

WHAT IS CLAIMED IS:

1. A method of treating spinal muscular atrophy (SMA) in a human subject in need thereof, comprising administering to the human subject a therapeutically effective amount of an SMA therapy, wherein the human subject has been previously determined to have, in a
5 biological sample obtained from the human subject, a neurofilament level prior to initiation of the SMA therapy that is higher than a control.

2. A method of treating spinal muscular atrophy (SMA) in a human subject in need thereof, comprising:

10 measuring a neurofilament level in a biological sample obtained from the human subject before initiation of an SMA therapy; and

administering a therapeutically effective amount of the SMA therapy to the human subject.

15 3. The method of claim 1 or 2, wherein the neurofilament level in the biological sample is above 400 pg/mL.

4. A method of treating spinal muscular atrophy (SMA) in a human subject in need thereof, comprising:

20 measuring a neurofilament level in a first biological sample obtained from the human subject before initiation of an SMA therapy;

administering an SMA therapy to the human subject; and

measuring a neurofilament level in a second biological sample obtained from the human subject after initiation of the SMA therapy.

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5. The method of claim 4, wherein the neurofilament level measured in the second biological sample is lower than the neurofilament level measured in the first biological sample.

6. The method of claim 5, wherein the neurofilament level measured in the second biological sample is between 10% to 95% of the neurofilament level measured in the first biological sample.

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7. The method of any one of claims 4 to 6, wherein the second biological sample is obtained from the human subject 40-90 days after initiation of the SMA therapy.

8. The method of any one of claims 4 to 6, wherein the second biological sample is
10 obtained from the human subject 50-80 days after initiation of the SMA therapy.

9. The method of any one of claims 4 to 6, wherein the second biological sample is obtained from the human subject 60-70 days after initiation of the SMA therapy.

15 10. The method of any one of claims 4 to 6, wherein the second biological sample is obtained from the human subject about 64 days after initiation of the SMA therapy.

11. The method of any one of claims 7 to 10, wherein the neurofilament level measured in the second biological sample is reduced by at least 50% compared to the
20 neurofilament level measured in the first biological sample.

12. The method of any one of claims 7 to 10, wherein the neurofilament level measured in the second biological sample is reduced by at least 60% compared to the neurofilament level measured in the first biological sample.

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13. The method of any one of claims 7 to 10, wherein the neurofilament level measured in the second biological sample is reduced by at least 70% compared to the neurofilament level measured in the first biological sample.

14. The method of any one of claims 7 to 10, wherein the neurofilament level measured in the second biological sample is reduced by less than 50% compared to the neurofilament level measured in the first biological sample.

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15. The method of any one of claims 7 to 10, wherein the neurofilament level measured in the second biological sample is reduced by less than 40% compared to the neurofilament level measured in the first biological sample.

10 16. The method of any one of claims 7 to 15, wherein the dose of the SMA therapy is changed for a subsequent administration to the human subject based upon the percent reduction in neurofilament level measured in the second biological sample as compared to the neurofilament level measured in the first biological sample.

15 17. The method of claim 4, wherein the neurofilament level measured in the second biological sample is higher than the neurofilament level measured in the first biological sample.

18. The method of any one of claims 4 to 17, wherein administration of the SMA
20 therapy is continued.

19. The method of claim 17, wherein administration of the SMA therapy is discontinued.

25 20. A method of treating spinal muscular atrophy (SMA) in a human subject in need thereof, comprising:

measuring a neurofilament level in a first biological sample obtained from the human subject before administration of a candidate amount of an SMA therapy;

measuring a neurofilament level in a second biological sample obtained from the human subject after administration of the candidate amount of the SMA therapy, wherein the neurofilament level in the second biological sample is lower than the neurofilament level in the first biological sample, thereby indicating that the candidate amount of the SMA therapy is a therapeutically effective amount;

administering the therapeutically effective amount of the SMA therapy to the human subject after having measured the lowered neurofilament level in the second biological sample.

21. A method of predicting the prognosis of spinal muscular atrophy (SMA), comprising:

measuring a neurofilament level in a biological sample obtained from a human subject having mutations in both copies of the SMN1 gene that lead to functional SMN protein deficiency; and

comparing the neurofilament level measured in the biological sample to a control,

wherein the neurofilament level measured in the biological sample, as compared to the control, is predictive of the severity or type of SMA that the subject will develop.

22. The method of claim 21, wherein the biological sample is obtained from the human subject before initiation of an SMA therapy, and wherein the neurofilament level measured in the biological sample, as compared to the control, is predictive of the severity or type of SMA that the human subject will develop in the absence of treatment.

23. The method of claim 21, wherein the biological sample is obtained from the human subject after initiation of an SMA therapy, and wherein the neurofilament level measured in the biological sample, as compared to the control, is predictive of the severity or type of SMA that the subject will develop while receiving the SMA therapy.

24. The method of claim 23, wherein the biological sample is obtained from the human subject at least two weeks after initiation of the SMA therapy.

25. The method of claim 23, wherein the biological sample is obtained from the human subject at least two months after initiation of the SMA therapy.

26. A method of predicting the prognosis of spinal muscular atrophy (SMA), comprising:

measuring, before initiation of an SMA therapy, a neurofilament level in a first biological sample obtained from a human subject having mutations in both copies of the SMN1 gene that lead to functional SMN protein deficiency;

measuring a neurofilament level in a second biological sample obtained from the human subject after initiation of the SMA therapy; and

comparing the neurofilament level measured in the second biological sample to the neurofilament level measured in the first biological sample,

wherein the neurofilament level measured in the second biological sample, as compared to the neurofilament level measured in the first biological sample, is predictive of the severity or type of SMA that the subject will develop.

27. The method of claim 26, wherein the second biological sample is obtained from the human subject 40-90 days after initiation of the SMA therapy.

28. The method of claim 26, wherein the second biological sample is obtained from the human subject 50-80 days after initiation of the SMA therapy.

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29. The method of claim 26, wherein the second biological sample is obtained from the human subject 60-70 days after initiation of the SMA therapy.

30. The method of claim 26, wherein the second biological sample is obtained from the human subject about 64 days after initiation of the SMA therapy.

31. The method of any one of claims 26 to 30, wherein the neurofilament level
5 measured in the second biological sample is reduced by at least 50% compared to the neurofilament level measured in the first biological sample.

32. The method of any one of claims 26 to 30, wherein the neurofilament level
10 measured in the second biological sample is reduced by at least 60% compared to the neurofilament level measured in the first biological sample.

33. The method of any one of claims 26 to 30, wherein the neurofilament level
15 measured in the second biological sample is reduced by at least 70% compared to the neurofilament level measured in the first biological sample.

34. The method of any one of claims 26 to 30, wherein the neurofilament level
measured in the second biological sample is reduced by less than 50% compared to the neurofilament level measured in the first biological sample.

20 35. The method of any one of claims 26 to 30, wherein the neurofilament level measured in the second biological sample is reduced by less than 40% compared to the neurofilament level measured in the first biological sample.

36. The method of any one of the preceding claims, wherein the SMA therapy is
25 nusinersen or a nusinersen salt.

37. The method of any one of claims 1 to 35, wherein the SMA therapy is nusinersen sodium.

38. The method of any one of claims 1 to 35, wherein the SMA therapy is olesoxime, AVX-101, CK-2127107, RG7916, RG7800, RO7034067, LMI070, or SRK-015.

5 39. The method of any one of the preceding claims, wherein the control is a pre-established neurofilament cut-off value.

 40. The method of any one of claims 1 to 38, wherein the control is the neurofilament level in a biological sample or biological samples obtained from one or more
10 human subjects that do not have SMA.

 41. A method for measuring a neurofilament level, comprising:
 providing a biological sample obtained from a human subject having mutations in
 both copies of the SMN1 gene that lead to functional SMN protein deficiency; and
15 measuring a neurofilament level in the biological sample.

 42. The method of any one of the preceding claims, wherein the neurofilament is a neurofilament heavy chain.

20 43. The method of any one of the preceding claims, wherein the neurofilament is a phosphorylated neurofilament heavy chain.

 44. The method of any one of claims 1 to 41, wherein the neurofilament is a neurofilament medium/intermediate chain.

25 45. The method of any one of claims 1 to 41, wherein the neurofilament is a neurofilament light chain.

46. The method of any one of the preceding claims, wherein the biological sample is blood, serum, plasma, or cerebrospinal fluid.