

WHAT IS CLAIMED IS:

1. A method of detecting misfolded transthyretin (TTR) in a biological sample, the method comprising:

(a) contacting a biological sample with a capture antibody that specifically binds to an epitope within residues 89-97 of TTR, wherein the capture antibody comprises three Kabat heavy chain CDRs, CDR-H1 of SEQ ID NO:75, CDR-H2 of SEQ ID NO:76, and CDR-H3 of SEQ ID NO:77, and three Kabat light chain CDRs, CDR-L1 of SEQ ID NO:78, CDR-L2 of SEQ ID NO:79, and CDR-L3 of SEQ ID NO:80, and a reporter antibody that specifically binds to a different epitope of TTR; wherein if misfolded TTR is present in the sample, the capture antibody and reporter antibody bind to the misfolded TTR forming a sandwich complex, wherein the biological sample is a plasma sample from a hereditary ATTR patient carrying a E89K or E89Q mutation in the amino acid sequence of TTR; and

(b) detecting the reporter antibody that forms a sandwich complex in step (a), if any, to indicate presence or absence of the misfolded TTR.

~~2. The method of claim 1, wherein the biological sample is from a hereditary ATTR patient.~~

~~3. The method of claim 2, wherein the biological sample is from a hereditary ATTR patient carrying a mutation selected from the group consisting of V30M, Y114C, G47R, S50I, T49S, F33V, A45T, E89K, E89Q, and V122I.~~

~~4. The method of claim 3, wherein the mutation is selected from the group consisting of V30M, Y114C, and S50I.~~

~~5. The method of claim 3, wherein the mutation is V30M.~~

~~6. The method of claim 3, wherein the mutation is Y114C.~~

~~7. The method of claim 3, wherein the mutation is S50I.~~

~~8. The method of claim 3, wherein the mutation is E89K.~~

~~9. — The method of claim 3, wherein the mutation is E89Q.~~

~~240.~~ The method of claim 1, wherein the capture antibody is 9D5.

~~11. — The method of claim 10, wherein the capture antibody is 9D5 and the reporter antibody is a polyclonal anti-TTR antibody.~~

~~312.~~ The method of any of claims 1-~~240~~, wherein the reporter antibody is 18C5, 8C3, 7G7, AD7F6, RT24, NI-301.35G11, MFD101, MDF102, MFD103, MFD105, MFD107, MFD108, MFD109, MFD111, MFD114, or a chimeric version or humanized version thereof or a polyclonal anti-TTR antibody.

~~13. — The method of claim 1 or 2, wherein the capture antibody is 9D5 and the reporter antibody is 18C5, or a chimeric version or humanized version thereof.~~

~~14. — The method of claim 1, wherein the capture antibody is 9D5 and the reporter antibody is 8C3, or a chimeric version or humanized version thereof.~~

~~15. — The method of claim 1, wherein the capture antibody is 9D5 and the reporter antibody is 7G7, or a chimeric version or humanized version thereof.~~

~~16. — The method of claim 1, wherein the capture antibody is 9D5 and the reporter antibody is AD7F6, or a chimeric version or humanized version thereof.~~

~~17. — The method of claim 1, wherein the capture antibody is 9D5 and the reporter antibody is RT24, or a chimeric version or humanized version thereof.~~

~~18. — The method of claim 1, wherein the capture antibody is 9D5 and the reporter antibody is NI-301.35G11, or a chimeric version or humanized version thereof.~~

~~19. — The method of claim 1, wherein the capture antibody is 9D5 and the reporter antibody is MFD101, or a chimeric version or humanized version thereof.~~

~~20. — The method of claim 1, wherein the capture antibody is 9D5 and the reporter antibody is MDF102, or a chimeric version or humanized version thereof.~~

~~21. The method of claim 1, wherein the capture antibody is 9D5 and the reporter antibody is MFD103, or a chimeric version or humanized version thereof.~~

~~22. The method of claim 1, wherein the capture antibody is 9D5 and the reporter antibody is MFD105, or a chimeric version or humanized version thereof.~~

~~23. The method of claim 1, wherein the capture antibody is 9D5 and the reporter antibody is MFD107, or a chimeric version or humanized version thereof.~~

~~24. The method of claim 1, wherein the capture antibody is 9D5 and the reporter antibody is MFD108, or a chimeric version or humanized version thereof.~~

~~25. The method of claim 1, wherein the capture antibody is 9D5 and the reporter antibody is MFD109, or a chimeric version or humanized version thereof.~~

~~26. The method of claim 1, wherein the capture antibody is 9D5 and the reporter antibody is MFD111, or a chimeric version or humanized version thereof.~~

~~27. The method of claim 1, wherein the capture antibody is 9D5 and the reporter antibody is MFD114, or a chimeric version or humanized version thereof.~~

~~428.~~ The method of any one of claims 1-~~240~~, wherein the reporter antibody is an antibody that binds within residues 101-109, 118-122, 115-124, 53-63, 54-61, 36-49, 49-61, 109-121, 30-66, 70-127, 80-127, 90-127, 100-127, 110-127, or 115-127 of TTR.

~~529.~~ The method of any preceding claim, wherein the misfolded TTR includes an E89K substitution or :

~~30. The method of any preceding claim, wherein the misfolded TTR includes an E89Q substitution.~~

~~346.~~ The method of any one of claims 1-~~530~~, wherein the biological sample is a first aliquot of a collected sample and the method further comprises repeating step (a) and (b) on a second aliquot of the collected sample further comprising a test antibody that competes with the capture antibody for binding to TTR, ~~wherein reduced reporter antibody forming the~~

~~sandwich complex on repeating the steps provides an indication of the test antibody's ability to bind to misfolded TTR.~~

732. The method of claim 631, wherein the test antibody is 14G8 or a chimeric or humanized form thereof, the capture antibody is 9D5, and the reporter antibody is a polyclonal anti-TTR antibody.

~~33.—The method of claim 32 wherein the test antibody is a humanized form of 14G8.~~

~~34.—A method of determining in vivo target engagement of a test antibody administered to a subject, which target is an epitope within residues 89-97 of misfolded transthyretin (mis-TTR) by detecting the mis-TTR remaining in a biological sample from the subject treated with the test antibody, the method comprising:~~

~~(a) contacting the biological sample with a capture antibody that specifically binds to an epitope within residues 89-97 and a reporter antibody that specifically binds to a different epitope within TTR from that of the capture antibody; wherein if misfolded TTR is present in the sample, the capture antibody and reporter antibody bind to the misfolded TTR forming a sandwich complex; and~~

~~(b) detecting the reporter antibody forming a sandwich complex in step (a), if any, to indicate presence or absence of the misfolded TTR.~~

~~35.—The method of claim 34, wherein the wherein the biological sample is from a hereditary ATTR patient.~~

~~36.—The method of claim 35, wherein the biological sample is from a hereditary ATTR patient carrying a mutation selected from the group consisting of V30M, Y114C, G47R, S50I, T49S, F33V, A45T, E89K, E89Q, and V122I.~~

~~37.—The method of claim 36, wherein the mutation is selected from the group consisting of V30M, Y114C, and S50I.~~

~~38.—The method of claim 36, wherein the mutation is V30M.~~

~~39. — The method of claim 36, wherein the mutation is Y114C.~~

~~40. — The method of claim 36, wherein the mutation is S50I.~~

~~41. — The method of claim 36, wherein the mutation is E89K.~~

~~42. — The method of claim 36, wherein the mutation is E89Q.~~

~~43. — The method of claim 34 or 35, wherein a reduction of detection of misfolded TTR in the treated subject relative to the detection of misfolded TTR in a biological sample from an untreated subject correlates with positive target engagement and treating the subject with the same or a lesser amount of the test antibody.~~

~~44. — The method of claim 35, wherein the treated subject and the untreated subject are the same individual.~~

~~45. — The method of claim 34, wherein the capture antibody is 9D5 and the reporter antibody is 9D5, wherein the capture antibody and the reporter antibody have different labels.~~

~~46. — The method of claim 34, wherein the capture antibody is 9D5 and the reporter antibody is 14G8.~~

~~47. — The method of claim 34, wherein the capture antibody is 9D5 and the reporter antibody is 5A1.~~

~~48. — The method of claim 34, wherein the capture antibody is 9D5 and the reporter antibody is 6C1.~~

~~49. — The method of claim 45, wherein the reporter antibody competes for binding with the capture antibody for binding multimeric misfolded transthyretin.~~

850. The method of any preceding claim, wherein the reporter antibody has an electrochemiluminescent label and is detected by electrochemiluminescence.

951. The method of any preceding claim, wherein the capture antibody has a biotin label.

~~52. The method of any preceding claim, performed qualitatively.~~

~~53. The method of any preceding claim, performed quantitatively to indicate an absolute or relative amount of the misfolded TTR.~~

1054. The method of any preceding claim, wherein the capture antibody is bound to a solid phase before the contacting step.

1155. The method of claim 1054, wherein the capture antibody is attached to the solid phase via a linker.

1256. The method of claim 1054, wherein the solid phase comprises at least one electrode.

~~57. The method of any preceding claim, further comprising: comparing a signal from the reporter antibody with a signal from the reporter antibody in a control sample containing a known amount of misfolded TTR to determine the amount of misfolded TTR in the sample.~~

~~58. The method of any preceding claim, further comprising comparing a signal from the reporter antibody from a calibration curve of signal versus amount of misfolded TTR to determine the amount of misfolded TTR in the sample.~~

~~59. The method of any preceding claim, wherein a signal from the reporter antibody is proportional to the amount of misfolded TTR in the sample.~~

~~60. The method of any preceding claim, wherein the sample is a sample from a human.~~

~~61. The method of any preceding claim, wherein the sample is a body fluid.~~

~~62. The method of any preceding claim, wherein the sample is plasma of a human.~~

~~63.—The method of any preceding claim, wherein presence of misfolded TTR is used to diagnose a subject from whom the sample was obtained with a transthyretin-mediated amyloidosis.~~

~~64.—The method of claim 63, wherein the transthyretin-mediated amyloidosis is a familial transthyretin amyloidosis or a sporadic wild-type transthyretin amyloidosis.~~

~~65.—The method of claim 64, wherein the subject has been identified as at risk of a familial transthyretin amyloidosis based on genetic testing.~~

~~66.—The method of claim 64, wherein the subject does not show symptoms of a familial transthyretin amyloidosis.~~

~~67.—The method of claim 66 wherein the subject does not have polyneuropathy or cardiomyopathy.~~

~~68.—The method of claim 64, wherein the familial transthyretin amyloidosis is familial amyloid cardiomyopathy (FAC), familial amyloid polyneuropathy (FAP), or central nervous system selective amyloidosis (CNSA).~~

1369. The method of any preceding claim, wherein the biological sample is from a patient receiving treatment for a transthyretin-mediated amyloidosis.

~~70.—A method of adjusting treatment of a subject with a transthyretin-mediated amyloidosis, comprising~~

~~comparing the amount of misfolded TTR detected by the method of claim 34 or 35 in a sample from a subject previously treated for transthyretin-mediated amyloidosis with the amount of misfolded TTR detected in the subject prior to treatment or during an earlier stage of treatment; and~~

~~increasing the dose or frequency of administration of the prior treatment if the amount of misfolded TTR is the same or greater than that previously detected; or~~

decreasing the dose or frequency of administration of the prior treatment or discontinuing the prior treatment if the amount of misfolded TTR is less than that previously detected.

71.—The method of claim 70, wherein the prior treatment is by intravenous administration of an anti-TTR antibody and if the amount of misfolded TTR is less than that previously detected, the prior treatment is discontinued and replaced with treatment with a TTR stabilizer, antisense oligonucleotide based therapy, RNA interference therapy or combination therapy with doxycycline and tauroursodeoxycholic acid.

72.—The method of claim 71, wherein the subject no longer receives treatment with the anti-TTR antibody.

73.—The method of claim 71, wherein the TTR tetramer stabilizer is tafamidis or diflunisal.

74.—The method of claim 71, wherein the TTR tetramer stabilizer is diflunisal.

75.—The method of claim 71, wherein the antisense oligonucleotide based therapeutic is inotersen.

76.—The method of claim 71, wherein the RNAi based therapeutic is patisiran or revusiran.

77.—The method of claim 71, wherein the anti-TTR antibody is 14G8.

78.—The method of claim 77, wherein the subject no longer receives treatment with the anti-TTR antibody.

79.—The method of claim 77, wherein the TTR tetramer stabilizer is tafamidis or diflunisal.

80.—The method of claim 77, wherein the TTR tetramer stabilizer is diflunisal.

81.—The method of claim 77, wherein the antisense oligonucleotide based therapeutic is inotersen.

~~82.—The method of claim 77, wherein the RNAi based therapeutic is patisiran or revusiran.~~

~~83.—A method of adjusting treatment of a subject with a transthyretin mediated amyloidosis, comprising~~

~~(a) comparing the amount of reporter antibody binding detected by the method of claim 51 in a sample from a subject before initiating treatment for transthyretin mediated amyloidosis with the amount of reporter antibody binding detected in the subject after initiating treatment; and~~

~~(b) increasing the dose or frequency of administration of the treatment if the amount of reporter antibody binding is the same or greater than that previously detected; or~~

~~(c) decreasing the dose or frequency of administration of the treatment or discontinuing the treatment if the amount of reporter antibody binding is less than that previously detected.~~

~~84.—The method of any of claims 1-69, wherein a transthyretin mediated amyloidosis is distinguished from amyloid light chain (AL) amyloidosis.~~

~~85.—The method of any of claims 1-54 wherein the sample is from a transgenic mouse with a transgene expressing human TTR.~~

~~86.—A method of determining a ratio of the level of total multimeric misfolded transthyretin (TTR) to the level of total misfolded TTR in a biological sample; the method comprising:~~

~~(a) dividing a biological sample into two portions;~~

~~(b) detecting total misfolded TTR in a first portion of the biological sample by~~

~~(i) contacting the first portion of the biological sample with a capture antibody that specifically binds to an epitope within residues 89-97 of TTR and a reporter antibody that specifically binds to a different epitope of TTR; wherein if misfolded TTR is present in the~~

sample, the capture antibody and reporter antibody bind to the misfolded TTR forming a sandwich complex; and

(ii) detecting the reporter antibody forming a sandwich complex in step (b)(i), if any, to indicate presence or absence of the misfolded TTR;

(c) detecting total multimeric misfolded TTR in a second portion of the biological sample by

(i) contacting the second portion of the biological sample with a capture antibody that specifically binds to an epitope within residues 89-97 and a reporter antibody that specifically binds to an epitope within residues 89-97 of TTR; wherein if multimeric misfolded TTR is present in the sample, the capture antibody and reporter antibody bind to the multimeric misfolded TTR forming a sandwich complex; and

(ii) detecting the reporter antibody forming a sandwich complex in step (c)(i), if any, to indicate presence or absence of the multimeric misfolded TTR.

(d) calculating a ratio of the level of total multimeric misfolded TTR of (c) to the level of total misfolded TTR of (b).

87. — A method of detecting misfolded transthyretin (TTR) in a biological sample, the method comprising:

(a) contacting a biological sample with a capture antibody that specifically binds to an epitope within residues 101-109 of TTR and a reporter antibody that specifically binds to a different epitope of TTR; wherein if misfolded TTR is present in the sample, the capture antibody and reporter antibody bind to the misfolded TTR forming a sandwich complex; and

(b) detecting the reporter antibody that binds to the misfolded TTR in step (a), if any, to indicate presence or absence of the misfolded TTR.

88. — The method of claim 87, wherein the biological sample is from a hereditary ATTR patient.

89. — ~~The method of claim 88, wherein the biological sample is from a hereditary ATTR patient carrying a mutation selected from the group consisting of V30M, Y114C, and S50I.~~

90. — ~~The method of claim 89, wherein the mutation is V30M.~~

91. — ~~The method of claim 89, wherein the mutation is Y114C.~~

92. — ~~The method of claim 89, wherein the mutation is S50I.~~

93. — ~~The method of claim 87, wherein the capture antibody is 18C5.~~

94. — ~~The method of claim 93 wherein the capture antibody is 18C5 and the reporter antibody is a polyclonal anti-TTR antibody.~~

95. — ~~The method of any one of claims 87-93, wherein the reporter antibody is 9D5, 14G8, 5A1, 6C1, 8C3, 7G7, AD7F6, RT24, NI-301.35G11, MFD101, MDF102, MFD103, MFD105, MFD107, MFD108, MFD109, MFD111, MFD114, or a chimeric version or humanized version thereof.~~

96. — ~~The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is 9D5, or a chimeric version or humanized version thereof.~~

97. — ~~The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is 14G8, or a chimeric version or humanized version thereof.~~

98. — ~~The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is 5A87, or a chimeric version or humanized version thereof.~~

99. — ~~The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is 6C87, or a chimeric version or humanized version thereof.~~

100. — ~~The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is 8C3, or a chimeric version or humanized version thereof.~~

~~101.—The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is 7G7, or a chimeric version or humanized version thereof.~~

~~102.—The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is AD7F6, or a chimeric version or humanized version thereof.~~

~~103.—The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is RT24, or a chimeric version or humanized version thereof.~~

~~104.—The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is NI-301.35G187, or a chimeric version or humanized version thereof.~~

~~105.—The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is MFD1087, or a chimeric version or humanized version thereof.~~

~~106.—The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is MDF102, or a chimeric version or humanized version thereof.~~

~~107.—The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is MFD103, or a chimeric version or humanized version thereof.~~

~~108.—The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is MFD105, or a chimeric version or humanized version thereof.~~

~~109.—The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is MFD107, or a chimeric version or humanized version thereof.~~

~~110.—The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is MFD108, or a chimeric version or humanized version thereof.~~

~~111.—The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is MFD109, or a chimeric version or humanized version thereof.~~

~~112.—The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is MFD1187, or a chimeric version or humanized version thereof.~~

~~113.—The method of claim 87, wherein the capture antibody is 18C5 and the reporter antibody is MFD114, or a chimeric version or humanized version thereof.~~

~~114.—The method of any one of claims 87-93, wherein the reporter antibody is an antibody that binds within residues 89-97, 118-122, 115-124, 53-63, 54-61, 36-49, 49-61, 109-121, 30-66, 70-127, 80-127, 90-127, 100-127, 110-127, or 115-127 of TTR.~~

~~115.—A method of determining in vivo target engagement of a test antibody administered to a subject, which target is an epitope within residues 101-109 of misfolded transthyretin (mis-TTR) by detecting the mis-TTR remaining in a biological sample from the subject treated with the test antibody, the method comprising:~~

~~(a) contacting the biological sample with a capture antibody that specifically binds to an epitope within residues 101-109 and a reporter antibody that specifically binds to a different epitope within TTR from that of the capture antibody; wherein if misfolded TTR is present in the sample, the capture antibody and reporter antibody bind to the misfolded TTR forming a sandwich complex; and~~

~~(b) detecting the reporter antibody forming a sandwich complex in step (a), if any, to indicate presence or absence of the misfolded TTR.~~

~~116.—The method of claim 115, wherein the biological sample is from a hereditary ATTR patient.~~

~~117.—The method of claim 116, wherein the biological sample is from a hereditary ATTR patient carrying a mutation selected from the group consisting of V30M, Y114C, and S50I.~~

~~118.—The method of claim 117, wherein the mutation is V30M.~~

~~119.—The method of claim 117, wherein the mutation is Y114C.~~

~~120.—The method of claim 117, wherein the mutation is S50I.~~

~~121.—The method of claim 115 or 116, wherein the capture antibody is 18C5, wherein the capture antibody and the reporter antibody have different labels.~~

~~122.—The method of claim 115, wherein the reporter antibody competes for binding with the capture antibody for binding multimeric misfolded transthyretin.~~

~~123.—The method of any preceding claim, wherein the reporter antibody has an electrochemiluminescent label and is detected by electrochemiluminescence.~~

~~124.—The method of any preceding claim, wherein the capture antibody has a biotin label.~~

~~125.—The method of any preceding claim, performed qualitatively.~~

~~126.—The method of any preceding claim, performed quantitatively to indicate an absolute or relative amount of the misfolded TTR.~~

~~127.—The method of any preceding claim, wherein the capture antibody is bound to a solid phase before the contacting step.~~

~~128.—The method of claim 127, wherein the capture antibody is attached to the solid phase via a linker.~~

~~129.—The method of claim 127, wherein the solid phase comprises at least one electrode.~~

~~130.—The method of any preceding claim, further comprising: comparing a signal from the reporter antibody with a signal from the reporter antibody in a control sample containing a known amount of misfolded TTR to determine the amount of misfolded TTR in the sample.~~

~~131.—The method of any preceding claim, further comprising comparing a signal from the reporter antibody from a calibration curve of signal versus amount of misfolded TTR to determine the amount of misfolded TTR in the sample.~~

132.—The method of any preceding claim, wherein a signal from the reporter antibody is proportional to the amount of misfolded TTR in the sample.

133.—The method of any preceding claim, wherein the sample is a sample from a human.

134.—The method of any preceding claim, wherein the sample is a body fluid.

135.—The method of any preceding claim, wherein the sample is plasma of a human.

136.—The method of any preceding claim, wherein presence of misfolded TTR is used to diagnose a subject from whom the sample was obtained with a transthyretin-mediated amyloidosis.

137.—The method of claim 136, wherein the transthyretin-mediated amyloidosis is a familial transthyretin amyloidosis or a sporadic wild-type transthyretin amyloidosis.

138.—The method of claim 137, wherein the subject has been identified as at risk of a familial transthyretin amyloidosis based on genetic testing.

139.—The method of claim 137, wherein the subject does not show symptoms of a familial transthyretin amyloidosis.

140.—The method of claim 139 wherein the subject does not have polyneuropathy or cardiomyopathy.

141.—The method of claim 137, wherein the familial transthyretin amyloidosis is familial amyloid cardiomyopathy (FAC), familial amyloid polyneuropathy (FAP), or central nervous system selective amyloidosis (CNSA).

142.—The method of any preceding claim, wherein the biological sample is from a patient receiving treatment for a transthyretin-mediated amyloidosis.

143.—A method of adjusting treatment of a subject with a transthyretin-mediated amyloidosis, comprising

~~(a) comparing the amount of misfolded TTR detected by the method of claim 25 in a sample from a subject previously treated for transthyretin mediated amyloidosis with the amount of misfolded TTR detected in the subject prior to treatment or during an earlier stage of treatment; and~~

~~(b) increasing the dose or frequency of administration of the prior treatment if the amount of misfolded TTR is the same or greater than that previously detected; or~~

~~(c) decreasing the dose or frequency of administration of the prior treatment or discontinuing the prior treatment if the amount of misfolded TTR is less than that previously detected.~~

~~144.—The method of claim 143 wherein the prior treatment is by intravenous administration of an anti-TTR antibody and if the amount of misfolded TTR is less than that previously detected, the prior treatment is discontinued and replaced with treatment with a TTR stabilizer, antisense oligonucleotide based therapy, RNA interference therapy or combination therapy with doxycycline and tauroursodeoxycholic acid.~~

~~145.—The method of claim 144, wherein the subject no longer receives treatment with the anti-TTR antibody.~~

~~146.—The method of claim 144, wherein the TTR tetramer stabilizer is tafamidis or diflunisal.~~

~~147.—The method of claim 144, wherein the TTR tetramer stabilizer is diflunisal.~~

~~148.—The method of claim 144, wherein the antisense oligonucleotide based therapeutic is inotersen.~~

~~149.—The method of claim 144, wherein the RNAi based therapeutic is patisiran or revusiran.~~

~~150.—The method of claim 144, wherein the anti-TTR antibody is 14G8.~~

~~151.—The method of claim 150, wherein the subject no longer receives treatment with the anti-TTR antibody.~~

~~152.—The method of claim 150, wherein the TTR tetramer stabilizer is tafamidis or diflunisal.~~

~~153.—The method of claim 150, wherein the TTR tetramer stabilizer is diflunisal.~~

~~154.—The method of claim 150, wherein the antisense oligonucleotide-based therapeutic is inotersen.~~

~~155.—The method of claim 150, wherein the RNAi based therapeutic is patisiran or revusiran.~~

~~156.—A method of adjusting treatment of a subject with a transthyretin-mediated amyloidosis, comprising~~

~~(a) comparing the amount of reporter antibody binding detected by the method of claim 46 in a sample from a subject before initiating treatment for transthyretin-mediated amyloidosis with the amount of reporter antibody binding detected in the subject after initiating treatment; and~~

~~(b) increasing the dose or frequency of administration of the treatment if the amount of reporter antibody binding is the same or greater than that previously detected; or~~

~~(c) decreasing the dose or frequency of administration of the treatment or discontinuing the treatment if the amount of reporter antibody binding is less than that previously detected.~~

~~157.—The method of any of claims 87-142, wherein a transthyretin-mediated amyloidosis is distinguished from amyloid light chain (AL) amyloidosis.~~

~~158.—The method of any of claim 87, wherein the sample is from a transgenic mouse with a transgene expressing human TTR.~~

159. — A method of determining a ratio of the level of total multimeric misfolded transthyretin (TTR) to the level of total misfolded TTR in a biological sample; the method comprising:

(a) dividing a biological sample into two portions;

(b) detecting total misfolded TTR in a first portion of the biological sample by

(i) contacting the first portion of the biological sample with a capture antibody that specifically binds to an epitope within residues 101–109 of TTR and a reporter antibody that specifically binds to a different epitope of TTR; wherein if misfolded TTR is present in the sample, the capture antibody and reporter antibody bind to the misfolded TTR forming a sandwich complex; and

(ii) detecting the reporter antibody bound to the misfolded TTR in step (i), if any, to indicate presence or absence of the misfolded TTR;

(c) detecting total multimeric misfolded TTR in a second portion of the biological sample by

(i) contacting the second portion of the biological sample with a capture antibody that specifically binds to an epitope within residues 101–109 and a reporter antibody that specifically binds to an epitope within residues 101–109 of TTR; wherein if multimeric misfolded TTR is present in the sample, the capture antibody and reporter antibody bind to the multimeric misfolded TTR forming a sandwich complex; and

(ii) detecting the reporter antibody bound to the multimeric misfolded TTR in step (a), if any, to indicate presence or absence of the multimeric misfolded TTR.

(d) calculating a ratio of the level of total multimeric misfolded TTR of (c) to the level of total misfolded TTR of (b).