WHAT IS CLAIMED IS:

1. A method comprising:

a) providing a blood sample from a subject;

b) isolating central nervous system ("CNS") derived exosomes from the blood sample;

c) removing proteins from the surface of the isolated exosomes to produce scrubbed exosomes;

d) isolating the internal contents of the scrubbed exosomes;

~~e) determining, in the isolated internal contents, a quantitative measure of oligomeric α-synuclein protein and, optionally, one or a plurality of protein forms selected from: monomeric α-synuclein, phosphorylated α-synuclein, monomeric tau, oligomeric tau, phosphorylated tau, amyloid beta ("a-beta") 1-40, amyloid beta 1-42, and oligomeric amyloid beta;~~

~~f)~~e) separating from the isolated internal contents, species of oligomeric α-synuclein into a plurality of fractions;

~~g)~~f) determining a quantitative measure of each of one or a plurality of the separated oligomeric α-synuclein species. ~~and, optionally, one or a plurality of species selected from: monomeric α-synuclein, tau-synuclein co-polymers, amyloid beta-synuclein co-polymers and tau-amyloid beta-synuclein co-polymers.~~

2. The method of claim **1**, wherein the blood sample is a plasma sample.

3. The method of claim **1 or 2**, wherein the blood sample comprises between ~~about~~ 5 ml and 20 ml of blood.

4. The method of any one of claims **1 to 3**, wherein the subject is a human subject.

5. The method of any one of claims 1 to **4**, wherein the subject has a synucleinopathy ~~(e.g., Parkinson's Disease, Lewy Body dementia or multiple system atrophy)~~.

6. The method of claim 5, wherein the synucleinopathy is selected from Parkinson's Disease, Lewy Body dementia and multiple system atrophy.

~~6.~~**7.** The method of any one of claims **1 to 6**, wherein isolating CNS-derived exosomes comprises: (i) isolating total exosomes from the blood sample and (ii) isolating CNS-derived exosomes from total exosomes.

~~7.~~**8.** The method of any one of claims **1 to 7**, wherein isolating CNS-derived exosomes comprises:

(i) ultra-centrifugation;

(ii) density gradient centrifugation; or

(iii) size exclusion chromatography.

~~8.~~**9.** The method of any one of claims **1 to 8**, wherein isolating CNS-derived exosomes comprises capturing the CNS-derived exosomes using a binding moiety that binds to CNS-specific protein.

~~9.~~**10.** The method of claim ~~8~~**9**, wherein the CNS-specific protein is LCAM.

~~**10.** The method of claim **1**, wherein removing proteins from the surface of the isolated exosomes comprises washing the isolated exosomes with an aqueous solution (e.g., phosphate buffered saline ("PBS")).~~

11. The method of any one of claims **1 to 10**, wherein the quantitative measures are total amounts of the protein forms.

12. The method of any one of claims **1 to 10**, comprising determining, in the isolated internal contents, a quantitative measure of monomeric α-synuclein.

13. The method of any one of claims **1 to 10**, comprising determining, in the isolated internal contents, a quantitative measure of one or a plurality of species selected from monomeric tau, oligomeric tau and phosphorylated tau.

14. The method of any one of claims **1 to 10**, comprising determining p129 alpha-synuclein.

15. The method of any one of claims **1 to 10**, comprising determining, in the isolated internal contents, a quantitative measure of one or a plurality of species selected from amyloid beta 1-40, amyloid beta 1-42, and oligomeric amyloid beta.

16. The method of any one of claims **1 to 15**, wherein separating species comprises into a plurality of fractions comprises: (i) separating by electrophoresis~~.~~; or

~~**17.** The method of claim **1**, wherein separating species into a plurality of fractions comprises~~ (ii) separating by chromatography.

~~**18.**~~**17.** The method of any one of claims **1 to 16**, comprising determining among the separated species, at least one oligomeric form of α-synuclein selected from forms having between 2 and ~~about~~ 100 monomeric units, between 4 and 16 monomeric units and no more than ~~about~~ 30 monomeric units.

~~**19.**~~**18.** The method of any one of claims **1 to 17**, comprising determining among the separated species~~.~~: (i) a quantitative measure of monomeric α-synuclein~~.~~;

~~**20.** The method of claim **1**, comprising determining among the separated species,~~ (ii) a quantitative measure of a plurality of different oligomeric α-synuclein species~~.~~;

~~**21.** The method of claim **1**, comprising determining among the separated species,~~ (iii) a quantitative measure of a co-polymer comprising α-synuclein and tau~~.~~;

~~**22.** The method of claim **1**, comprising determining among the separated species,~~ (iv) a quantitative measure of a co-polymer comprising α-synuclein and amyloid beta.

~~**23.**~~**19.** The method of claim ~~**1**~~**18**, wherein determining a quantitative measure in the separated species comprises detecting one or a plurality of separated species by immunoassay.

~~**24.**~~**20.** The method of claim ~~**22**~~**19**, wherein the immunoassay comprises immunoblotting or Western blot.

~~**25.** The method of claim **22**, wherein the immunoassay comprises Western blot.~~

~~**26.**~~**21.** The method of claim **22**, wherein the immunoassay uses an antibody coupled to a direct label or~~.~~

~~**27.** The method of claim **22**, wherein the immunoassay uses~~ an antibody coupled to an indirect label.

~~**28.**~~**22.** The method of any one of claims **1** **to 21**, further comprising:

~~f)~~g) based on the quantitative measures of one or a plurality of the separated oligomeric α-synuclein species, determining a diagnosis of Parkinson's disease in the subject.

~~**29.**~~**23.** The method of any one of claims **1** **to 21**, further comprising:

~~f)~~g) determining quantitative amounts of proteins in the subject before and after administration of a putative neuroprotective agent; and

~~g)~~h) determining changes in amounts of proteins or patterns of biomarker profiles, wherein changes toward normal amounts or profile indicate efficacy of the neuroprotective agent.

~~**30.**~~**24.** The method of any one of claims **1** **to 21**, further comprising:

~~f)~~g) determining quantitative amounts of proteins in the subject at two different times; and

~~g)~~h) determining changes in amounts of proteins or patterns of biomarker profiles, wherein changes indicate a change in a neurodegenerative state.

~~**31.** A method comprising:~~

~~a) providing a sample comprising a mixture of proteins, said proteins consisting essentially of proteins from an internal compartment of CNS-derived exosomes;~~

~~b) fractionating oligomeric α-synuclein species in the sample; and~~

~~c) determining a quantitative measure of each of one or a plurality of the separated oligomeric α-synuclein species and, optionally, one or a plurality of species selected from: monomeric α-synuclein, tau-synuclein co-polymers, amyloid beta-synuclein co-polymers and tau-amyloid beta-synuclein co-polymers.~~

~~**32.** The method of claim **31**, wherein the product comprises oligomeric α-synuclein species isolated from a product enriched for scrubbed, CNS-derived exosomes.~~

~~**33.**~~**25.** A method comprising:

a) enriching each ~~biological~~blood sample in a collection of ~~biological~~blood samples for brain-derived exosomes, wherein:

(i) the collection of ~~biological~~blood samples is from subjects in a cohort of subjects, wherein the cohort comprises subjects including:

(1) a plurality of subjects diagnosed with a ~~neurodegenerative~~ synucleopathic condition at each of a plurality of different disease stages, wherein each of the diagnosed subjects has received a putative neuroprotective agent, and/or

(2) a plurality of healthy control subjects,

wherein the ~~biological~~blood samples were collected before and again at one or more times during ~~and, optionally, after~~ administration of the putative neuroprotective agent;

b) isolating protein contents from an internal compartment of the exosomes from which external proteins have been removed to produce a biomarker sample;

c) measuring, in the biomarker sample, amounts of each of one or a plurality of neurodegenerative protein forms to create a dataset, wherein the neurodegenerative protein forms include one or more oligomeric forms of α -synuclein~~and, optionally, one or more monomeric forms~~; and

d) performing statistical analysis on the dataset to compare differences in the amounts of each of the neurodegenerative protein forms:

(i) in individual subjects over time to determine a diagnostic algorithm that predicts rates of disease progression or degree of response to the putative neuroprotective agent; or

(ii) between different subjects to determine a diagnostic algorithm that (1) makes a pathogenic diagnosis, (2) separates clinically similar but etiologically different neurodegenerative disorder subgroups, or (3) predicts whether or the degree to which a subject is likely to respond to the putative neuroprotective agent.

26. The method according to claim **25** wherein the neurodegenerative protein forms include one or more monomeric forms of α -synuclein.

~~**34.** A method comprising:~~

~~a) enriching a biological sample from a subject for brain-derived exosomes;~~

~~b) isolating protein contents from an internal compartment of the exosomes to produce a biomarker sample;~~

~~c) measuring, in the biomarker sample, amounts of each of one or a plurality of neurodegenerative protein forms to create a neurodegenerative protein profile wherein the~~

neurodegenerative protein forms include one or more oligomeric forms and, optionally, one or more monomeric forms; and

d) correlating the neurodegenerative protein profile to perform one of the following: (1) make a pathogenic diagnosis, (2) classify the subject into one of a plurality of clinically similar but etiologically different neurodegenerative disorder subgroups, or (3) predict whether or the degree to which the subject is likely to respond to the putative neuroprotective agent.

35.27. A method comprising:

a) providing a dataset comprising, for each of a plurality of subjects, values indicating (1) state of a neurodegenerativesynucleopathic condition, and (2) quantitative measures of amounts of each of one or a plurality of neurodegenerative protein forms in a biologicalblood sample enriched for internal contents of CNS-derived microsomal particles exosomes from which external proteins have been removed, wherein the neurodegenerative protein forms include one or more oligomeric forms of α-synucleinand, optionally, one or more monomeric forms; and

b) performing a statistical analysis on the dataset to develop a model that infers the state of the neurodegenerativesynucleopathic condition in an individual.

28. The method according to claim **27**, wherein the neurodegenerative protein forms include one or more monomeric forms of α-synuclein.

36. A method of inferring a risk of developing, a diagnosis of, a stage of, a prognosis of or a progression of a neurodegenerative condition characterized by a neurodegenerative protein, wherein the method comprises:

a) determining, from a biological sample from a subject that is enriched for CNS-derived microsomal particles, a neurodegenerative protein profile comprising quantitative measures of each of one or a plurality of neurodegenerative protein forms to create a dataset, wherein the neurodegenerative protein forms include one or more oligomeric forms and, optionally, one or more monomeric forms; and

b) executing a model, e.g., a model of claim **35,** on the dataset to infer a risk of developing, a diagnosis of, a stage of, a prognosis of or a progression of the neurodegenerative condition.

37. A method for determining effectiveness of a therapeutic intervention in treating a neurodegenerative condition characterized by a neurodegenerative protein, wherein the method comprises:

(a) inferring, in each subject in a population comprising a plurality of subjects, an initial state of a neurodegenerative condition by:

(1) determining, from a biological sample from a subject that is enriched for CNS-derived microsomal particles, a neurodegenerative protein profile comprising quantitative measures of each of one or a plurality of neurodegenerative protein forms to create a dataset, wherein the neurodegenerative protein forms include one or more oligomeric forms and, optionally, one or more monomeric forms; and

(2) inferring the initial state using a model, e.g., a model of claim **35**;

(b) after inferring, administering the therapeutic intervention to the subjects;

(c) after administering, inferring, in each subject individual in the population, a subsequent a subsequent state of the neurodegenerative condition by:

(1) determining, from a biological sample from a subject that is enriched for CNS-derived microsomal particles, a neurodegenerative protein profile comprising quantitative measures of each of one or a plurality of neurodegenerative protein forms to create a dataset, wherein the neurodegenerative protein forms include one or more oligomeric forms and, optionally, one or more monomeric forms; and

(2) inferring the subsequent state using the model; and

(d) based on the initial and subsequent inferences in the population, determining that the therapeutic intervention is effective if the subsequent inferences exhibit a statistically significant change toward a normal state compared with the initial inferences, or that the therapeutic intervention is not effective if the subsequent inferences do not exhibit a statistically significant change compared with the initial inferences toward a normal state.

38.29. A method for qualifying subjects for a clinical trial of a therapeutic intervention for the treatment or prevention of a neurodegenerativesynucleopathic condition comprising:

a) determining that a subject is abnormal with respect with a to the neurodegenerativesynucleopathic condition characterized by a neurodegenerative protein by:

i) determining, from a biologicalblood sample from a subject that is enriched for CNS-derived microsomal particlesexosomes from which external

proteins have been removed, a neurodegenerative protein profile comprising quantitative measures of each of one or a plurality of neurodegenerative protein forms to create a dataset, wherein the neurodegenerative protein forms include one or more oligomeric forms of α-synuclein ~~and, optionally, one or more monomeric forms~~; and

ii) executing a model, e.g., a model of claim ~~35~~27**,** on the profile to infer that the subject is abnormal with respect with the ~~neurodegenerative~~synucleopathic condition; and

c) enrolling the subject in the clinical trial of a potentially therapeutic intervention for said ~~neurodegenerative~~synucleopathic condition.

30. The method according to claim **29**, wherein the neurodegenerative protein forms include one or more monomeric forms of α-synuclein.

~~**39.** A method of monitoring progress of a subject on a therapeutic intervention for a neurodegenerative condition comprising:~~

~~(a) inferring, in the subject, an initial state of a neurodegenerative condition by:~~

~~(1) determining, from a biological sample from a subject that is enriched for CNS-derived microsomal particles, a neurodegenerative protein profile comprising quantitative measures of each of one or a plurality of neurodegenerative protein forms to create a dataset, wherein the neurodegenerative protein forms include one or more oligomeric forms and, optionally, one or more monomeric forms; and~~

~~(2) executing a model, e.g., a model of claim **35**, to infer an initial state of the neurodegenerative condition;~~

~~(b) after inferring, administering the therapeutic intervention to the subject;~~

~~(c) after administering, inferring, in the subject, a subsequent state of the neurodegenerative condition by:~~

~~(1) determining, from a biological sample from a subject that is enriched for CNS-derived microsomal particles, a neurodegenerative protein profile comprising quantitative measures of each of one or a plurality of neurodegenerative protein forms to create a dataset, wherein the neurodegenerative protein forms include one or more oligomeric forms and, optionally, one or more monomeric forms; and~~

(2) executing a model, e.g. a model of claim **35**, to infer a subsequent state of the neurodegenerative condition;

(d) based on the initial and subsequent state inferences, determining that the subject is responding positively to the therapeutic intervention if the subsequent inference exhibits a change toward a normal state compared with the initial inferences, or that the therapeutic intervention is not effective if the subsequent inferences do not exhibit a change compared with the initial inferences toward a normal state.

40. A method comprising:

(a) determining, by the method of claim **36**, that a subject has a neurodegenerative condition characterized by a neurodegenerative protein, and

(b) administering to the subject a palliative or neuroprotective therapeutic intervention efficacious to treat the condition.

41.31. A kit comprising first reagents sufficient to detect an oligomeric form of a protein selected from alpha-synuclein, tau, amyloid beta and huntingtin and second reagents sufficient to detect a monomeric form of a protein selected from alpha-synuclein, tau, amyloid beta and huntingtin.

42.32. A method of inferring a risk of developing, a diagnosis of, a stage of, a prognosis of or a progression of a neurodegenerativesynucleopathic condition characterized by a neurodegenerative protein, wherein the method comprises:

a) determining, from a biologicalblood sample from a subject that is enriched for CNS-derived microsomal particlesexosomes from which external proteins have been removed, a neurodegenerative protein profile comprising quantitative measures of each of one or a plurality of neurodegenerative protein forms to create a dataset, wherein the neurodegenerative protein forms include one or more oligomeric forms and, optionally, one or more monomeric formsof α-synuclein; and

b) correlating the neurodegenerative protein profile with a risk of developing, a diagnosis of, a stage of, a prognosis of or a progression of the neurodegenerativesynucleopathic condition.

33. The method according to claim **32**, wherein the neurodegenerative protein forms include one or more monomeric forms of α-synuclein.

34. A method of making a diagnosis of a synucleopathic condition in a human subject, comprising:

a) providing a blood sample from the human subject;

b) enriching the blood sample for central nervous system ("CNS") derived exosomes;

c) removing proteins from the surface of the isolated exosomes to produce scrubbed exosomes;

d) isolating the internal contents of the scrubbed exosomes;

e) measuring an amount of at least one toxic form of oligomeric α-synuclein in the isolated internal contents;

f) making a diagnosis of a synucleopathic condition, wherein an amount of the toxic form of oligomeric α-synuclein greater than an amount of the form of oligomeric α-synuclein in a normal subject indicates presence of the synucleopathic condition.

35. The method of claim **34**, wherein the synucleopathic condition is Parkinson's Disease, Lewy Body Dementia or multiple system atrophy.

36. The method of claim **34** or **35**, wherein the blood sample is a plasma sample.

37. The method of claim **36**, further comprising storing the blood sample at -80 degrees C.

38. The method of claim **34**, wherein the toxic form of oligomeric α-synuclein species measured is selected from a form having between 2 and 100 monomeric units, between 4 and 16 monomeric units, and no more than 30 monomeric units.

39. The method of claim **34**, wherein the toxic form of oligomeric α-synuclein species measured is selected from a 10-mer, 11-mer, 12-mer, 13-mer, 14-mer, 15-mer, 16-mer, and 18-mer.

40. The method of claim **34**, wherein the amount of the toxic form of oligomeric α-synuclein is a normalized amount.

41. The method of claim **40**, wherein the amount is normalized against an amount of monomeric α-synuclein.

42. The method of claim **34**, wherein measuring comprises separating forms of oligomeric α-synuclein into a plurality of fractions.

43. The method of claim **42**, wherein separating comprises electrophoresis.

44. The method of claim **34**, wherein measuring comprises immunoassay or Western blot.

45. The method according to any one of claims **1 to 30** or claims **32 to 44** wherein the blood sample is stored at -80˚C.