to any one of claims 10 to 18, wherein the detecting step, determining step, or assay comprises sequencing at least a portion of the nucleotide sequence of the PCSK1 nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to a loss-of-function variant position, wherein when a variant nucleotide at the loss-of-function variant position is detected, the PCSK1 nucleic acid molecule in the biological sample is a PCSK1 loss-of-function variant nucleic acid molecule.~~

~~20. The method according to claim 19, wherein the detecting step, determining step, or assay comprises:~~

~~a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the PCSK1 nucleic acid molecule that is proximate to a loss-of-function variant position;~~

~~b) extending the primer at least through the loss-of-function variant position; and~~

~~c) determining whether the extension product of the primer comprises a variant nucleotide at the loss-of-function variant position.~~

~~21. The method according to claim 19 or claim 20, wherein the detecting step, determining step, or assay comprises sequencing the entire nucleic acid molecule.~~

~~22. The method according to any one of claims 10 to 18, wherein the detecting step, determining step, or assay comprises sequencing at least a portion of the nucleotide sequence of the PCSK1 nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to a missense variant position, wherein when a variant nucleotide at the missense variant position is detected, the PCSK1 nucleic acid molecule in the biological sample is a PCSK1 missense variant nucleic acid molecule.~~

~~23. The method according to claim 22, wherein the detecting step, determining step, or assay comprises:~~

~~a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the PCSK1 nucleic acid molecule that is proximate to a missense variant position;~~

~~b) extending the primer at least through the missense variant position; and~~

~~c) determining whether the extension product of the primer comprises a variant nucleotide at the missense variant position.~~

~~24. The method according to claim 22 or claim 23, wherein the detecting step, determining step, or assay comprises sequencing the entire nucleic acid molecule.~~

~~25. The method according to any one of claims 10 to 18, wherein the detecting step, determining step, or assay comprises:~~

~~a) amplifying at least a portion of the PCSK1 nucleic acid molecule, wherein the portion comprises a loss-of-function variant position;~~

~~b) labeling the amplified nucleic acid molecule with a detectable label;~~

~~c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the loss-of-function variant position; and~~

~~d) detecting the detectable label.~~

~~26. The method according to claim 25, wherein the nucleic acid molecule in the sample is mRNA and the mRNA is reverse-transcribed into a cDNA prior to the amplifying step.~~

~~27. The method according to claim 25 or claim 26, wherein the detecting step, determining step, or assay comprises:~~

~~contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to a loss-of-function variant position; and~~

~~detecting the detectable label.~~

~~28. The method according to any one of claims 10 to 18, wherein the detecting step, determining step, or assay comprises:~~

~~a) amplifying at least a portion of the PCSK1 nucleic acid molecule, wherein the portion comprises a missense variant position;~~

~~b) labeling the amplified nucleic acid molecule with a detectable label;~~

~~c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the missense variant position; and~~

~~d) detecting the detectable label.~~

~~29. The method according to claim 28, wherein the nucleic acid molecule in the sample is mRNA and the mRNA is reverse-transcribed into a cDNA prior to the amplifying step.~~

~~30. The method according to claim 28 or claim 29, wherein the detecting step, determining step, or assay comprises:~~

~~contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to a missense variant position; and~~

~~detecting the detectable label.~~

~~31~~16. A method of identifying susceptibility of an obese subject to treatment with an agonist of the leptin-melanocortin signaling pathway, the method comprising: detecting the presence or absence of one copy of a PCSK1 genetic variant associated with an increased risk of developing obesity and/or elevated BMI in a biological sample from the subject, wherein when one copy of a PCSK1 genetic variant is detected, the obese subject is susceptible to treatment with the agonist of the leptin-melanocortin signaling pathway.

~~32~~17. A method of identifying susceptibility of a subject having elevated BMI to treatment with an agonist of the leptin-melanocortin signaling pathway, the method comprising: detecting the presence or absence of one copy of a PCSK1 genetic variant associated with an increased risk of developing obesity and/or elevated BMI in a biological sample from the subject, wherein when one copy of a PCSK1 genetic variant is detected, the subject is susceptible to treatment with the agonist of the leptin-melanocortin signaling pathway.

~~33~~18. The method according to claim ~~31~~16 or claim ~~32~~17, wherein the PCSK1 genetic variant associated with an increased risk of developing obesity and/or elevated BMI is a PCSK1 loss-of-function variant or PCSK1 missense variant.

~~34~~19. The method according to any one of claims ~~31~~16 to ~~33~~18, wherein detecting the PCSK1 genetic variant associated with an increased risk of developing obesity and/or elevated BMI comprises detecting a PCSK1 variant genomic nucleic acid molecule associated with an increased risk of developing obesity and/or elevated BMI, a PCSK1 variant mRNA molecule associated with an increased risk of developing obesity and/or elevated BMI, a PCSK1 variant cDNA molecule produced from the mRNA molecule, and/or a PCSK1 variant polypeptide associated with an increased risk of developing obesity and/or elevated BMI, by:

obtaining or having obtained a biological sample from the subject; and

performing or having performed an assay on the biological sample to determine whether the subject is heterozygous for a PCSK1 variant nucleic acid molecule or PCSK1 variant polypeptide associated with an increased risk of developing obesity and/or elevated BMI.

~~35. The method according to claim 34, wherein the assay is a sequence analysis or genotyping assay for nucleic acid molecules.~~

~~36. The method according to claim 34, wherein the assay is an immunoassay for polypeptides.~~

~~37. The method according to claim 34, wherein the detecting step, determining step, or assay is carried out *in vitro*.~~

~~38. The method according to any one of claims 34 to 37, wherein the detecting step, determining step, or assay comprises sequencing at least a portion of the nucleotide sequence of the PCSK1 nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to a loss-of-function variant position, wherein when a variant nucleotide at the loss-of-function variant position is detected, the PCSK1 nucleic acid molecule in the biological sample is a PCSK1 loss-of-function variant nucleic acid molecule.~~

~~39. The method according to claim 35, wherein the detecting step, determining step, or assay comprises:~~

~~a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the PCSK1 nucleic acid molecule that is proximate to the loss-of-function variant position;~~

~~b) extending the primer at least through the loss-of-function variant position; and~~

~~c) determining whether the extension product of the primer comprises a variant nucleotide at the loss-of-function variant position.~~

~~40. The method according to claim 38 or claim 39, wherein the detecting step, determining step, or assay comprises sequencing the entire nucleic acid molecule.~~

~~41. The method according to any one of claims 34 to 37, wherein the detecting step, determining step, or assay comprises:~~

~~a) amplifying at least a portion of the PCSK1 nucleic acid molecule, wherein the portion comprises the loss-of-function variant position;~~

~~b) labeling the amplified nucleic acid molecule with a detectable label;~~

~~c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the loss-of-function variant position; and~~

~~d) detecting the detectable label.~~

~~42. The method according to claim 41, wherein the nucleic acid molecule in the sample is mRNA and the mRNA is reverse-transcribed into a cDNA prior to the amplifying step.~~

~~43. The method according to claim 41 or claim 42, wherein the detecting step, determining step, or assay comprises:~~

~~contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the loss-of-function variant position; and~~

~~detecting the detectable label.~~

~~44~~20. The method according to any one of claims ~~31~~ 16 to ~~43~~19, ~~further comprising administering~~wherein the agonist of the leptin-melanocortin signaling pathway is to be further administered to the subject identified as susceptible to the leptin-melanocortin signaling pathway agonist treatment.

~~45~~21. The method according to any one of claims ~~31~~ 16 to ~~44~~20, wherein the agonist of the leptin-melanocortin signaling pathway is an MC4R agonist or a PCSK1 agonist.

~~46~~22. The method according to claim ~~45~~21, wherein the MC4R agonist comprises a protein, a peptide, a nucleic acid molecule, or a small molecule.

~~47~~23. The method according to claim ~~46~~22, wherein the protein is a peptide analog of MC4R.

~~48~~24. The method according to claim ~~46~~22, wherein the peptide is setmelanotide.

~~49~~25. The method according to claim ~~46~~22, wherein the MC4R agonist is peptide comprising the amino acid sequence His-Phe-Arg-Trp.

~~50~~26. The method according to claim ~~46~~22, wherein the MC4R agonist is 1,2,3R,4-tetrahydroisoquinoline-3-carboxylic acid.

~~51~~27. The method according to claim ~~46~~22, wherein the MC4R agonist is ALB-127158(a).