CLAIMS

1. A method for measuring time to dementia onset in a subject with or without cognitive or behavioral symptoms of Alzheimer's disease, the method comprising

(a_i) *in vitro*, measuring phosphorylation occupancy at residue T205 of tau and measuring MTBR-tau299/MTBR-tau354 ratio, and optionally measuring, *in vitro*, MTBR-tau212, phosphorylation occupancy at residue T217 MTBR-tau243, MTBR-tau3R, or a combination thereof, in a blood sample or a CSF sample obtained from the subject, or

(a_{ii}) measuring, *in vitro*, phosphorylation occupancy at residue T205 of tau, measuring, *in vitro*, phosphorylation occupancy at residue T217 of tau, and measuring, *in vitro*, MTBR-tau212, in a blood sample or a CSF sample obtained from the subject; and

(b) using the measurements of (a_i) or (a_{ii}) to calculate time to dementia onset, wherein time to dementia onset is time in years to a Clinical Dementia Rating greater than zero.

2. A method for measuring time to dementia onset in a subject without cognitive or behavioral symptoms of Alzheimer's disease, the method comprising

(a) processing, *in vitro*, a blood sample or a CSF sample from the subject to obtain a first population of tau species and a depleted sample, and then processing the depleted sample *in vitro* to obtain a second population of tau species,

wherein the first population of tau species is enriched for N-terminal tau and/or mid-domain tau, and

wherein the second population of enriched tau species is enriched for MTBR-tau;

(b_i) measuring phosphorylation occupancy at residue T205 of tau in the first population of tau species and measuring MTBR-tau299/MTBR-tau354 ratio in the second population of tau species, and optionally measuring MTBR-tau212 in the second population of tau species, or

(b_{ii}) measuring phosphorylation occupancy at residue T205 of tau and measuring phosphorylation occupancy at residue T217 of tau in the first population of tau species, and measuring MTBR-tau212 in the second population of tau species; and

(c) calculating time to dementia onset using the measurements of (b_i) or (b_{ii}), wherein time to dementia onset is time in years to a Clinical Dementia Rating greater than zero.

3. The method of claim 2, wherein processing a blood sample or a CSF sample from the subject to obtain a first population of enriched tau species and a depleted sample comprises

contacting the blood sample or the CSF sample *in vitro* with an epitope-binding agent that specifically binds to an epitope within the N-terminus of tau, or

contacting the blood sample or the CSF sample *in vitro* with an epitope-binding agent that specifically binds to an epitope within the mid-domain of tau, or

contacting the blood sample or the CSF sample *in vitro* with a first epitope-binding agent that specifically binds to an epitope within the N-terminus of tau and with a second epitope-binding agent that specifically binds to an epitope within the mid-domain of tau, wherein the first and second epitope-binding agents are used sequentially or at the same time;

optionally wherein the epitope-binding agent that specifically binds to an epitope within the N-terminus of tau is HJ8.5 or another epitope-binding agent that specifically binds the same epitope as HJ8.5, and optionally wherein the epitope-binding agent that specifically binds to an epitope within the mid-domain of tau is Tau1 or another epitope-binding agent that specifically binds the same epitope as Tau1.

4. The method of claim 2, wherein processing the depleted sample to obtain a second population of enriched tau species comprises

performing a chemical extraction step to enrich for MTBR-tau species,

optionally wherein the chemical extract step comprises admixing an acid to precipitate proteins of the depleted sample, optionally wherein the acid is perchloric acid, and wherein the MTBR-tau species are in the supernatant after removal of the precipitated proteins; or

contacting the depleted sample with an epitope-binding agent that specifically binds to at least one epitope within the MTBR of tau,

optionally wherein the epitope-binding agent is 77G7, RD3, RD4, UCB1017, or PT76 described in Vandermeeren et al., J Alzheimers Dis, 2018, 65:265-281, or 7G6 described in Roberts et al., Acta Neuropathol Commun, 2020, 8: 13, or antigen-binding fragments of 77G7, RD3, RD4, UCB1017, PT76, or 7G6, or other epitope-binding agents that specifically bind the same epitopes as 77G7, RD3, RD4, UCB1017, PT76, or 7G6.

5. The method of claim 2, wherein

processing a blood sample or a CSF sample from the subject to obtain a first population of enriched tau species and a depleted sample comprises

contacting the blood sample or the CSF sample *in vitro* with an epitope-binding agent the specifically binds to an epitope within the N-terminus of tau, or

contacting the blood sample or the CSF sample *in vitro* with an epitope-binding agent the specifically binds to an epitope within the mid-domain of tau, or

contacting the blood sample or the CSF sample *in vitro* with a first epitope-binding agent that specifically binds to an epitope within the N-terminus of tau and with a second epitope-binding agent that specifically binds to an epitope within the mid-domain of tau, wherein the first and second epitope-binding agents are used sequentially or at the same time,

optionally wherein the epitope-binding agent that specifically binds to an epitope within the N-terminus of tau is HJ8.5 or another epitope-binding agent that specifically binds the same epitope as HJ8.5, and optionally wherein the epitope-binding agent that specifically binds to an epitope within the mid-domain of tau is Tau1 or another epitope-binding agent that specifically binds the same epitope as Tau1; and

processing the depleted sample to obtain a second population of enriched tau species comprises

performing a chemical extraction step to enrich for MTBR-tau species, optionally wherein the chemical extract step comprises admixing an acid to precipitate proteins of the depleted sample, optionally wherein the acid is perchloric acid, and wherein the MTBR-tau species are in the supernatant after removal of the precipitated proteins; or

contacting the depleted sample with an epitope-binding agent that specifically binds to at least one epitope within the MTBR of tau, optionally wherein the epitope-binding agent is 77G7, RD3, RD4, UCB1017, or PT76 described in Vandermeeren et al., J Alzheimers Dis, 2018, 65:265-281, or 7G6 described in Roberts et al., Acta Neuropathol Commun, 2020, 8: 13, or antigen-binding fragments of 77G7, RD3, RD4, UCB1017, PT76, or 7G6, or other epitope-binding agents that specifically bind the same epitopes as 77G7, RD3, RD4, UCB1017, PT76, or 7G6.

6. The method of any one of claims 1 to 5, wherein the subject has a CDR of zero.

7. Use of a time to dementia onset measurement of any one of claims 1 to 6 to stage a subject’s disease progression.

8. Use of a time to dementia onset measurement of any one of claims 1 to 6 to stage a subject's brain pathology.

9. A method for measuring time from dementia onset in a subject with cognitive or behavioral symptoms of Alzheimer's disease, the method comprising

(a_i) *in vitro,* measuring phosphorylation occupancy at residue T205 of tau and measuring MTBR-tau299/MTBR-tau354 ratio, and optionally measuring, *in vitro*, MTBR-tau212, phosphorylation occupancy at residue T217 MTBR-tau243, MTBR-tau3R, or a combination thereof, in a blood sample or a CSF sample obtained from the subject, or

(a_{ii}) *in vitro,* measuring phosphorylation occupancy at residue T205 of tau, measuring phosphorylation occupancy at residue T217 of tau, and measuring, *in vitro*, MTBR-tau212, in a blood sample or a CSF sample obtained from the subject; and

(b) using the measurements of (a_i) or (a_{ii}) to calculate time from dementia onset, wherein time from dementia onset is time in years from a Clinical Dementia Rating greater than zero.

10. A method for measuring time from dementia onset in a subject with cognitive or behavioral symptoms of Alzheimer's disease, the method comprising

(a) *in vitro,* processing a blood sample or a CSF sample from the subject to obtain a first population of tau species and a depleted sample, and then processing the depleted sample *in vitro* to obtain a second population of tau species,

wherein the first population of tau species is enriched for N-terminal tau and/or mid-domain tau, and

wherein the second population of enriched tau species is enriched for MTBR-tau;

(b_i) measuring phosphorylation occupancy at residue T205 of tau in the first population of tau species and measuring MTBR-tau299/MTBR-tau354 ratio

in the second population of tau species, and optionally measuring MTBR-tau212 in the second population of tau species, or

(b_{ii}) measuring phosphorylation occupancy at residue T205 of tau and measuring phosphorylation occupancy at residue T217 of tau in the first population of tau species, and measuring MTBR-tau212 in the second population of tau species; and

(c) calculating time from dementia onset using the measurements of (b_i) or (b_{ii}), wherein time from dementia onset is time in years from a Clinical Dementia Rating greater than zero.

11. The method of claim 10, wherein processing a blood sample or a CSF sample from the subject to obtain a first population of enriched tau species and a depleted sample comprises

contacting the blood sample or the CSF sample *in vitro* with an epitope-binding agent the specifically binds to an epitope within the N-terminus of tau, or

contacting the blood sample or the CSF sample *in vitro* with an epitope-binding agent the specifically binds to an epitope within the mid-domain of tau, or

contacting the blood sample or the CSF sample *in vitro* with a first epitope-binding agent that specifically binds to an epitope within the N-terminus of tau and with a second epitope-binding agent that specifically binds to an epitope within the mid-domain of tau, wherein the first and second epitope-binding agents are used sequentially or at the same time;

optionally wherein the epitope-binding agent that specifically binds to an epitope within the N-terminus of tau is HJ8.5 or another epitope-binding agent that specifically binds the same epitope as HJ8.5, and optionally wherein the epitope-binding agent that specifically binds to an epitope within the mid-domain of tau is Tau1 or another epitope-binding agent that specifically binds the same epitope as Tau1.

12. The method of claim 10, wherein processing the depleted sample to obtain a second population of enriched tau species comprises

performing a chemical extraction step to enrich for MTBR-tau species,

optionally wherein the chemical extract step comprises admixing an acid to precipitate proteins of the depleted sample, optionally wherein the acid is perchloric acid, and wherein the MTBR-tau species are in the supernatant after removal of the precipitated proteins; or

contacting the depleted sample with an epitope-binding agent that specifically binds to at least one epitope within the MTBR of tau,

optionally wherein the epitope-binding agent is 77G7, RD3, RD4, UCB1017, or PT76 described in Vandermeeren et al., J Alzheimers Dis, 2018, 65:265-281, or 7G6 described in Roberts et al., Acta Neuropathol Commun, 2020, 8: 13, or antigen-binding fragments of 77G7, RD3, RD4, UCB1017, PT76, or 7G6, or other epitope-binding agents that specifically bind the same epitopes as 77G7, RD3, RD4, UCB1017, PT76, or 7G6.

13. The method of claim 10, wherein

processing a blood sample or a CSF sample from the subject to obtain a first population of enriched tau species and a depleted sample comprises

contacting the blood sample or the CSF sample *in vitro* with an epitope-binding agent the specifically binds to an epitope within the N-terminus of tau, or

contacting the blood sample or the CSF sample *in vitro* with an epitope-binding agent the specifically binds to an epitope within the mid-domain of tau, or

contacting the blood sample or the CSF sample *in vitro* with a first epitope-binding agent that specifically binds to an epitope within the N-terminus of tau and with a second epitope-binding agent that specifically

binds to an epitope within the mid-domain of tau, wherein the first and second epitope-binding agents are used sequentially or at the same time,

optionally wherein the epitope-binding agent that specifically binds to an epitope within the N-terminus of tau is HJ8.5 or another epitope-binding agent that specifically binds the same epitope as HJ8.5, and optionally wherein the epitope-binding agent that specifically binds to an epitope within the mid-domain of tau is Tau1 or another epitope-binding agent that specifically binds the same epitope as Tau1; and

processing the depleted sample to obtain a second population of enriched tau species comprises

performing a chemical extraction step to enrich for MTBR-tau species,

optionally wherein the chemical extract step comprises admixing an acid to precipitate proteins of the depleted sample, optionally wherein the acid is perchloric acid, and wherein the MTBR-tau species are in the supernatant after removal of the precipitated proteins; or

contacting the depleted sample with an epitope-binding agent that specifically binds to at least one epitope within the MTBR of tau,

optionally wherein the epitope-binding agent is 77G7, RD3, RD4, UCB1017, or PT76 described in Vandermeeren et al., J Alzheimers Dis, 2018, 65:265-281, or 7G6 described in Roberts et al., Acta Neuropathol Commun, 2020, 8: 13, or antigen-binding fragments of 77G7, RD3, RD4, UCB1017, PT76, or 7G6, or other epitope-binding agents that specifically bind the same epitopes as 77G7, RD3, RD4, UCB1017, PT76, or 7G6.

14. The method of any one of claims 9 to 13, wherein the subject has a CDR of greater than or equal to 0.5, a CDR greater than or equal to 1, or a CDR greater than or equal to 2.

15. Use of a time to dementia onset measurement of any one of claims 9 to 13 to stage a subject's disease progression.

16. Use of a time to dementia onset measurement of any one of claims 9 to 13 to stage a subject's brain pathology.

17. A method for measuring change in cognition in a subject, the method comprising

(a) *in vitro,* measuring phosphorylation occupancy at one or more residue of tau selected from T111, T153, T181, T217 and T231 in a blood sample or a CSF sample obtained from the subject, and

Measuring, *in vitro*, at least one of MTBR-tau275, MTBR-tau299, and MTBR-3R in a blood sample or a CSF sample obtained from the subject, and

optionally measuring, *in vitro*, total tau in a blood sample or a CSF sample obtained from the subject; and

(b) using the measurements of (a) to calculate a change in cognition.

18. The method of claim 17, wherein the change in cognition is equivalent to the change in cognition measured by cognitive composite score consisting of the delayed recall score from the International Shopping List Test, the Logical Memory delayed recall score from the Wechsler Memory Scale-Revised, the Digit Symbol Coding test total score from the Wechsler Adult Intelligence Scale-Revised, and the MMSE total score.

19. The method of claim 17 or claim 18, wherein the subject has a CDR of zero.

20. The method of claim 17 or claim 18, wherein the subject has a CDR greater than or equal to 0.5.