

CLAIMS

1. A molecular signature of the silent phase of Alzheimer's disease, wherein said molecular signature comprises at least five biomarkers selected from the group of biomarkers of Table 1A.
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2. The molecular signature of the silent phase of Alzheimer's disease according to claim 1, comprising the biomarkers of Table 10A, Table 10B, Table 10C or Table 10D.
3. A method for diagnosing a silent stage of Alzheimer's disease in a subject, comprising the steps of:
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 - a) determining a molecular signature by measuring the level, amount or concentration of at least five biomarkers selected from the group of biomarkers of Table 1A, in a sample previously obtained from said subject,
 - b) comparing the molecular signature obtained at step a) with a reference signature, and
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 - c) diagnosing the subject as being affected with a silent stage of Alzheimer's disease based on a correlation of the molecular signature with the reference signature.
4. A method of prognosticating the progress of a silent phase of Alzheimer's disease in a subject, comprising the steps of:
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 - a) determining a molecular signature by measuring the level, amount or concentration of at least five biomarkers selected from the group of biomarkers of Table 1A, in a sample obtained from said subject,
 - b) comparing the molecular signature obtained at step a) with a reference signature, and
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 - c) prognosticating the progress of Alzheimer's disease, based on a correlation of the molecular signature with the reference signature.
5. A method of determining a personalized course of treatment in a subject affected with a silent phase of Alzheimer's disease, comprising the steps of:

- 5 a) determining a molecular signature by measuring the level, amount or concentration of at least five biomarkers selected from the group of biomarkers of Table 1A, in a sample obtained from said subject,
- b) comparing the molecular signature obtained at step a) with a reference signature, and
- c) determining the personalized course of treatment for the subject, based on a correlation of the molecular signature with the reference signature.
- 10 6. A method of stratifying a silent phase of Alzheimer's disease in a subject into different grades of the silent phase, preferably into S1, S2 or S3 grades, comprising the steps of:
- a) determining a molecular signature by measuring the level, amount or concentration of at least five biomarkers selected from the group of biomarkers of Table 1A, in a sample obtained from said subject,
- 15 b) comparing the molecular signature obtained at step a) with a reference signature, and
- c) stratifying the subject into a grade of the silent phase of Alzheimer's disease, based on a correlation of the molecular signature with the reference signature.
- 20 7. The method according to claim 6, wherein the molecular signature comprises at least 14 biomarkers selected from the group of biomarkers of Table 1A.
8. The methods according to any one of claims 3 to 7, wherein the reference signature comprises the level, amount or concentration of the same at least five biomarkers measured in a sample previously obtained from a substantially healthy subject, preferably measured in samples previously obtained from a population of substantially healthy subjects.
- 25 9. The methods according to any one of claims 3 to 8, wherein the correlation at step c) is measured by comparing the variation of level, amount or concentration of the at least five biomarkers in the molecular signature and in the reference signature with the biomarker variation profile of Table 3.

10. The methods according to any one of claims **3** to **9**, wherein the molecular signature comprises the biomarkers of Table 10A, Table 10B, Table 10C or Table 10D.
11. The methods according to any one of claims **3** to **10**, wherein the comparison at step b) is conducted using at least one machine learning algorithm.
- 5 12. The methods according to claim **11**, wherein said at least one machine learning algorithm is selected from the group comprising an artificial neural network (ANN), a perceptron algorithm, a deep neural network, a clustering algorithm, a k-nearest neighbors algorithm (k-NN), a decision tree algorithm, a random forest algorithm, a linear regression algorithm, a linear discriminant analysis (LDA) algorithm, a quadratic discriminant analysis (QDA) algorithm, a support vector machine (SVM), a Bayes algorithm, a simple rule algorithm, a clustering algorithm, a meta-classifier algorithm, a Gaussian mixture model (GMM) algorithm, a nearest centroid algorithm, an extreme gradient boosting (XG Boost) algorithm, a linear mixed effects model algorithm, and a combination thereof.
- 10 13. The methods according to claim **11** or **12**, wherein the at least one machine learning algorithm is trained with a training dataset comprising information relating to the level, amount or concentration of the same at least five biomarkers of Table 1A from samples previously obtained from substantially healthy subject and from subjects known to be affected with a silent stage of Alzheimer's disease.
- 15 14. The methods according to any one of claims **11** to **13**, wherein the at least one machine learning algorithm is trained with a training dataset comprising the biomarker variation profile of Table 3.
- 20 15. A computer system for diagnosing a silent phase of Alzheimer's disease in a subject, the computer system comprising:
- 25 (i) at least one processor, and
- (ii) at least one storage medium that stores at least one code readable by the processor, and which, when executed by the processor, causes the processor to:

- 5 a. receive an input level, amount or concentration of at least five biomarkers selected from the group of biomarkers of Table 1A, determined in a sample previously obtained from said subject,
- b. analyze and transform the input level, amount or concentration of the at least five biomarkers by organizing and/or modifying each input level, amount or concentration to derive a probability score and/or a classification label via a machine learning algorithm, wherein the machine learning algorithm is trained with a training dataset,
- 10 wherein the training dataset comprises information relating to the level, amount or concentration of the same at least five biomarkers of Table 1A from samples previously obtained from subjects of known Alzheimer's disease status,
- c. generate an output, wherein the output is the classification label or the probability score, and
- 15 d. provide a diagnosis of the subject as being affected or not with a silent stage of Alzheimer's disease based on the output.
- 16.** A computer-implemented method for diagnosing a silent phase of Alzheimer's disease in a subject, said method comprising:
- 20 a. receiving an input level, amount or concentration of at least five biomarkers selected from the group of biomarkers of Table 1A, determined in a sample previously obtained from said subject,
- b. analyzing and transforming the input level, amount or concentration of the at least five biomarkers by organizing and/or modifying each input level, amount or concentration to derive a probability score and/or a classification label via a machine learning algorithm,
- 25 wherein the machine learning algorithm is trained with a training dataset, wherein the training dataset comprises information relating to the level, amount or concentration of the same at least five biomarkers of Table 1A from samples previously obtained from subjects of known Alzheimer's disease status,
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- c. generate an output, wherein the output is the classification label or the probability score, and
- d. provide a diagnosis of the subject as being affected or not with a silent stage of Alzheimer's disease based on the output.

- 5 **17.** The computer system according to claim **15** or the computer-implemented method according to claim **16**, wherein the training dataset comprises information relating to the level, amount or concentration of the same at least five biomarkers of Table 1A from samples previously obtained from substantially healthy subject and from subjects known to be affected with a silent stage of Alzheimer's disease.
- 10 **18.** The computer system or the computer-implemented method according to any one of claims **15** to **17**, wherein providing a diagnosis at step d. comprises providing a stratification of the subject being affected with a silent stage of Alzheimer's disease into a grade of said silent phase of Alzheimer's disease, preferably into a S1, S2 or S3 grade.
- 15 **19.** The computer system or the computer-implemented method according to claim **18**, wherein step a. comprises receiving an input level, amount or concentration of at least 14 biomarkers selected from the group of biomarkers of Table 1A.
- 20 **20.** The computer system or the computer-implemented method according to any one of claims **15** to **19**, wherein the training dataset comprises the biomarker variation profile of Table 3.
- 21.** A computer program comprising software code readable by a processor adapted to perform, when executed by said processor, the computer-implemented method according to any one of claims **16** to **20**.
- 25 **22.** A non-transitory computer-readable storage medium comprising code which, when executed by a computer, causes a processor to carry out the computer-implemented method according to any one of claims **16** to **20**.

CLAIMS

1. A method for diagnosing a silent stage of Alzheimer's disease in a subject, comprising the steps of:
 - 5 a) determining a molecular signature by measuring the level, amount or concentration of at least five biomarkers selected from the group of biomarkers of Table 1A, in a sample previously obtained from said subject,
 - b) comparing the molecular signature obtained at step a) with a reference signature, and
 - 10 c) diagnosing the subject as being affected with a silent stage of Alzheimer's disease based on a correlation of the molecular signature with the reference signature.

2. A method of prognosticating the progress of a silent phase of Alzheimer's disease in a subject, comprising the steps of:
 - 15 a) determining a molecular signature by measuring the level, amount or concentration of at least five biomarkers selected from the group of biomarkers of Table 1A, in a sample obtained from said subject,
 - b) comparing the molecular signature obtained at step a) with a reference signature, and
 - 20 c) prognosticating the progress of Alzheimer's disease, based on a correlation of the molecular signature with the reference signature.

3. A method of determining a personalized course of treatment in a subject affected with a silent phase of Alzheimer's disease, comprising the steps of:
 - 25 a) determining a molecular signature by measuring the level, amount or concentration of at least five biomarkers selected from the group of biomarkers of Table 1A, in a sample obtained from said subject,
 - b) comparing the molecular signature obtained at step a) with a reference signature, and
 - 30 c) determining the personalized course of treatment for the subject, based on a correlation of the molecular signature with the reference signature.

4. A method of stratifying a silent phase of Alzheimer's disease in a subject into different grades of the silent phase, comprising the steps of:
 - a) determining a molecular signature by measuring the level, amount or concentration of at least five biomarkers selected from the group of biomarkers of Table 1A, in a sample obtained from said subject,
 - b) comparing the molecular signature obtained at step a) with a reference signature, and
 - c) stratifying the subject into a grade of the silent phase of Alzheimer's disease, based on a correlation of the molecular signature with the reference signature.
5. The method according to claim 4, wherein the molecular signature comprises at least 14 biomarkers selected from the group of biomarkers of Table 1A.
6. The method according to any one of claims 1 to 5, wherein the reference signature comprises the level, amount or concentration of the same at least five biomarkers measured in a sample previously obtained from a substantially healthy subject, preferably measured in samples previously obtained from a population of substantially healthy subjects.
7. The method according to any one of claims 1 to 6, wherein the silent phase of Alzheimer's disease is an asymptomatic stage of Alzheimer's disease.
8. The method according to any one of claims 1 to 6, wherein the silent phase of Alzheimer's disease is a prodromal stage of Alzheimer's disease.
9. The method according to any one of claims 1 to 8, wherein the comparison at step b) is conducted using at least one machine learning algorithm.
10. The method according to claim 9, wherein said at least one machine learning algorithm is selected from the group comprising an artificial neural network (ANN), a perceptron algorithm, a deep neural network, a clustering algorithm, a k-nearest neighbors algorithm (k-NN), a decision tree algorithm, a random forest algorithm, a linear regression algorithm, a linear discriminant analysis (LDA) algorithm, a quadratic discriminant analysis (QDA) algorithm, a

support vector machine (SVM), a Bayes algorithm, a simple rule algorithm, a clustering algorithm, a meta-classifier algorithm, a Gaussian mixture model (GMM) algorithm, a nearest centroid algorithm, an extreme gradient boosting (XG Boost) algorithm, a linear mixed effects model algorithm, and a combination thereof.

11. The methods according to claim 9 or 10, wherein the at least one machine learning algorithm is trained with a training dataset comprising information relating to the level, amount or concentration of the same at least five biomarkers of Table 1A from samples previously obtained from substantially healthy subject and from subjects known to be affected with a silent stage of Alzheimer's disease.
12. The methods according to any one of claims 1 to 11, wherein the sample is a bodily fluid sample, preferably wherein the sample is selected from the group consisting of blood, plasma and serum.
13. A computer system for diagnosing a silent phase of Alzheimer's disease in a subject, the computer system comprising:
 - (i) at least one processor, and
 - (ii) at least one storage medium that stores at least one code readable by the processor, and which, when executed by the processor, causes the processor to:
 - a. receive an input level, amount or concentration of at least five biomarkers selected from the group of biomarkers of Table 1A, determined in a sample previously obtained from said subject,
 - b. analyze and transform the input level, amount or concentration of the at least five biomarkers by organizing and/or modifying each input level, amount or concentration to derive a probability score and/or a classification label via a machine learning algorithm,
wherein the machine learning algorithm is trained with a training dataset,
wherein the training dataset comprises information relating to the level, amount or concentration of the same at least five biomarkers of

- Table 1A from samples previously obtained from subjects of known Alzheimer's disease status,
- c. generate an output, wherein the output is the classification label or the probability score, and
 - d. provide a diagnosis of the subject as being affected or not with a silent stage of Alzheimer's disease based on the output.
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14. A computer-implemented method for diagnosing a silent phase of Alzheimer's disease in a subject, said method comprising:
- a. receiving an input level, amount or concentration of at least five biomarkers selected from the group of biomarkers of Table 1A, determined in a sample previously obtained from said subject,
 - b. analyzing and transforming the input level, amount or concentration of the at least five biomarkers by organizing and/or modifying each input level, amount or concentration to derive a probability score and/or a classification label via a machine learning algorithm,
 - wherein the machine learning algorithm is trained with a training dataset, wherein the training dataset comprises information relating to the level, amount or concentration of the same at least five biomarkers of Table 1A from samples previously obtained from subjects of known Alzheimer's disease status,
 - c. generating an output, wherein the output is the classification label or the probability score, and
 - d. providing a diagnosis of the subject as being affected or not with a silent stage of Alzheimer's disease based on the output.
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- 25 15. The computer system according to claim 13 or the computer-implemented method according to claim 14, wherein the training dataset comprises information relating to the level, amount or concentration of the same at least five biomarkers of Table 1A from samples previously obtained from substantially healthy subject and from subjects known to be affected with a silent stage of Alzheimer's disease.

16. The computer system or the computer-implemented method according to any one of claims 13 to 15, wherein providing a diagnosis at step d. comprises providing a stratification of the subject being affected with a silent stage of Alzheimer's disease into a grade of said silent phase of Alzheimer's disease.
- 5 17. The computer system or the computer-implemented method according to claim 16, wherein step a. comprises receiving an input level, amount or concentration of at least 14 biomarkers selected from the group of biomarkers of Table 1A.
- 10 18. A computer program comprising software code readable by a processor adapted to perform, when executed by said processor, the computer-implemented method according to any one of claims 14 to 17.
19. A non-transitory computer-readable storage medium comprising code which, when executed by a computer, causes a processor to carry out the computer-implemented method according to any one of claims 14 to 17.