CLAIMS

1. A method to determine an individual's risk of Alzheimer's disease, comprising:

having obtained a biological sample of an individual, wherein the biological sample ~~contains dicarboxylic acids~~ is derived from a collection of blood or urine;

adding an internal standard of dicarboxylic acid molecules to the biological sample;

performing an assay on the biological sample to determine an amount of at least one ~~long~~ dicarboxylic acid species in the sample, wherein the determined amount of the at least one ~~long~~ dicarboxylic acid species indicates the individual's risk of Alzheimer's disease, wherein the at least one dicarboxylic acid species is succinic acid (C4), glutaric acid (C5), pimelic acid (C7), suberic acid (C8), an unsaturated C4, C5, C7, or C8 dicarboxylic acid species, or a substituted C4, C5, C7 or C8 dicarboxylic acid species.

~~2. The method as in claim 1, wherein the biological sample is urine.~~

~~3~~2. The method as in claim 1 ~~or 2~~, wherein the assay is gas chromatography combined with mass spectrometry.

~~4~~3. The method as in claim ~~3~~2 further comprising: converting the dicarboxylic acids within the biological to dipentafluorobenzyl esters prior to performing gas chromatography combined with mass spectrometry.

~~5~~4. The method as in any one of claims 1-~~4~~3, wherein the internal standard of dicarboxylic acid molecules includes at least one of: succinic acid (C4), glutaric acid (C5), pimelic acid (C7), suberic (C8), azelaic acid (C9) and sebacic acid (C10).

~~6~~5. The method as in any one of claims 1-~~5~~4, wherein the internal standard of dicarboxylic acid molecules is a set of deuterated dicarboxylic acid molecules with known concentrations.

~~7~~6. The method as in any one of claims 1-~~6~~5, wherein the amount of at least one ~~long~~ dicarboxylic acid species is a relative amount to a set of one or more dicarboxylic acid species measured.

~~8~~7. The method as in any one of claims 1-~~6~~5, wherein the amount of at least one ~~long~~ dicarboxylic acid species is a concentration.

~~9~~8. The method as in any one of claims 1-~~8~~7,

wherein the at least one dicarboxylic acid species is pimelic acid (C7), suberic acid (C8), an unsaturated C7 or C8 dicarboxylic acid species, or a substituted C7 or C8 dicarboxylic acid species, wherein the determined amount of the at least one ~~long~~ dicarboxylic acid species of the individual is greater than a threshold, and wherein the individual is determined to have a high risk of Alzheimer's disease based on the amount of the at least one ~~long~~ dicarboxylic acid species being greater than the threshold; or

wherein the at least one short dicarboxylic acid species is succinic acid (C4), glutaric acid (C5), an unsaturated C4 or C5 dicarboxylic acid species, or a substituted C4 or C5 dicarboxylic acid species, wherein the determined amount of the at least one dicarboxylic acid species of the individual is less than a threshold, and wherein the individual is determined to have a high risk of Alzheimer's disease based on the amount of the at least one dicarboxylic acid species being less than the threshold.

~~10~~9. The method as in claim ~~9~~8, wherein the threshold is based on the amount of the at least one long dicarboxylic acid species in a cognitively healthy population or in a population of individuals having Alzheimer's disease.

~~11. The method as in any one of claims 1-10, wherein the at least one long dicarboxylic acid species is pimelic acid (C7), suberic acid (C8), azelaic acid (C9), sebacic acid (C10), an unsaturated C7, C8, C9 or C10 dicarboxylic acid species, or a substituted C7, C8, C9 or C10 dicarboxylic acid species.~~

~~12~~10. The method as in any one of claim 1-~~11~~9 further comprising:

performing an assay on the biological sample to determine a relative amount of at least one short dicarboxylic acid species and at least one long dicarboxylic acid species in the sample, wherein the at least one short dicarboxylic acid species is succinic acid (C4), glutaric acid (C5), an unsaturated C4 or C5 dicarboxylic acid species, or a substituted C4 or C5 dicarboxylic acid species, wherein the at least one long dicarboxylic acid species is pimelic acid (C7), suberic acid (C8), an unsaturated C7 or C8 dicarboxylic acid species, or a substituted C7 or C8 dicarboxylic acid species; and

determining a ratio of the relative amount of at least one long dicarboxylic acid species to the relative amount of at least one short dicarboxylic acid species, wherein the determined ratio indicates the individual's risk of Alzheimer's disease.

~~13~~11. The method as in claim ~~12~~10, wherein the determined ratio of the individual is greater than a threshold, and wherein the individual is determined to have a high risk of Alzheimer's disease based on the ratio being greater than the threshold.

~~14~~12. The method as in claim ~~13~~11, wherein the threshold is based on the ratio of the concentration of at least one long dicarboxylic acid species to the concentration of at least one short dicarboxylic acid species in a cognitively healthy population or in a population of individuals having Alzheimer's disease.

~~15. The method as in claim 12, 13, or 14, wherein the at least one short dicarboxylic acid specie is succinic acid (C4), glutaric acid (C5), an unsaturated C4 or C5 dicarboxylic acid specie, or a substituted C4 or C5 dicarboxylic acid specie.~~

~~16~~13. The method as in any one of claims 1-~~15~~12 further comprising:

having obtained at least a second biological sample of the individual, wherein each of the obtained biological samples contain dicarboxylic acids and at least two biological samples were acquired two different time points;

adding an internal standard of dicarboxylic acid molecules to each biological sample; and

performing an assay on each of the biological samples to determine concentrations

of at least one long dicarboxylic acid species or of at least one short dicarboxylic species, wherein the temporal change of the concentration of the at least one long dicarboxylic acid species or the at least one short dicarboxylic species indicates the individual's risk of Alzheimer's disease.

~~17~~14. The method as in claim ~~16~~13, wherein an increase of the concentration of the long dicarboxylic acid species over time indicates a high risk of Alzheimer's disease and a decrease of the short dicarboxylic acid species over time indicates a high risk of Alzheimer's disease.

~~18~~15. The method as in claim ~~17~~14, wherein the increase of the concentration of the long dicarboxylic acid species over time is greater than a threshold or the decrease of the concentration of the short dicarboxylic acid species over time is less than a threshold, indicating the high risk of Alzheimer's disease.

~~19~~16. The method as in claim ~~18~~15, wherein the threshold is based on the increase or decrease of the concentration of the long or short dicarboxylic acid species over time in a cognitively healthy population or in a population of individuals having Alzheimer's disease.

~~20~~17. The method as in any one of claim ~~16~~13-~~19~~16 further comprising:

performing an assay on the biological samples to determine a concentration of at least one short dicarboxylic acid species and at least one long dicarboxylic species in each sample; and

determining a ratio of the concentration of at least one long dicarboxylic acid species to the concentration of at least one short dicarboxylic acid species at each time point, wherein the temporal change of the determined ratios indicates the individual's risk of Alzheimer's disease.

~~21~~18. The method as in claim ~~20~~17, wherein an increase of the concentration of at least one long dicarboxylic acid species to the concentration of at least one short

dicarboxylic acid species over time indicates a high risk of Alzheimer's disease.

~~22~~19. The method as in claim ~~21~~18, wherein the increase of the ratio of the concentration of at least one long dicarboxylic acid species to the concentration of at least one short dicarboxylic acid species over time is greater than a threshold, indicating the high risk of Alzheimer's disease.

~~23~~20. The method as in claim ~~22~~19, wherein the threshold is based on the increase of the ratio of the concentration of at least one long dicarboxylic acid species to the concentration of at least one short dicarboxylic acid species over time in a cognitively healthy population or in a population of individuals having Alzheimer's disease.

~~24~~21. The method as in any one of claims 1-~~23~~20 further comprising:

determining that the individual is at a high risk of Alzheimer's disease; and

providing a diagnostic test to be administered to further assess the individual for Alzheimer's disease.

~~25~~22. The method as in claim ~~24~~21, wherein the diagnostic test is a cognitive test, a neuropsychological test, or medical imaging.

~~26~~23. The method as in claim ~~24~~21, wherein the diagnostic test is the Mini Mental State Exam or the Montreal Cognitive Assessment.

~~27~~24. The method as in any one of claims 1-~~26~~23 further comprising:

determining that the individual is at a high risk of Alzheimer's disease; and

providing a cognitive exercise to the individual for Alzheimer's disease.

~~28~~25. The method as in claim ~~27~~24, wherein the cognitive exercise is an activity that utilizes at least one of memory, reasoning, or information processing.

~~29~~26. The method as in any one of claims 1-~~28~~25 further comprising:

determining that the individual is at a high risk of Alzheimer's disease; and

providing a medication to be administered to the individual for Alzheimer's disease.

~~30~~27. The method as in claim ~~29~~26, wherein the medication is a cholinesterase inhibitor or a N-methyl D-aspartate receptor agonist.