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Remarks:
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(54) Methods for the diagnosis of dementia and other neurological disorders

(57) The present invention is directed to a method for diagnosing a patient's non-Alzheimer's disease dementia or the risk of non-Alzheimer's disease dementia in a patient. The method comprises analyzing a blood sample from a patient by high resolution mass spectrometry to obtain accurate mass intensity data; b) comparing the accurate mass intensity data to corresponding data obtained for one or more than one reference sample to identify an increase or decrease in accurate mass intensity; and c) using said increase or decrease in accurate mass intensity to diagnose said patient's non-Alzheimer's disease dementia or the risk of non-Alzheimer's disease dementia in said patient.

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Description

FIELD OF INVENTION

[0001] The present invention relates to small molecules or metabolites that are found to have significantly different abundances between clinically diagnosed dementia or other neurological disorders, and normal patients. The present invention also relates to methods for diagnosing dementia and other neurological disorders.

BACKGROUND OF THE INVENTION

[0002] The most severe consequence of the aging brain is dementia, which is defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) as

[0003] "the development of multiple cognitive deficits that included memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functions. The cognitive impairment must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previously higher level of functioning." [1]

[0004] The number of elderly people is increasing rapidly within our society and as a consequence, dementia is growing into a major health problem. In 1991, the Canadian Study of Health and Aging had estimated 25% of the population over the age of 65 had a form of dementia. The study also estimated the number of people living with dementia will double and triple in Canada by 2011 and 2031, respectively [2].

[0005] The clinical manifestation of dementia can result from neurodegeneration (e.g. Alzheimer's Disease [AD], dementia with Lewy bodies [DLB] and frontotemporal lobe dementia [FTLD]), vascular (e.g. multi-infarct dementia) or anoxic event (e.g. cardiac arrest), trauma to the brain (e.g. dementia pugilistica [boxer's dementia]), or exposure to an infectious (e.g. Creutzfeldt-Jakob Disease) or toxic agent (e.g. alcohol-induced dementia) [3].

[0006] AD is the most common cause of dementia, followed by vascular dementia (VaD), DLB and FTLD [4]. The differential diagnosis of the types of dementia is not straightforward, and is typically based on exclusion of other disorders [5]. For example, blood chemistry values are measured to determine if Vitamin B 12 deficiency, anemia, infection, venereal disease or thyroid disorder may be possible reasons for the dementia symptoms. Various neuroimaging techniques may be employed, such as magnetic resonance imaging or computerized tomography scans to determine if the symptoms may be due to the presence of a tumor, infection or vascular event [4].

[0007] If the dementia symptoms can not be explained by another disorder, a diagnosis of AD, DLB or FTLD is made exclusively based on the clinical symptoms (e.g. frequency of falls, rapid onset, presence of visual or auditory hallucinations, etc). It is not until a histopathological evaluation of the brain during autopsy is performed that a definitive diagnosis can be obtained [5-7]. A prospective study on the prevalence of AD in people over the age of 85 indicated that more than half of the individuals with neuropathological criteria for AD were either non-demented or were incorrectly diagnosed with VaD. As well, 35% of those individuals diagnosed with AD based on clinical features were incorrectly diagnosed as the neuropathological evaluation did not support that diagnosis [8]. The degree of misdiagnosis is understandable since the clinical symptoms of the various dementias often overlap and is dependent upon whether the pertinent information is made known to the clinician.

[0008] The different types of dementias are based on specific neuropathological features. A definitive diagnosis of AD relies on the deposition of two types of neuronal protein: tau in the form of intraneuronal neurofibrillary tangles (NFTs) and the accumulation of extracellular β-amyloid to form senile plaques (SPs). Tau is important for the formation of microtubules in the neuronal axon by binding and promoting polymerization of tubules. In AD, tau becomes hyperphosphorylated thereby disrupting its main function. The tau accumulates and forms tangles within the axon. The neuron can no longer function and dies. Tau protein is released into the extracellular space where it can be detected in the cerebrospinal fluid (CSF) [9]. The formation of SPs, however, is due to the accumulation of a 40 and 42 residue protein β-amyloid from amyloid precursor protein (APP) [10]. The formation and secretion of β-amyloid is closely regulated by homeostasis, but something occurs in AD that disrupts homeostasis resulting in the accumulation of the protein within the brain and disrupting the neurons within its vicinity [11-12]. The increased amount of tau and the absence of β-amyloid in CSF have been proposed as possible diagnostic markers for AD, but results have not been consistent. The problem may be due to the presence of NFTs and SPs that increase in number during normal aging [13]. In order for the NFTs and SPs to be diagnostic of AD, they must be localized together in specific areas of the brain (neocortex and limbic region) [12]. SPs without NFTs are present in the same area in individuals with mild cognitive impairment (MCI) and in 27% of non-demented individuals greater then 75 years old [13].

[0009] A diagnosis of DLB is based on the presence of protein deposits called alpha-synuclein, which is referred to as Lewy Bodies, within brainstem and cortical neurons [6]. The cognitive deficit corresponds to the amount of Lewy Bodies within the brain.

[0010] FTLD is not characterized by a specific neuropathological feature. Typically, areas of the frontal/temporal

cortices have neuronal loss, spongiform changes (microvacuolation) and severe astrocytic gliosis. The clinical symptoms in FTLD are dependent upon where the pathology is found rather than the type of pathology [7].

[0011] Currently, various neuropsychological tests are used to help diagnose dementia. For example, the Alzheimer's Disease Assessment Scale (ADAS)-cognitive subset is used to test the language ability (speech and comprehension), memory, ability to copy geometric figures and orientation to current time and place. The Folstein's Mini-Mental State Exam (MMSE), which also measures cognitive impairment, is an extensively validated test of orientation, short and long-term memory, praxis, language and comprehension. While these tests may indicate the level of cognitive impairment in an individual, they give no indication of whether the dementia may be caused by AD or by non-AD dementias.

[0012] It is commonly accepted that by the time any symptom is evident in any of the dementias described, irreversible neuronal loss has occurred [14]. MCI is characterized by a prominent impairment in memory with normal cognitive functions [15]. MCI is considered a transitional stage between normal aging and several types of dementia since a large proportion of individuals with MCI are later diagnosed with AD, DLB, or FTLD and all individuals with fully developed dementia first exhibit mild dementia symptoms similar to MCI [16].

[0013] There is a need to objectively differentiate the types of dementia from one another. Preferably, such a method would be specific, accurate, and efficient. Clearly, there is a pressing need for differential diagnosis of dementia prior to autopsy.

[0014] A biomarker that could detect neuropathological changes prior to clinical symptoms would be of enormous value. A consensus was reached in 1999 [17] as to what would be expected in a biomarker in AD:

1. Detect a fundamental feature of neuropathology
2. Diagnostic sensitivity of >80 % for detecting AD
3. Specificity of >80% for distinguishing other dementias
4. Reliable
5. Reproducible
6. Noninvasive
7. Simple to perform
8. Inexpensive

[0015] The identification of AD-specific biomarkers in human serum would be extremely useful since it would be noninvasive and could be used to detect the presence of AD pathology prior to the manifestation of clinical symptoms and differentiate those patients who may have a different form of dementia but similar clinical symptoms.

SUMMARY OF THE INVENTION

[0016] The present invention relates to small molecules or metabolites that are found to have significantly different abundances between clinically diagnosed dementia or other neurological disorders, and normal patients. The present invention also relates to methods for diagnosing dementia and other neurological disorders.

[0017] The present invention provides a method of identifying one or more than one metabolite marker for differentially diagnosing AD dementia, non-AD dementia, cognitive impairment, or a combination thereof, comprising the steps of:

introducing one or more than one sample from one or more than one patient with clinically diagnosed AD dementia, clinically diagnosed non-AD dementia, significant cognitive impairment, or any combination thereof, said sample containing a plurality of metabolites into a high resolution mass spectrometer obtaining quantifying data for the metabolites;

creating a database of said quantifying data;

comparing the identifying and quantifying data from the sample with corresponding data from a sample from a reference sample;

identifying one or more than one metabolite marker that differs between same sample and said reference sample,

[0018] wherein the metabolites metabolite markers are selected from the metabolites listed in Tables 1-7,10-13, and 18, or any combination thereof. The method may further comprising selecting a minimal number of metabolite markers needed for optimal diagnosis. In a non-limiting example, the the high resolution mass spectrometer is a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (FTMS).

[0019] The present invention also provides novel compounds selected from the group consisting of the metabolites listed in Tables 7-13. The 15. The metabolite may be selected from the group consisting of phosphatidylcholine-related compounds, ethanolamine plasmalogens, endogenous fatty acids, essential fatty acids, lipid oxidation byproducts, metabolite derivatives of said metabolite classes, and any metabolite that may contribute in any way to the anabolic/catabolic metabolism of said metabolite classes.

[0020] In one embodiment of the present invention, the compounds maybe selected from the group consisting of metabolites with accurate masses measured in Daltons of, or substantially equivalent to, 541.3432, 569.3687, 699.5198, 723.5195, 723.5197, 751.5555, 803.568, 886.5582, 565.3394, 569.369, 801.555, and 857.6186. The metabolites with accurate masses measured in Daltons of, or substantially equivalent to, a) 541.3432, b) 569.3687, c) 699.5198, d) 723.5195, e) 751.5555, and f) 803.568 may also be characterized by

a) an extracted ion chromatogram (EIC) as shown in Figure 4A, and an MS/MS spectrum as shown in Figure 6;

b) an EIC as shown in Figure 4B, and an MS/MS spectrum as shown in Figure 7;

c) an EIC as shown in Figure 4C, and an MS/MS spectrum as shown in Figure 8;

d) an EIC as shown in Figure 4D, and an MS/MS spectrum as shown in Figure 9;

e) an EIC as shown in Figure 4E, and an MS/MS spectrum as shown in Figure 10; and

f) an EIC as shown in Figure 4F, and an MS/MS spectrum as shown in Figure 11, respectively.

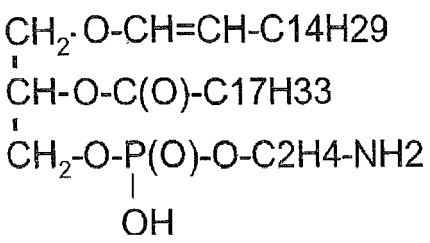
[0021] The compounds as described above may also be further characterized by molecular formula a) $C_{25}H_{51}NO_9P$, b) $C_{27}H_{55}NO_9P$, c) $C_{39}H_{74}NO_7P$, d) $C_{41}H_{74}NO_7P$, e) $C_{43}H_{78}NO_7P$, and f) $C_{43}H_{81}NO_{10}P$, respectively; and/or by the structures shown in a) figure 12; b) figure 13; c) figure 17; d) figure 18; e) figure 19; and f) figure 14, respectively.

[0022] The compounds may also be selected from the group consisting of metabolites with accurate masses measured in Daltons of, or substantially equivalent to, a) 567.3547, b) 565.3394, c) 805.5832, d) 827.57, e) 829.5856, f) 831.5997, and g) 853.5854. These compounds may be further characterized by molecular formula a) $C_{27}H_{55}NO_9P$, b) $C_{27}H_{55}NO_9P$, c) $C_{43}H_{83}NO_{10}P$, d) $C_{45}H_{81}NO_{10}P$, e) $C_{45}H_{83}NO_{10}P$, f) $C_{45}H_{85}NO_{10}P$, and g) $C_{47}H_{83}NO_{10}P$, respectively; and/or by the structure shown in a) Figure 15A; b) Figure 15B; c) Figure 15C; d) Figure 15D; e) Figure 15E; f) Figure 15F; and g) Figure 15G, respectively.

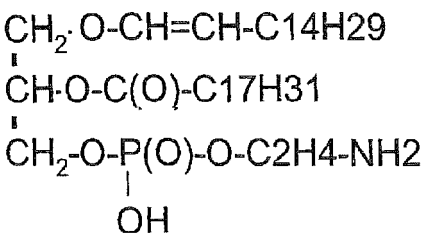
[0023] The compounds may further be selected from the group consisting of metabolites M05 to M24 with accurate masses of, or substantially equivalent to those listed in Table 18. Of these compounds, the metabolites with accurate masses measured in Daltons of, or substantially equivalent to, a) 701.53591, b) 699.52026, c) 723.52026, d) 747.52026, e) 729.56721, f) 727.55156, g) 779.58286, and h) 775.55156 maybe further characterized by a MS/MS spectrum as shown in a) figure 21; b) figure 22; c) figure 23; d) figure 24; e) figure 25; f) figure 26; g) figure 27; and h) figure 28, respectively.

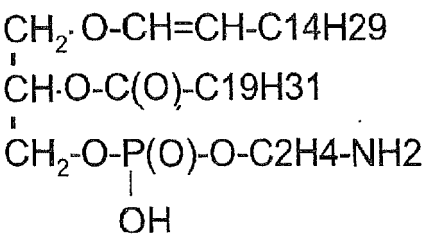
[0024] The compounds as described above may also be further characterized by molecular formula a) $C_{39}H_{76}NO_7P$, b) $C_{39}H_{74}NO_7P$, c) $C_{41}H_{74}NO_7P$, d) $C_{43}H_{74}NO_7P$, e) $C_{41}H_{80}NO_7P$, f) $C_{41}H_{78}NO_7P$, g) $C_{45}H_{82}NO_7P$, and h) $C_{45}H_{78}NO_7P$, respectively and/or by the structure

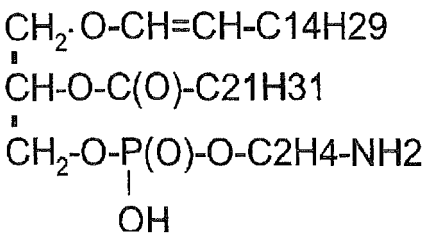
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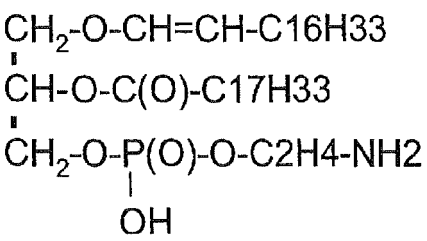


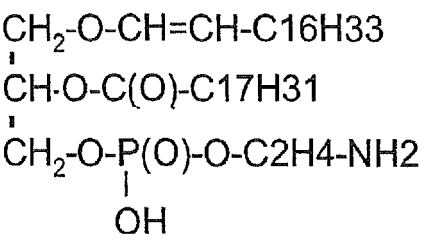
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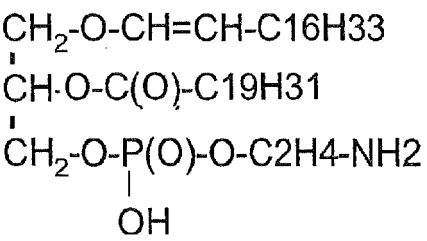


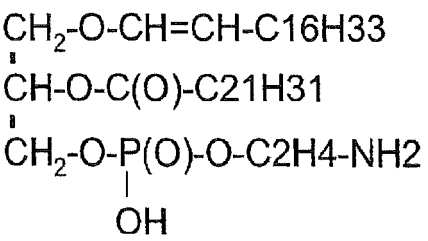
c) 

d) 

e) 

f) 

g) 

and h) 

respectively.

[0025] The novel compounds may also be selected from the group consisting of the metabolites listed in Table 30. Of these compounds, the metabolites with accurate masses measured in Daltons of, or substantially equivalent to, 207.0822, 275.8712, 371.7311, 373.728, 432.1532, 485.5603, 487.6482, 562.46, 622.2539, 640.2637, 730.6493, and 742.2972 are of particular interest.

[0026] One or more than one of the compounds of the present invention may be used for the differential diagnosis of dementia.

[0027] In another embodiment, the present invention provides a method for differentially diagnosing dementia or the risk of dementia in a patient, the method comprising the steps of:

a) obtaining a sample from said patient;

b) analyzing said sample to obtain quantifiying data for one or more than one metabolite marker;

c) comparing the quantifying data for said one or more than one metabolite marker to corresponding data obtained from one or more than one reference sample; and

d) using said comparison to differentially diagnose dementia or the risk of dementia.

[0028] The the step of analyzing (step b) may comprise analyzing the sample by liquid chromatography mass spectrometry (LC-MS), or alternatively may comprise analyzing the sample by liquid chromatography and linear ion trap mass spectrometry when the method is a highthroughput method.

[0029] In the method as just described, the one or more than one reference sample is a first reference sample obtained from a non-demented control individual. The one or more than one reference sample may also comprise a second reference sample obtained from a patient with clinically diagnosed AD-dementia; a third reference sample obtained from a patient with clinically diagnosed non-AD dementia; and/or a fourth reference sample obtained from a patient suffering from significant cognitive impairment.

[0030] In one alternative of the method described above, the sample and the reference sample are serum samples, and the one or more than one metabolite marker is selected from the metabolites listed in Tables 1 to 7, or a combination thereof. These metabolite markers may be selected from the group consisting of phosphatidylcholine-related compounds, ethanolamine plasmalogens, endogenous fatty acids, essential fatty acids, lipid oxidation byproducts, metabolite deriv-

atives of said metabolite classes, and any metabolite that may contribute in any way to the anabolic/catabolic metabolism of said metabolite classes.

[0031] The one or more than one metabolite marker needed for optimal diagnosis may comprise metabolites with accurate masses measured in Daltons of, or substantially equivalent to, 541.3432, 569.3687, 699.5198, 723.5195, 723.5197, 751.5555, 803.568, 886.5582 , and any combination thereof. Of these, the metabolite of accurate masses 699.5198, 723.5195, 723.5197, and 751.555 are ethanolamine plasmalogens and are specifically decreased in patients with AD dementia; and the metabolite markers of accurate masses 541.3432, 569.3687, 803.568, and 886.5582 are phosphatidylchoine metabolites, are decreased in patients with cognitive impairment on ADAS-cog, and severity of cognitive impairment correlates to the degree of decrease.

[0032] The one or more than one metabolite marker may be the metabolites with accurate masses measured in Daltons of, or substantially equivalent to, a) 541.3432, b) 569.3687, c) 699.5198, d) 723.5195, e) 751.5555, and f) 803.568. These metabolites may be further characterized by

a) an extracted ion chromatogram (EIC) as shown in Figure 4A, and an MS/MS spectrum as shown in Figure 6;

b) an EIC as shown in Figure 4B, and an MS/MS spectrum as shown in Figure 7;

c) an EIC as shown in Figure 4C, and an MS/MS spectrum as shown in Figure 8;

d) an EIC as shown in Figure 4D, and an MS/MS spectrum as shown in Figure 9;

e) an EIC as shown in Figure 4E, and an MS/MS spectrum as shown in Figure 10; and

f) an EIC as shown in Figure 4F, and an MS/MS spectrum as shown in Figure 11,

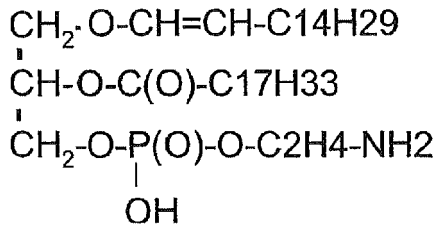
[0033] respectively. The metabolite may also be further characterized by molecular formula a) $C_{25}H_{51}NO_9P$, b) $C_{27}H_{55}NO_9P$, c) $C_{39}H_{74}NO_7P$, d) $C_{41}H_{74}NO_7P$, e) $C_{43}H_{78}NO_7P$, and f) $C_{43}H_{81}NO_{10}P$, respectively; and/or by the structure shown in a) figure 12; b) figure 13; c) figure 17; d) figure 18; e) figure 19; and f) figure 14, respectively.

[0034] In another alternative of the method described above, the sample and the reference sample may be cerebrospinal fluid (CSF) samples, and the one or more than one metabolite marker is selected from the metabolites listed in Table 13, or a combination thereof. Of particular interest are metabolite markers needed for optimal diagnosis, which may comprise metabolites with accurate masses measured in Daltons of, or substantially equivalent to, 207.0822, 275.8712, 371.7311, 373.728, 432.1532, 485.5603, 487.6482, 562.46, 622.2539, 640.2637, 730.6493, 742.2972, and any combination thereof. Of these, metabolite markers 207.0822, 432.1532, 562.46, 622.2539,640.2637, 730.6493, and 742.2972 are increased in patients with AD dementia; and metabolite markers 275.8712, 371.7311, 373.728, 485.5603, and 487.6482 are decreased in patients with AD dementia.

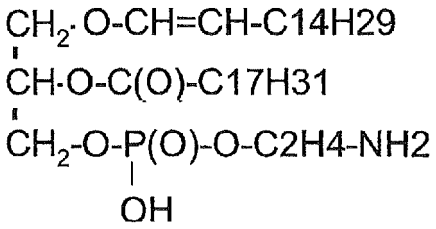
[0035] In yet another alternative of the method described above, the sample and the reference sample are serum samples, and the one or more than one metabolite marker may be selected from metabolites M05 to M24 with accurate masses of, or substantially equivalent to those listed in Table 18. Of these, the one or more than one metabolite marker of particular interest may comprise metabolites with accurate masses measured in Daltons of, or substantially equivalent to, a) 701.53591, b) 699.52026, c) 723.52026, d) 747.52026, e) 729.56721, f) 727.55156, g) 779.58286, and h) 775.55156, and wherein a decrease in the level of a) to h) indicates AD dementia with a severe cognitive impairment.

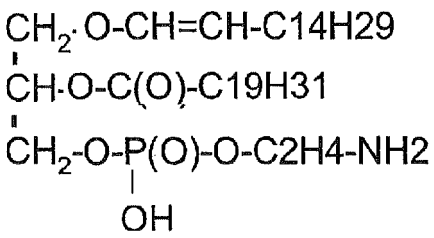
[0036] The metabolites listed above may be further characterized by a MS/MS spectrum as shown in a) figure 21, b) figure 22, c) figure 23, d) figure 24, e) figure 25, f) figure 26, g) figure 27, and h) figure 28, respectively. The metabolites may also be further characterized by molecular formula a) $C_{39}H_{76}NO_7P$, b) $C_{39}H_{74}NO_7P$, c) $C_{41}H_{74}NO_7P$, d) $C_{43}H_{74}NO_7P$, e) $C_{41}H_{80}NO_7P$, f) $C_{41}H_{78}NO_7P$, g) $C_{45}H_{82}NO_7P$, and h) $C_{45}H_{78}NO_7P$, respectively; and/or by the structure

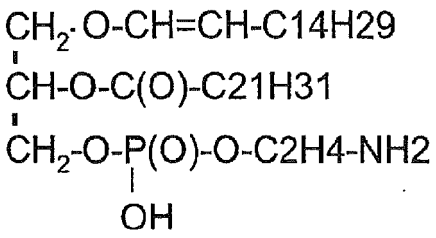
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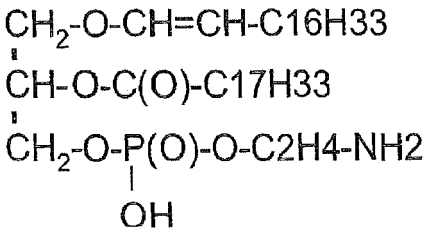


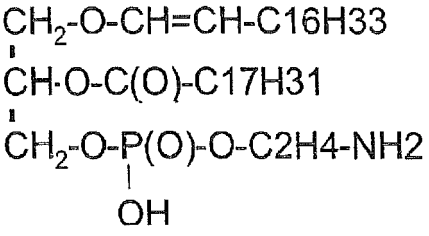
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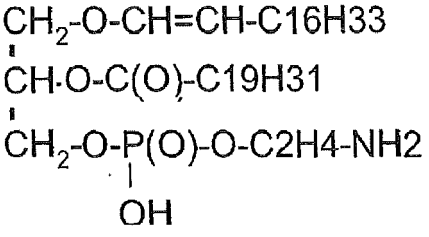


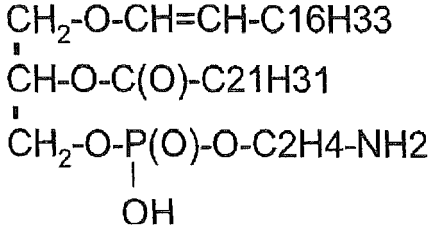
c) 

d) 

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respectively.

[0037] In yet another aspect of the present invention, there is provided a method for assessing dementia or the risk of dementia in a patient, the method comprising the steps of:

a) obtaining a serum sample from said patient;

b) analyzing said sample to obtain quantifiying data for one or more than one metabolite marker;

c) comparing the quantifying data for said one or more than one metabolite marker to corresponding data obtained from one or more than one reference sample; and

d) using said comparison to assess dementia or the risk of dementia.

[0038] The the step of analyzing (step b) may comprise analyzing the sample by liquid chromatography mass spectrometry (LC-MS), or alternatively may comprise analyzing the sample by liquid chromatography and linear ion trap mass spectrometry when the method is a highthroughput method.

[0039] In the method as just described, the one or more than one reference sample may be a first reference sample obtained from a non-demented control individual. The one or more than one reference sample may also further comprise a second reference sample obtained from a patient with cognitive impairment as measured by ADAS-cog, and/or a third reference sample obtained from a patient with with cognitive impairment as measured by MMSE.

[0040] The one or more than one metabolite marker in the method described above may be selected from the metabolites listed in Tables 10-12, or a combination thereof. Of particular interest are the one or more than one metabolite markers is selected from the group consisting of metabolites with accurate masses measured in Daltons of, or substantially equivalent to 541.3432, 569.3687, 699.5198, 723.5195, 723.5197, 751.5555, 803.568, 886.5582, 565.3394, 569.369, 801.555, 857.6186, and any combination thereof. Of these, a decrease in the patient sample in metabolite markers 699.5198, 723.5195, 723.5197, and 751.555 indicates AD pathology; a decrease in the patient sample in metabolite markers 541.3432, 569.3687, 803.568, and 886.5582 indicates cognitive impairment on ADAS-cog; and a decrease in the patient sample in metabolite markers 565.3394, 569.369, 801.555, and 857.6186 indicates cognitive impairment on MMSE.

[0041] In yet another embodiment of the present invention, a method is provided for differentially diagnosing dementia or the risk of dementia in a patient, the method comprising the steps of:

a) obtaining a sample from said patient;

b) analyzing said sample to obtain quantifiying data for one or more than one metabolite marker;

c) obtaining a ratio for each of the one or more than one metabolite marker to an internal control metabolite;

d) comparing each ratio of said one or more than one metabolite marker to the internal control metabolite to corresponding data obtained from one or more than one reference sample; and

e) using said comparison to differentially diagnose dementia or the risk of dementia.

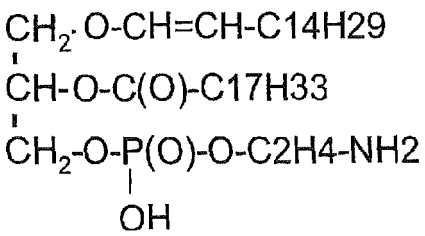
[0042] The the step of analyzing (step b) may comprise analyzing the sample by liquid chromatography mass spectrometry (LC-MS), or alternatively may comprise analyzing the sample by liquid chromatography and linear ion trap mass spectrometry when the method is a highthroughput method.

[0043] In the method as just described, the one or more than one reference sample may be a first reference sample obtained from a non-demented control individual. The one or more than one reference sample may further comprise a second reference sample obtained from a patient with clinically diagnosed AD-dementia; a third reference sample obtained from a patient with clinically diagnosed non-AD dementia; and/or a fourth reference sample obtained from a patient suffering from significant cognitive impairment.

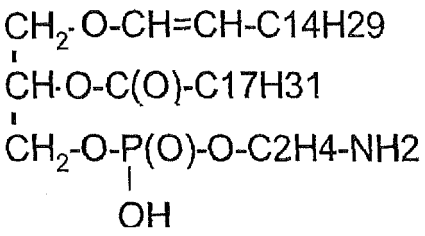
[0044] In one aspect of the method described above, the sample and the reference sample are serum samples, and the one or more than one metabolite marker is selected from metabolites M05 to M24 with accurate masses of, or substantially equivalent to those listed in Table 18. Of particular interest is the one or more than one metabolite marker comprising metabolites with accurate masses measured in Daltons of, or substantially equivalent to, a) 701.53591, b) 699.52026, c) 723.52026, d) 747.52026, e) 729.56721, f) 727.55156, g) 779.58286, and h) 775.55156, and the internal control metabolite comprising the metabolite with accurate mass measured in Daltons of, or substantially equivalent to, 719.54648. When these metabolites and internal control metabolite are used, a decrease in the ratio of metabolite to the internal control metabolite indicates AD dementia with a severe cognitive impairment.

[0045] The metabolites described above may be further characterized by a MS/MS spectrum as shown in a) figure 21, b) figure 22, c) figure 23, d) figure 24, e) figure 25, f) figure 26, g) figure 27, and h) figure 28, respectively. These metabolites may also be further characterized by molecular formula a) $C_{39}H_{76}NO_7P$, b) $C_{39}H_{74}NO_7P$, c) $C_{41}H_{74}NO_7P$, d) $C_{43}H_{74}NO_7P$, e) $C_{41}H_{80}NO_7P$, f) $C_{41}H_{78}NO_7P$, g) $C_{45}H_{82}NO_7P$, and h) $C_{45}H_{78}NO_7P$, respectively, and the internal control metabolite may be characterized by molecular formula $C_{39}H_{78}NO_8P$; and/or by the structure

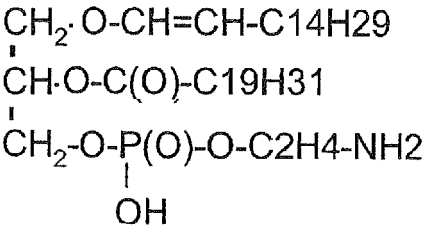
a)



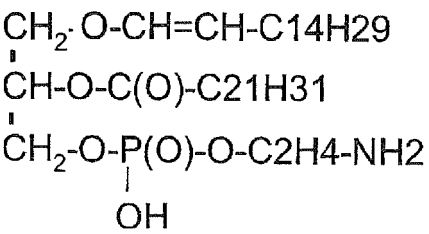
b)

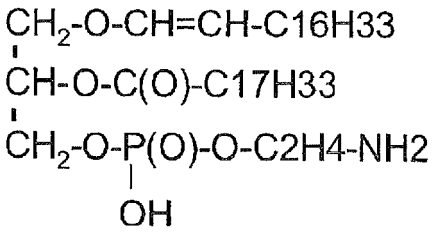


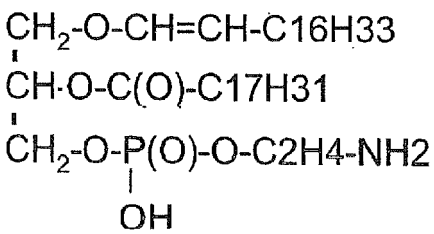
c)

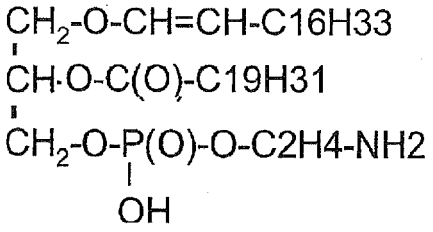


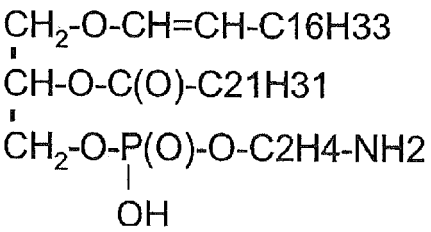
d)



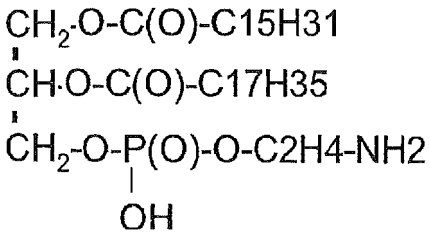
e) 

f) 

g) 

and h) 

respectively, and the internal control metabolite may be further characterized by the structure



[0046] In yet another embodiment of the present invention, there is provided a method for evaluating the efficacy of a therapy for treating dementia in a patient, comprising:

a) obtaining a sample from said patient;

b) analyzing said sample to obtain quantifying data for one or more than one metabolite marker;

c) comparing said quantifying data to corresponding data obtained from one or more than one reference sample; and

d) using said comparison to determine whether the therapy is improving the demented state of the patient.

[0047] The the step of analyzing (step b) may comprise analyzing the sample by liquid chromatography mass spectrometry (LC-MS), or alternatively may comprise analyzing the sample by liquid chromatography and linear ion trap mass spectrometry when the method is a highthroughput method.

[0048] In the method as just described, the one or more than one reference sample may be a plurality of samples obtained from from a non-demented control individuals; a plurality of samples obtained from from a clinically diagnosed AD patient; one or more than one pre-therapy baseline sample obtained from the patient; or any combination thereof.

[0049] In one aspect of the above method, the sample and the reference sample are serum samples, and the one or more than one metabolite marker is selected from the metabolites listed in Tables 1 to 7, or a combination thereof. These metabolite marker markers needed for optimal diagnosis may be selected from the group consisting of phosphatidylcholine-related compounds, ethanolamineplasmalogens, endogenous fatty acids, essential fatty acids, lipid oxidation byproducts, metabolite derivatives of said metabolite classes, and any metabolite that may contribute in any way to the anabolic/catabolic metabolism of said metabolite classes. Of particular interest are the metabolites with accurate masses measured in Daltons of, or substantially equivalent to, 541.3432, 569.3687, 699.5198, 723.5195, 723.5197, 751.5555, 803.568, 886.5582.

[0050] In another aspect, the sample and the reference sample are cerebrospinal fluid (CSF) samples, and the one or more than one metabolite marker is selected from the metabolites listed in Table 13, or a combination thereof. Of particular interest are the metabolites with accurate masses measured in Daltons of, or substantially equivalent to, 207.0822, 275.8712, 371.7311, 373.728, 432.1532, 485.5603, 487.6482, 562.46, 622.2539,640.2637, 730.6493,

742.2972.

[0051] In a third aspect, the sample and the reference sample are serum samples, and the one or more than one metabolite marker maybe selected from metabolites M05 to M24 with accurate masses of, or substantially equivalent to those listed in Table 18. Of these metabolites, the metabolites with accurate masses measured in Daltons of, or substantially equivalent to, 701.53591, 699.52026, 723.52026, 747.52026, 729.56721, 727.55156, 779.58286, and 775.55156 maybe of particular interest.

[0052] The present invention also provides a method for evaluating the efficacy of a therapy for treating dementia in a patient, comprising:

a) obtaining a sample from said patient;

b) analyzing said sample to obtain quantifying data for one or more than one metabolite marker;

c) obtaining a ratio for each of the one or more than one metabolite marker to an internal control metabolite;

d) comparing each ratio of said one or more than one metabolite marker to the internal control metabolite to corresponding data obtained from one or more than one reference sample; and

e) using said comparison to determine whether the therapy is improving the demented state of the patient.

[0053] The the step of analyzing (step b) may comprise analyzing the sample by liquid chromatography mass spectrometry (LC-MS), or alternatively may comprise analyzing the sample by liquid chromatography and linear ion trap mass spectrometry when the method is a highthroughput method.

[0054] In the method as just described, the one or more than one reference sample may be a plurality of samples obtained from from a non-demented control individuals; a plurality of samples obtained from from a clinically diagnosed AD patient; one or more than one pre-therapy baseline sample obtained from the patient; or any combination thereof.

[0055] In the method as described above, the sample and said reference sample are serum samples, and the one or more than one metabolite marker may be selected from metabolites M05 to M24 with accurate masses of, or substantially equivalent to those listed in Table 18. Of particular interest are the metabolites with accurate masses measured in Daltons of, or substantially equivalent to, 701.53591, 699.52026, 723.52026, 747.52026, 729.56721, 727.55156, 779.58286, and 775.55156, and the internal control metabolite with accurate mass measured in Daltons of, or substantially equivalent to, 719.54648.

[0056] The methods of the present invention, including HTS assays, can be used for the following, wherein the specific "health-state" in this application refers to, but is not limited to dementia:

[0057] 1. identifying small-molecule metabolite biomarkers which can discriminate between multiple health-states using any biological sample taken from an individual,

[0058] 2. specifically diagnosing a health-state using metabolites identified in serum, plasma, whole blood, serum, CSF, and/or other tissue biopsy as described in this application,

[0059] 3. selecting the minimal number of metabolite features required for optimal diagnostic assay performance statistics using supervised statistical methods such as those mentioned in this application,

[0060] 4. identifying structural characteristics of biomarker metabolites selected from non-targeted metabolomic analysis using LC-MS/MS, MSn and NMR,

[0061] 5. developing a high-throughput LC-MS/MS method for assaying selected metabolite levels in serum,

[0062] 6. diagnosing a given health-state, or risk for development of a health-state by determining the levels of any combination of metabolite features disclosed from the FTMS analysis patient serum, using any method including but not limited to mass spectrometry, NMR, UV detection, ELISA (enzyme-linked immunosorbant assay), chemical reaction, image analysis, or other.

[0063] The impact of the present invention on the diagnosis of dementia would be tremendous, as literally everyone could be screened longitudinally throughout their lifetime to assess risk. Given that the performance characteristics of the test of the present invention are representative for the general population, this test alone may be superior to any other currently available screening method, as it may have the potential to detect disease progression prior to the emergence of clinical symptoms.

[0064] This summary of the invention does not necessarily describe all features of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0065] These and other features of the invention will become more apparent from the following description in which reference is made to the appended drawings wherein:

FIGURE 1 shows a mean signal-to-noise +/-SEM of the AD serum 8 biomarker panel for each different clinical group (AD with significant cognitive impairment, Non-AD dementia, and AD with no significant cognitive impairment) relative to non-demented controls.

FIGURE 2 shows a mean signal-to-noise +/-SEM of the AD serum 8 biomarker panel for two clinical groups with a significant cognitive impairment (AD and Non-AD dementia).

FIGURE 3 shows a mean signal-to-noise +/-SEM of the AD CSF 12 biomarker panel for two clinical groups with a significant cognitive impairment (AD and Non-AD dementia).

FIGURE 4 shows Q-Star extracted ion chromatograms (EIC) for the metabolites 541.3432 (A), 569.3687 (B), 699.5198 (C), 723.5195 (D), 751.5555 (E), and 803.568 (F). Top panel, 8 samples from non-demented subjects, bottom panel, 8 samples from clinically-diagnosed AD subjects.

FIGURE 5 shows averaged AD biomarker intensities of the 8 AD and 8 non-demented controls samples from FTMS and Q-Star Analysis.

FIGURE 6 shows MS/MS spectra for metabolite 541.3432 with CE voltage -50V.

FIGURE 7 shows MS/MS spectra for metabolite 569.3687 with CE voltage -50V.

FIGURE 8 shows MS/MS spectra for metabolite 699.5198 with CE voltage -50V.

FIGURE 9 shows MS/MS spectra for metabolite 723.5195 with CE voltage -50V.

FIGURE 10 shows MS/MS spectra for metabolite 751.5555 with CE voltage-50V.

FIGURE 11 shows MS/MS spectra for metabolite 803.568 with CE voltage -50V.

FIGURE 12 shows structural determination of ADAS-cog serum biomarker 541.3432.

FIGURE 13 shows structural determination of ADAS-cog serum biomarker 569.3687.

FIGURE 14 shows structural determination of ADAS-cog serum biomarker 803.568.

FIGURE 15 shows putative structures of additional serum biomarkers. A-metabolite with mass of 567.3547; B - metabolite with mass of 565.3394; C - metabolite with mass of 805.5832; D - metabolite with mass of 827.57; E - metabolite with mass of 829.5856; F - metabolite with mass of 531.5997; and G - metabolite with mass of 853.5854.

FIGURE 16 shows the fragments obtained for the MS/MS analysis of the 751.5555 metabolite, along with its proposed structure.

FIGURE 17 shows the fragments obtained for the MS/MS analysis of the 699.5198 metabolite, along with its proposed structure.

FIGURE 18 shows the fragments obtained for the MS/MS analysis of the 723.5195 metabolite, along with its proposed structure.

FIGURE 19 shows the LC-MS and MS/MS analysis of the 751.5555 metabolite (18:0/20:4 EtnPls). Panel A1 is an extracted ion chromatogram (EIC) of parent ion 750 (M-H-) of a pure standard; panel A2 is MS/MS spectra of parent ion M/Z 750 @ retention time 4.8-5.0 minutes. Panel B1 is the EIC of parent ion 750 from a cognitively normal subject; panel B2 is the MS/MS spectra of parent ion M/Z 750 @ 4.8-5.0 min. Panel C1 is the EIC of parent ion 750 from an AD subject; and panel C2 is the MS/MS spectra of parent ion M/Z 750 @ 4.8-5.0 min.

FIGURE 20 shows the general structure of ethanolamine phospholipids, as well as the naming convention used herein.

FIGURE 21 is an extracted ion chromatogram (upper panel) and MS/MS spectrum (lower panel) of EtnPls 16:0/18:1

(M15) in human serum.

FIGURE 22 is an extracted ion chromatogram (upper panel) and MS/MS spectrum (lower panel) of EtnPls 16:0/18:2 (M16) in human serum.

FIGURE 23 is an extracted ion chromatogram (upper panel) and MS/MS spectrum (lower panel) of EtnPls 16:0/20:4 (M17) in human serum.

FIGURE 24 is an extracted ion chromatogram (upper panel) and MS/MS spectrum (lower panel) of EtnPls 16:0/22:6 (M19) in human serum.

FIGURE 25 is an extracted ion chromatogram (upper panel) and MS/MS spectrum (lower panel) of EtnPls 18:0/18:1 (M20) in human serum.

FIGURE 26 is an extracted ion chromatogram (upper panel) and MS/MS spectrum (lower panel) of EtnPls 18:0/18:2 (M21) in human serum.

FIGURE 27 is an extracted ion chromatogram (upper panel) and MS/MS spectrum (lower panel) of EtnPls 18:0/20:4 (M23) in human serum.

FIGURE 28 is an extracted ion chromatogram (upper panel) and MS/MS spectrum (lower panel) of EtnPls 18:0/22:6 (M24) in human serum.

FIGURE 29 is an extracted ion chromatogram (upper panel) and MS/MS spectrum (lower panel) of EtnPls 18:1/18:2 and Plasmanyl 16:0/20:4 (M07) in human serum.

FIGURE 30 is an extracted ion chromatogram (upper panel) and MS/MS spectrum (lower panel) of EtnPls 20:0/20:4 and EtnPls 18:0/22:4 (M23) in human serum.

FIGURE 31 is an extracted ion chromatogram (upper panel) and MS/MS spectrum (lower panel) of Plasmanyl 18:0/20:4 (M12) and Plasmanyl 16:0/22:4 (M08) in human serum.

FIGURE 32 is an extracted ion chromatogram (upper panel) and MS/MS spectrum (lower panels) of EtnPls 18:1/20:4, EtnPls 16:0/22:5, Plasmanyl 16:0/22:6 (M09) in human serum.

FIGURE 33 shows a Q-Trap flow injection analysis standard curve of EtnPls 16:0/22:6 (M19) in healthy human serum.

FIGURE 34 shows ehe effect of dementia severity and SDAT pathology on serum EtnPl levels (male and female subjects combined). (A) Mono and di-unsaturated EtnPls and saturated PtdEt internal control. (B) Polyunsaturated EtnPls and free DHA (22:6). EtnPls abbreviations: (fatty acid carbons : double bonds, not including the vinyl ether double bond) and position on glycerol backbone (sn-1/sn-2). D16:0/18:0 represents diacylglycerophosphatidyleth-anolamine with palmitic acid (16:0) at sn-1 and stearic acid (18:0) at sn-2; 22:6 represents free DHA. Values are expressed as mean ± SEM (n=19-112).

FIGURE 35 shows serum DHA-EtnPls (Log(2) EtnPls 16:0/22:6 (M19) to PtdEt 16:0/18:0 (M01) ratio) distributions in subjects with different levels of dementia severity (male and female subjects combined).

FIGURE 36 is a comparison of theoretical distributions of AD pathology (A) compiled from references 5-8 and experimentally determined distributions of serum 22:6-containing EtnPls (Log(2) EtnPls 16:0/22:6 (M19) to PtdEt 16:0/18:0 (M01) ratio) (B) in cognitively normal and demented subjects. Arrow indicates positive diagnosis of AD.

FIGURE 37 is a linear regression analysis of disease severity (ADAS-cog) and serum 22:6-containing EtnPls (EtnPls 16:0/22:6 (M19) to PtdEt 16:0/18:0 (M01) ratio) levels in 256 AD subj ects. X = predicted initiation of EtnPls depletion. Values are expressed as mean ± SEM (n=66-112). Clinical progression assumes 7.5 ADAS-cog points/year.

FIGURE 38 shows serum 22:6-containing EtnPls (EtnPls 16:0/22:6 (M19) to PtdEt 16:0/18:0 (M01) ratio) levels in AD, Cognitive Normal, and general population subjects. (A) Mean ± SEM (n= 68-256). (B) Log(2) distributions.

FIGURE 39 shows the distribution of serum white and gray matter EtnPl scores in males and females.

DETAILED DESCRIPTION

[0066] The present invention relates to small molecules or metabolites that are found to have significantly different abundances between clinically diagnosed dementia or other neurological disorders, and normal patients. The present invention also relates to methods for diagnosing dementia and other neurological disorders.

[0067] The present invention provides novel methods for discovering, validating, and implementing a metabolite markers for one or more diseases or particular health-states. In one embodiment of the present invention, there is provided a method for identifying specific biomarkers for differentially diagnosing AD dementia, non-AD dementia, cognitive impairment, or a combination thereof, comprising the steps of: introducing one or more than one sample from one or more than one patient with clinically diagnosed AD dementia, clinically diagnosed non-AD dementia, or significant cognitive impairment, said sample containing a plurality of metabolites into a high resolution mass spectrometer (for example, and without wishing to be limiting, a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (FTMS)); obtaining, identifying and quantifying data for the metabolites; creating a database of said identifying and quantifying data; comparing the identifying and quantifying data from the sample with corresponding data from a sample from a non-demented normal patient; identifying one or more than one metabolites that differ. The metabolite markers identified using the method of the present invention may include the metabolites listed in Tables 1-7,10-13, and 18. The method may further comprise selecting the minimal number of metabolite markers needed for optimal diagnosis.

[0068] In order to determine the biochemical markers of a given health-state in a particular population, a group of patients representative of the health state (i.e. a particular disease) and/or a group of "normal" counterparts are required. Biological samples taken from the patients in the particular health-state category can then be compared to the same samples taken from the normal population as well as to patients in similar health-state category in the hopes of identifying biochemical differences between the two groups, by analyzing the biochemicals present in the samples using FTMS and/or LC-MS.

[0069] The method for the discovery of metabolite markers as described above may be done using non-targeted metabolomic strategies or methods. Multiple non-targeted metabolomics strategies have been described in the scientific literature including NMR [18], GC-MS [19-21], LC-MS, and FTMS strategies [18, 22-24]. The metabolic profiling strategy employed for the discovery of differentially expressed metabolites in the present invention was the non-targeted FTMS strategy by Phenomenome Discoveries [21,24-27; see also US Published Application No. 2004-0029120 A1, Canadian Application No. 2,298,181, and WO 0157518]. Non-targeted analysis involves the measurement of as many molecules in a sample as possible, without any prior knowledge or selection of components prior to the analysis. Therefore, the potential for non-targeted analysis to discover novel metabolite biomarkers is high versus targeted methods, which detect a predefined list of molecules. The present invention uses anon-targeted method to identify metabolite components in serum samples that differ between clinically diagnosed AD individuals and non AD individuals. The same technology was used to identify metabolite components that differ between clinically diagnosed AD individuals with dementia from clinically diagnosed non-AD individuals with dementia in CSF samples.

[0070] However, a person skilled in the art would recognize that other metabolite profiling strategies could be used to discover some or all of the differentially regulated metabolites disclosed in the present invention and that the metabolites described herein, however discovered or measured, represent unique chemical entities that are independent of the analytical technology that may be used to detect and measure them.

[0071] The present invention also provides a method for differentially diagnosing dementia or the risk of dementia in a patient, the method comprising the steps of:

a) obtaining a sample from said patient;

b) analyzing said sample to obtain quantifiying data for one or more than one metabolite marker;

c) comparing the quantifying data for said one or more than one metabolite marker to corresponding data obtained from one or more than one reference sample; and

d) using said comparison to differentially diagnose dementia or the risk of dementia.

[0072] The step of analyzing the sample (steb b) may comprise analyzing the sample using a mass spectrometer (MS). For example, and without wishing to be limiting, such mass spectrometer could be of the FTMS, orbitrap, time of flight (TOF) or quadrupole types. Alternatively, the mass spectrometer could be equipped with an additional pre-detector mass filter. For example, and without wishing to be limiting such instruments are commonly referred to as quadrupole-FTMS (Q-FTMS), quadrupole -TOF (Q-TOF) or triple quadrupole (TQ or QQQ). In addition, the mass spectrometer could

be operated in either the parent ion detection mode (MS) or in MSn mode, where n>=2. MSn refers to the situation where the parent ion is fragmented by collision induced dissociation (CID) or other fragmentation procedures to create fragment ions, and then one or more than one of said fragments are detected by the mass spectrometer. Such framents can then be further fragmented to create further fragments. Alternatively, the sample could be introduced into the mass spectrometer using a liquid or gas chromatographic system or by direct injection.

[0073] By the term "differential diagnosis" or "differentially diagnosing", it is meant that various aspects of a disease state may be distinguished from one another. In particular, the present invention allows for differential diagnosis a various states of dementia; for example and without wishing to be limiting, the present invention may provide differential diagnosis of AD dementia, non-AD dementia, cognitive impariment, or a combination thereof.

[0074] The diagnosis of or the exclusion of any types of neurological disorders is contemplated by the present invention, using all or a subset of the metabolites disclosed herein. The term "dementia" is used herein as a broad term indicating both cognitive imparment as well as pathologies causing cognitive impairment. Dementia may be caused by a number of neurological disorders. "AD dementia" as used herein refers to dementia caused by Alzheimer's disease (AD, which may also be referred to herein as "SDAT"); types of "non-AD dementia" include, but are not limited to, dementia with Lewy bodies (DLB), frontotemporal lobe dementia (FTD), vascular induced dementia (e.g. multi-infarct dementia), anoxic event induced dementia (e.g. cardiac arrest), trauma to the brain induced dementia (e.g. dementia pugilistica [boxer's dementia]), dementia resulting from exposure to an infectious (e.g. Creutzfeldt-Jakob Disease) or toxic agent (e.g. alcohol-induced dementia), Autism, Multiple Sclerosis, Parkinson's Disease, Bipolar Disorder, Ischemia, Huntington's Chorea, Major Depressive Disorder, Closed Head Injury, Hydrocephalus, Amnesia, Anxiety Disorder, Traumatic Brain Injury, Obsessive Compulsive Disorder, Schizophrenia, Mental Retardation, and/or Epilepsy. Of particular interest are AD dementia, and FTD and DLB non-AD dementias.

[0075] Cognitive impairment can be assessed by any method known in the art. For example, and without wishing to be limiting, the Alzheimer's Disease Assessment Scale (ADAS)-cognitive subset maybe used. This neuropsychological testis used to test the language ability (speech and comprehension), memory, ability to copy geometric figures and orientation to current time and place. Errors on the test are recorded resulting in a reverse score impairment (i.e., the higher the score on ADAS, the greater the cognitive impairment). A score of 0-15 is considered normal, 16-47 is considered mild-moderate impairment and a score of 48-70 is considered moderate-severe impairment [28]. Another neuropsychological test, Folstein's Mini-Mental State Exam (MMSE), which measures cognitive impairment, may be used. The MMSE is widely used and is an extensively validated test of orientation, short and long-term memory, praxis, language and comprehension. A person skilled in the art would recognize that additional neuropsychological assessment that measure aspects of the same cognitive deficit, such as, but not exclusive to, the Blessed Roth Dementia Rating Scale, the 7-Minute Screen, Wechsler Memory Scale (WMS), Halstead-Reitan Battery, Rey Auditory Verbal Learning Test, California Verbal Learning Test, Buschke Selective Reminding Test, Boston Naming Test, Clinical Evaluation of Language Functioning, Peabody Picture Vocabulary Tests, Mattis Dementia Rating Scale, Memory Assessment Scale, Tests of Memory and Learning, Wide Range Assessment of Memory and Learning, can also be used.

[0076] In addition, a person skilled in the art would recognize that any imaging technique that has the potential to show a cognitive impairment or structural change, such as, but not exclusive to, structural magnetic resonance imaging (MRI), positron emission tomography (PET), computerized tomography (CT), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), single positron emission tomography (SPECT), event related potentials, magnetoencephalography, multi-modal imaging, would be measuring the structural/regional brain areas that are responsible for that cognitive deficit and AD pathology, and therefore, would be related to the metabolites disclosed in this invention.

[0077] In accordance with the present invention, any type of biological sample that originates from anywhere within the body, for example but not limited to, blood (serum/plasma), CSF, urine, stool, breath, saliva, or biopsy of any solid tissue including tumor, adjacent normal, smooth and skeletal muscle, adipose tissue, liver, skin, hair, brain, kidney, pancreas, lung, colon, stomach, or other may be used. Of particular interest are samples that are serum or CSF. While the term "serum" is used herein, those skilled in the art will recognize that plasma or whole blood or a sub-fraction of wholeblood may also be used. CSF may be obtained by a lumbar puncture requiring a local anesthetic.

[0078] In a non-limiting example, when a blood sample is drawn from a patient there are several ways in which the sample can be processed. The range of processing can be as little as none (i.e. frozen whole blood) or as complex as the isolation of a particular cell type. The most common and routine procedures involve the preparation of either serum or plasma from whole blood. All blood sample processing methods, including spotting of blood samples onto solid-phase supports, such as filter paper or other immobile materials, are also contemplated by the present invention.

[0079] In another non-limiting example, CSF samples may be collected using a lumbar puncture procedure; a local anesthetic is applied to the lower back. A needle is then inserted into the numbed skin between the L4 and L5 vertebrae until it pierces the subdural space. The CSF may be collected into sterile tubes.

[0080] For example, but not considered to be limiting in any manner, while obtaining a CSF sample may result in more discomfort for the patient than taking ablood sample, a CSF assay used after a positive result on a AD-specific serum test, a differential diagnosis between AD and non-AD has a higher degree of confirmation.

[0081] Without wishing to be limiting in any manner, the processed blood, serum or CSF sample described above may then be further processed to make it compatible with the methodical analysis technique to be employed in the detection and measurement of the metabolites contained within the processed serum or CSF sample. The types of processing can range from as little as no further processing to as complex as differential extraction and chemical derivatization. Extraction methods could include sonication, soxhlet extraction, microwave assisted extraction (MAE), supercritical fluid extraction (SFE), accelerated solvent extraction (ASE), pressurized liquid extraction (PLE), pressurized hot water extraction (PHWE) and/or surfactant assisted extraction (PHWE) in common solvents such as methanol, ethanol, mixtures of alcohols and water, or organic solvents such as ethyl acetate or hexane. A method of particular interest for extracting metabolites for FTMS non-targeted analysis is to perform a liquid/liquid extraction whereby non-polar metabolites dissolve in an organic solvent and polar metabolites dissolve in an aqueous solvent.

[0082] The extracted samples may be analyzed using any suitable method know in the art. For example, and without wishing to be limiting in any manner, extracts of biological samples are amenable to analysis on essentially any mass spectrometry platform, either by direct injection or following chromatographic separation. Typical mass spectrometers are comprised of a source which ionizes molecules within the sample, and a detector for detecting the ionized molecules or fragments of molecules. Non-limiting examples of common sources include electron impact, electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), atmospheric pressure photo ionization (APPI), matrix assisted laser desorption ionization (MALDI), surface enhanced laser desorption ionization (SELDI), and derivations thereof. Common mass separation and detection systems can include quadrupole, quadrupole ion trap, linear ion trap, time-of-flight (TOF), magnetic sector, ion cyclotron (FTMS), Orbitrap, and derivations and combinations thereof The advantage of FTMS over other MS-based platforms is its high resolving capability that allows for the separation of metabolites differing by only hundredths of a Dalton, many which would be missed by lower resolution instruments.

[0083] By the term "metabolite", it is meant specific small molecules, the levels or intensities of which are measured in a sample, and that may be used as markers to diagnose a disease state. These small molecules may also be referred to herein as "metabolite marker", "metabolite component", "biomarker", or "biochemical marker".

[0084] The metabolites are generally characterized by their accurate mass, as measured by mass spectormetry technique used in the above method. The accurate mass may also be referred to as "accurate neutral mass" or "neutral mass". The accurate mass of a metabolite is given herein in Daltons (Da), or a mass substantially equivalent thereto. By "substantially equivalent thereto", it is meant that a +/- 5 ppm difference in the accurate mass would indicate the same metabolite, as would be recognized by a person of skill in the art. The accurate mass is given as the mass of the neutral metabolite. As would be recognized by a person of skill in the art, the ionization of the metabolites, which occurs during analysis of the sample, the metabolite will cause either a loss or gain of one or more hydrogen atoms and a loss or gain of an electron. This changes the accurate mass to the "ionized mass", which differs from the accurate mass by the mass of hydrogens and electrons lost or gained during ionization. Unless otherwise specified, the accurate neutral mass will be refered to herein.

[0085] Similarly, when a metabolite is described by its molecular formula or structure, the molecular formula or structure of the neutral metabolite will be given. Naturally, the molecular formula or structure of the ionized metabolite will differ from the neutral molecular formula or structure by the number of hydrogens lost or gained during ionization.

[0086] Data is collected during analysis and quantifying data for one or more than one metabolite is obtained. "Quantifying data" is obtained by measuring the levels or intensities of specific metabolites present in a sample.

[0087] The quantifying data is compared to correponding data from one or more than one reference sample. The "reference sample" is any suitable reference sample for the particular disease state. For example, and without wishing to be limiting in any manner, in the present invention the reference sample may be a sample from a non-demented control individual, i.e., a person not suffering from AD dementia, non-AD dementia or cognitive impairment (also refered to herein as a " 'normal' counterpart"); the reference sample may also be a sample obtained from a patient with clinically diagnosed with AD, a patient with clinically diagnosed non-AD dementia, or a patient di agnosed with significant cognitive impairment. As would be understood by a person of skill in the art, more than one reference sample may be used for comparison to the quantifying data. For example and without wishing to be limiting, the one or more than one reference sample may be a first reference sample obtained from a non-demented control individual. The one or more than one reference sample may further include a second reference sample obtained from a patient with clinically diagnosed AD-dementia, a third reference sample obtained from a patient with clinically diagnosed non-AD dementia, a fourth reference sample obtained from a patient suffering from significant cognitive impairment, or any combination thereof.

[0088] The present invention also provides novel compounds, identified using the methods of the present invention. The novel compounds may be used as metabolite markers in the differential diagnosis of dementia, as described above.

[0089] In one embodiment, the compounds may be selected from the metabolites listed in Tables 1 to 7, or a combination thereof. These metabolites were identified in serum samples, and may be phosphatidylcholine-related compounds, ethanolamine plasmalogens, endogenous fatty acids, essential fatty acids, lipid oxidation byproducts, metabolite derivatives of said metabolite classes, and any metabolite that may contribute in any way to the anabolic/catabolic metabolism of said metabolite classes.

[0090] An optimal panel of compounds may be indentified from those metabolites listed in Tables 1 to 7. For example and without wishing to be limiting, the metabolite markers maybe metabolites with accurate masses measured in Daltons of, or substantially equivalent to, 541.3432, 569.3687, 699.5198, 723.5195, 723.5197, 751.5555, 803.568, 886.5582. The metabolites of accurate masses 699.5198, 723.5195, 723.5197, and 751.555 have presently been identified as ethanolamine plasmalogens, and are specifically decreased in patients with AD dementia. The metabolite markers of accurate masses 541.3432, 569.3687, 803.568, and 886.5582 have presently been identified as phosphatidylcholine related metabolites, and are decreased in patients with cognitive impairment on ADAS-cog, and severity of cognitive impairment correlates to the degree of decrease.

[0091] The metabolites with accurate masses measured in Daltons of, or substantially equivalent to, a) 541.3432, b) 569.3687, c) 699.5198, d) 723.5195, e) 751.5555, f) 803.568, can be further characterized by

a) an extracted ion chromatogram (EIC) as shown in Figure 4A, and an MS/MS spectrum as shown in Figure 6; a molecular formula of $C_{25}H_{51}NO_9P$; and/or the structure shown in figure 12;

b) an EIC as shown in Figure 4B, and an MS/MS spectrum as shown in Figure 7; a molecular formula of $C_{27}H_{55}NO_9P$; and/or the structure shown in figure 13;

c) an EIC as shown in Figure 4C, and an MS/MS spectrum as shown in Figure 8; a molecular formula of $C_{39}H_{74}NO_7P$; and/or the structure shown in figure 17;

d) an EIC as shown in Figure 4D, and an MS/MS spectrum as shown in Figure 9; a molecular formula of $C_{41}H_{74}NO_7P$; and/or the structure shown in figure 18;

e) an EIC as shown in Figure 4E, and an MS/MS spectrum as shown in Figure 10; a molecular formula of $C_{43}H_{78}NO_7P$; and/or the structure shown in figure 19;

f) an EIC as shown in Figure 4F, and an MS/MS spectrum as shown in Figure 11; a molecular formula of $C_{43}H_{81}NO_{10}P$; and/or the structure shown in figure 14,

respectively.

[0092] It is presently shown that the ethanolamine plasmalogen metabolites (neutral masses 699.5198, 723.5195, 751.5555) and the phosphatidylcholine metabolites (neutral masses 699.5198, 723.5195, 751.5555) are decreased in the serum of AD subjects exhibiting significant cognitive impairment. This is the first report of serum-based changes in these metabolites associated with AD and dementia. It is further shown that the decrease in the disclosed serum phosphatidylcholine related metabolites occurs in all patients exhibiting a significant cognitive impairment as measured by the ADAS-cog regardless of AD status, and that the degree of decrease correlates with the severity of the cognitive impairment. However, the observed decrease in disclosed ethanolamine plasmalogens is independent of cognitive impairment, occurs specifically in subjects with AD and is therefore a true diagnostic of AD.

[0093] Ethanolamine plasmalogens are a type of ethanolamine phospholipid. Ethanolamine phospholipids can be further differentiated based on their sn-1 configurations (either acyl, ether, or vinyl ether). The sn-2 position is typically acyl and the sn-3 position contains the phosphoethanolamine moiety. Therefore, the three classes are described as either diacyl (also referred to herein as PtdEt), alkyl-acyl (also referred to herein as plasmanyl) or alkenyl-acyl (also referred to herein as EtnPl or plasmenyl). Various basic structures of ethanolamine phospholipids are shown in Figure 20, along with the standard naming convention used herein.

[0094] A decrease in the disclosed ethanolamine plasmalogens may represent the initial or early stages AD, and can be detected non-invasively in living subjects by measuring serum levels of specific ethanolamine plasmalogens. Similarly, cognitive impairment can be quantitated non-invasively by measuring the serum levels of specific phosphatidylcholine metabolites.

[0095] Other metabolites have also been identified. For example, the metabolites with accurate masses measured in Daltons of, or substantially equivalent to, a) 541.3432, b) 569.3687, c) 699.5198, d) 723.5195, e) 751.5555, f) 803.568, which maybe further characterized by

a) the molecular formula $C_{27}H_{55}NO_9P$; and/or the structure shown in Figure 15A

b) the molecular formula $C_{27}H_{55}NO_9P$; and/or the structure shown in Figure 15B

c) the molecular formula $C_{43}H_{83}NO_{10}P$; and/or the structure shown in Figure 15C;

d) the molecular formula $C_{45}H_{81}NO_{10}P$; and/or the structure shown in Figure 15D;

e) the molecular formula $C_{45}H_{83}NO_{10}P$; and/or the structure shown in Figure 15E;

f) the molecular formula $C_{45}H_{85}NO_{10}P$; and/or the structure shown in Figure 15F;

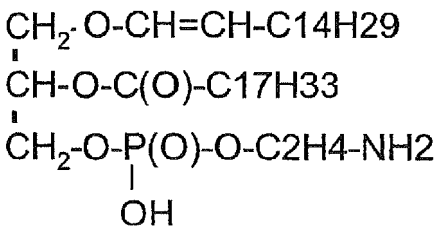
g) the molecular formula $C_{47}H_{83}NO_{10}P$; and/or the structure shown in Figure 15G,

respectively.

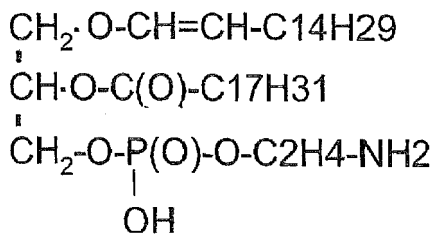
[0096] Based on the identification of metabolites specific to AD dementia (accurate masses 699.5198, 723.5195, 723.5197, 751.555) as ethanolamineplasmalogens, other ethanolamine phospholipid metabolite markers were identified. These are metabolites M05 to M24 as listed and characterized (accurate mass, name/composition, molecular formula) in Table 18. The structure of the metabolite can be deduced based on the metabolite name as indicated in Table 18 and the nomenclature, as indicated in Figure 20.

[0097] Of the compounds listed in Table 18, those of particular interest include metabolites with accurate masses measured in Daltons of, or substantially equivalent to, a) 701.53591, b) 699.52026, c) 723.52026, d) 747.52026, e) 729.56721, f) 727.55156, g) 779.58286, and h) 775.55156, which can be further characterized by

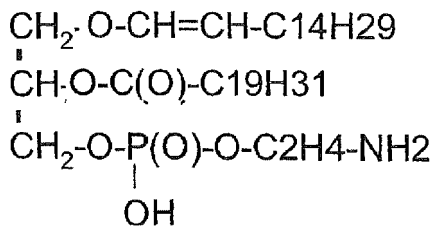
a) a MS/MS spectrum as shown in figure 21; molecular formula $C_{27}H_{55}NO_9P$; and/or the structure



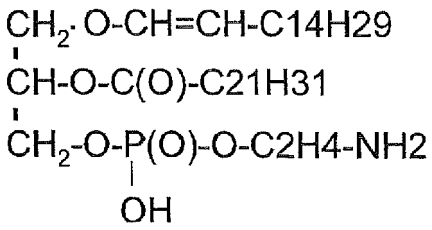
b) a MS/MS spectrum as shown in figure 22; molecular formula $C_{39}H_{74}NO_7P$; and/or the structure



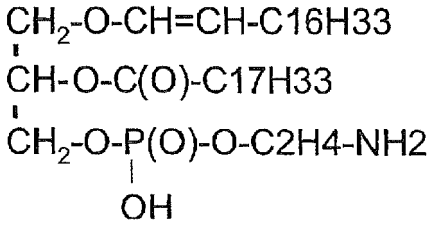
c) a MS/MS spectrum as shown in figure 23; molecular formula $C_{41}H_{74}NO_7P$; and/or the structure



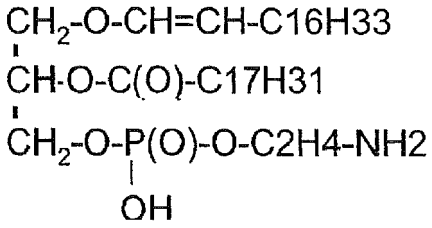
d) a MS/MS spectrum as shown in figure 24; molecular formula $C_{43}H_{74}NO_7P$; and/or the structure



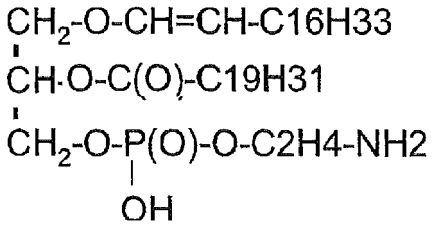
e) a MS/MS spectrum as shown in figure 25; molecular formula $C_{41}H_{80}NO_7P$; and/or the structure



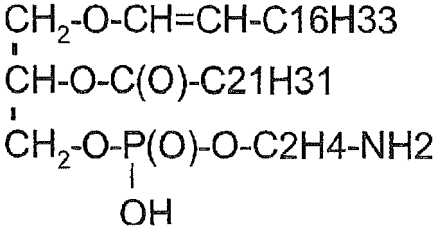
f) a MS/MS spectrum as shown in figure 26; molecular formula $C_{41}H_{78}NO_7P$; and/or the structure



g) a MS/MS spectrum as shown in figure 27; molecular formula $C_{45}H_{82}NO_7P$; and/or the structure



h) a MS/MS spectrum as shown in figure 28; molecular formula $C_{45}H_{78}NO_7P$; and/or the structure



respectively.

[0098] In another embodiment of the present invention, the compounds may be selected from the metabolites listed in Table 13, or a combination thereof. These metabolites were identified in CSF samples. Of particular interest are the metabolites with accurate masses measured in Daltons of, or substantially equivalent to, 207.0822, 275.8712, 371.7311, 373.728, 432.1532, 485.5603, 487.6482, 562.46, 622.2539, 640.2637, 730.6493, 742.2972. When used to diagnose

dementia, the metabolite markers 207.0822, 432.1532, 562.46,622.2539, 640.2637, 730.6493, and 742.2972 are increased in patients with AD dementia; and metabolite markers 275.8712, 371.7311, 373.728, 485.5603, and 487.6482 are decreased in patients with AD dementia.

[0099] In a further method of the present invention, a method for assessing dementia or the risk of dementia in a patient is described. The method comprises the steps of:

a) obtaining a serum sample from said patient;

b) analyzing said sample to obtain quantifiying data for one or more than one metabolite marker;

c) comparing the quantifying data for said one or more than one metabolite marker to corresponding data obtained from one or more than one reference sample; and

d) using said comparison to assess dementia or the risk of dementia.

[0100] The step of analyzing the sample (steb b)) may comprise analyzing the sample by liquid chromatography mass spectrometry (LC-MS). Alternatively, the step of analyzing the sample (step b)) may comprise analyzing the sample by linear ion trap mass spectrometry followed by liquid chromatograph, when the method is a highthroughput method.

[0101] The one or more than one reference sample may include a first reference sample obtained from a non-demented control individual, a second reference sample obtained from a patient with cognitive impairment as measured by ADAS-cog, a third reference sample obtained from a patient with with cognitive impairment as measured by MMSE, or a combination of one or more of these.

[0102] Without wishing to be limiting in any manner, the one or more than one metabolite marker used to asses dementia or the risk of dementia may be selected from the metabolites listed in Tables 10-12, or a combination thereof. Of particular interest are metabolites with accurate masses measured in Daltons of, or substantially equivalent to 541.3432, 569.3687, 699.5198, 723.5195, 723.5197, 751.5555, 803.568, 886.5582, 565.3394, 569.369, 801.555, 857.6186. A decrease in the patient sample in metabolite markers 699.5198,723.5195,723.5197, and 751.555 indicates AD pathology; a decrease in the patient sample in metabolite markers 541.3432,569.3687,803.568, and 886.5582 indicates cognitive impairment on ADAS-cog; and 565.3394, 569.369, 801.555, and 857.6186 indicates cognitive impairment on MMSE.

[0103] In yet another embodiment of the present invention, there is provided a method for differentially diagnosing dementia or the risk of dementia in a patient. The method comprising the steps of:

a) obtaining a sample from said patient;

b) analyzing said sample to obtain quantifiying data for one or more than one metabolite marker;

c) obtaining a ratio for each of the one or more than one metabolite marker to an internal control metabolite;

d) comparing each ratio of said one or more than one metabolite marker to the internal control metabolite to corresponding data obtained from one or more than one reference sample; and

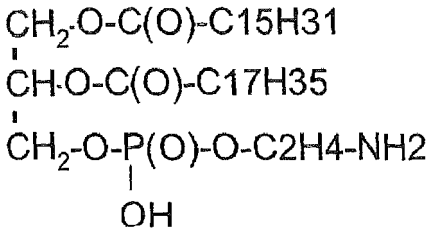
e) using said comparison to differentially diagnose dementia or the risk of dementia.

[0104] The step of analyzing the sample (steb b) may comprise analyzing the sample using a mass spectrometer (MS). For example, and without wishing to be limiting, such mass spectrometer could be of the FTMS, orbitrap, time of flight (TOF) or quadrupole types. Alternatively, the mass spectrometer could be equipped with an additional pre-detector mass filter. For example, and without wishing to be limiting such instruments are commonly referred to as quadrupole-FTMS (Q-FTMS), quadrupole-TOF (Q-TOF) or triple quadrupole (TQ or QQQ). In addition, the mass spectrometer could be operated in either the parent ion detection mode (MS) or in MSn mode, where n>=2. MSn refers to the situation where the parent ion is fragmented by collision induced dissociation (CID) or other fragmentation procedures to create fragment ions, and then one or more than one of said fragments are detected by the mass spectrometer. Such frament can then be further fragmented to create further fragments. Alternatively, the sample could be introduced into the mass spectrometer using a liquid or gas chromatographic system or by direct injection.

[0105] In the method as just described above, the one or more than one reference sample may be a first reference sample obtained from a non-demented control individual. The one or more than one reference sample may further include a second reference sample obtained from a patient with clinically diagnosed AD-dementia, a third reference sample obtained from a patient with clinically diagnosed non-AD dementia, a fourth reference sample obtained from a

patient suffering from significant cognitive impairment, or any combination thereof.

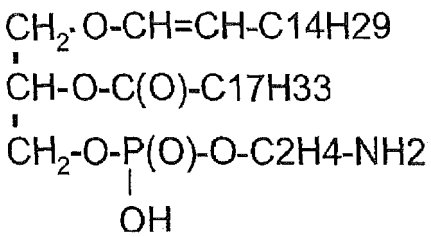
[0106] In the method as described above, the sample and reference sample maybe serum samples. The one or more than one metabolite marker may be selected from the metabolites as listed and characterized (accurate mass, name/composition, molecular formula) in Table 18. The "internal control metabolite" refers to an endogenous metabolite naturally present in the patient. Any suitable endogenous metabolite that does not vary over the disease states can be used as the internal control metabolite. For example, and without wishing to be limiting, the internal control metabolite may be phosphatidylethanolamine 16:0/18:0 (PtdEt 16:0/18:0, M01), as shown in Table 18; this internal control metabolite has a molecular formula of $C_{39}H_{78}NO_8P$, and a structure characterized as



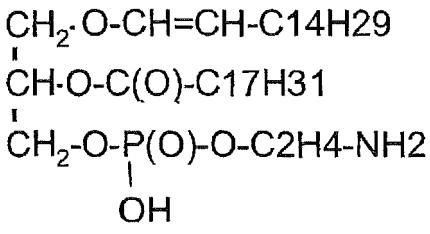
[0107] Use of the ratio of the metabolite marker to the internal control metabolite offers measurement that are more stable and reproducible than measurement of absolute levels of the metabolite marker. As the internal control metabolite is naturally present in all samples and does not appear to vary significantly over disease states, the sample-to-sample variability (due to handling, extraction, etc) is minimized.

[0108] Of the compounds listed in Table 18, those of particular interest in the above method include metabolites with accurate masses measured in Daltons of, or substantially equivalent to, a) 701.53591, b) 699.52026, c) 723.52026, d) 747.52026, e) 729.56721, f) 727.55156, g) 779.58286, and h) 775.55156. A decrease in the ratio of a) to h) to the internal control metabolite indicates AD dementia with a severe cognitive impairment. These metabolites can be further characterized by

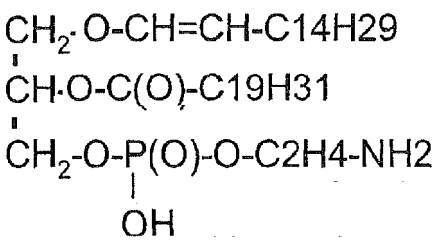
a) a MS/MS spectrum as shown in figure 21; molecular formula $C_{27}H_{55}NO_9P$; and/or the structure



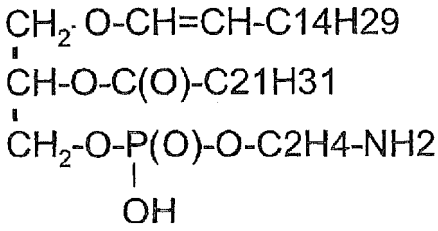
b) a MS/MS spectrum as shown in figure 22; molecular formula $C_{39}H_{74}NO_7P$; and/or the structure



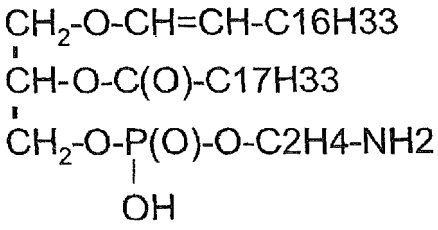
c) a MS/MS spectrum as shown in figure 23; molecular formula $C_{41}H_{74}NO_7P$; and/or the structure



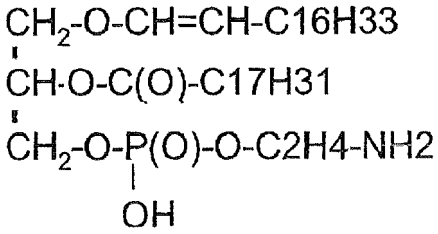
d) a MS/MS spectrum as shown in figure 24; molecular formula $C_{43}H_{74}NO_7P$; and/or the structure



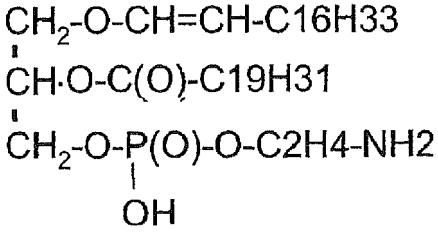
e) a MS/MS spectrum as shown in figure 25; molecular formula $C_{41}H_{80}NO_7P$; and/or the structure



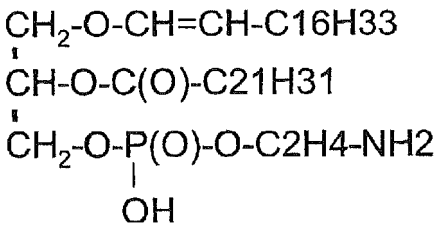
f) a MS/MS spectrum as shown in figure 26; molecular formula $C_{41}H_{78}NO_7P$; and/or the structure



g) a MS/MS spectrum as shown in figure 27; molecular formula $C_{45}H_{82}NO_7P$; and/or the structure



h) a MS/MS spectrum as shown in figure 28; molecular formula $C_{45}H_{78}NO_7P$; and/or the structure



respectively.

[0109] In yet another embodiment of the present invention, there is provided a method for evaluating the efficacy of a therapy for treating dementia in a patient, comprising:

a) obtaining a sample from said patient;

b) analyzing said sample to obtain quantifying data for one or more than one metabolite marker;

c) comparing said quantifying data to corresponding data obtained from one or more than one reference sample; and

d) using said comparison to determine whether the therapy is improving the demented state of the patient.

[0110] Optionally, after the step of analyzing (step b), a ratio for each of the one or more than one metabolite marker to an internal control metabolite may be obtained. In this case, each ratio of said one or more than one metabolite marker to the internal control metabolite to corresponding data obtained from one or more than one reference sample is compared to evaluate the efficacy of the therapy.

[0111] The step of analyzing (step b) may comprise analyzing the sample by liquid chromatography mass spectrometry (LC-MS), or alternatively may comprise analyzing the sample by liquid chromatography and linear ion trap mass spectrometry when the method is a highthroughput method.

[0112] By the term "therapy", it is meant any suitable course of therapy that may improve the health state or demented state of the patient being evaluated. When evaluating the efficacy of the therapy, the effect of the particular therapy in improving or degrading the health state of the patient will be measured. In doing so, a person of skill in the art would be capable of determining whether the therapy is effective for treating the demented state.

[0113] In the methods as described, the one or more than one reference sample may be any suitable reference sample. For example, and without wishing to be limiting in any manner, the reference sample may be a plurality of samples obtained from from non-demented control individuals; a plurality of samples obtained from clinically diagnosed AD patients; one or more than one pre-therapy baseline sample obtained from the patient; or any combination thereof. A pre-therapy baseline sample from the patient is particularly useful, as the variation in metabolites will then be specific to the patient.

[0114] The sample and the reference sample may be serum samples. In this case, the one or more than one metabolite marker could be selected from the metabolites listed in Tables 1 to 7, or a combination thereof, for example, metabolite markers with accurate masses measured in Daltons of, or substantially equivalent to, 541.3432, 569.3687, 699.5198, 723.5195, 723.5197, 751.5555, 803.568, 886.5582. Alternatively, the metabolite markers may be selected from metabolites M05 to M24 with accurate masses of, or substantially equivalent to those listed in Table 18, for example, metabolites with accurate masses measured in Daltons of, or substantially equivalent to, 701.53591, 699.52026, 723.52026, 747.52026, 729.56721, 727.55156, 779.58286, and 775.55156. Metabolites M05-M24 could also be used when a ratio is obtained between the metabolites and the internal control metabolite; the internal metabolite could be, for example, metabolite M01, as described in Table 18.

[0115] The sample and the reference sample may also be cerebrospinal fluid (CSF) samples. In this case, the one or more than one metabolite marker could be selected from the metabolites listed in Table 13, or a combination thereof; for example, metabolites with accurate masses measured in Daltons of, or substantially equivalent to, 207.0822, 275.8712, 371.7311, 373.728, 432.1532, 485.5603, 487.6482, 562.46, 622.2539, 640.2637, 730.6493, 742.2972.

[0116] The identified metabolites can be readily measured systemically. This point is of fundamental importance, since the majority of research pertaining to AD and other neurological disorders has ignored the peripheral systems. The ability to measure neurodegenerative processes within a blood sample is of substantial value in the diagnosis of dementia. With respect to the specific ethanolamine plasmalogen metabolites of the present invention, these are a valid biochemical marker of AD pathology since this molecular species' content does not change in Parkinson's disease, a disease which is often accompanied by dementia [29]. Furthermore, the specificity of the plasmalogen metabolites to AD indicates that its levels in serum could be readily measured longitudinally throughout the lifetime of an individual to assess the risk or

for early detection of the disease prior to the emergence of clinical symptoms.

[0117] The present invention also provides high throughput methods for differential diagnosis of AD dementia and non-AD dementia states. The method may involve fragmentation of the parent molecule; in a non-limiting example, this may be accomplished by a Q-Trap™ system. Detection of the metabolites may be performed using one of various assay platforms, including colorimetric chemical assays (UV, or other wavelength), antibody-based enzyme-linked immunosorbant assays (ELISAs), chip-based and polymerase-chain reaction for nucleic acid detection assays, bead-based nucleic-acid detection methods, dipstick chemical assays or other chemical reaction, image analysis such as magnetic resonance imaging (MRI), positron emission tomography (PET) scan, computerized tomography (CT) scan, nuclear magnetic resonance (NMR), and various mass spectrometry-based systems.

[0118] A high-throughput method for determining the levels of the metabolites in a person's blood and comparing the levels to levels in a normal "reference" population can lead to a prediction of whether the person has AD or not. This can be carried out in several ways. One way is to use a prediction algorithm to classify the test sample, as previously described, which would output a percentage probability for having AD. A predictive approach would work independently of the assay method, as long as the intensities of the metabolites could be measured. Another method could simply be based on setting a threshold intensity level from the mass spectrometer, and determining whether a person's profile is above or below the threshold which would indicate their AD status. Alternatively, and without wishing to be limiting in any manner, a preferred method is a truly quantitative assay could be performed to determine the molar concentration of the six metabolites in the non-demented normal and AD population. An absolute threshold concentration could then be determined for AD-positivity. In a clinical setting, this would mean that if the measured levels of the metabolites, or combinations of the metabolites, were below a certain concentration, there would be an associated probability that the individual is positive for AD. Therefore, the optimal diagnostic test could comprise a method of measuring the intensities of the metabolites in serum, and an algorithm for taking the intensity values and outputting a predicted probability for having AD as well as for being healthy (i.e., AD-negative).

[0119] The methods and identified biomarkers of the present invention, based on small molecules or metabolites in a sample, fulfills the criteria identified in 1999 for an ideal screening test [82], as development of assays capable of detecting specific metabolites is relatively simple and cost effective per assay. The test is minimally invasive and is indicative of cognitive impairment and of AD pathology. Translation of the method into a clinical assay compatible with current clinical chemistry laboratory hardware is commercially acceptable and effective. Furthermore, the method of the present invention does not require highly trained personnel to perform and interpret the test.

[0120] The present invention will be further illustrated in the following examples.

Example 1: Identification of Differentially Expressed Metabolites

[0121] Differentially expressed metabolites were identified in clinically diagnosed AD with and without significant cognitive impairment, clinically diagnosed non-AD and non-demented controls.

[0122] ***Clinical*** *Samples.* For the AD serum diagnostic assay described, samples were obtained from representative populations of non-demented healthy individuals and of clinically diagnosed AD and non-AD dementia patients. The biochemical markers of AD described in the invention were derived from the analysis of 75 serum samples from patients clinically diagnosed with probable AD (43 patients with significant cognitive impairment, 32 with no cognitive impairment), serum samples from 30 patients with clinically diagnosed non-AD dementia, and 31 serum samples from non-demented controls. Samples in the three groups were from a diverse population of individuals, ranging in age, ethnicity, weight, occupation, and displaying varying non-dementia-related health-states. All samples were single time-point collections. Cognitive impairment of the patients was also assessed using the Alzheimer's Disease Assessment Scale (ADAS)-cognitive subset.

[0123] For the AD CSF diagnostic assay described, samples were obtained from a group of patients that represented clinically diagnosed AD with dementia and non-AD patients with dementia. The biochemical markers of AD described in this invention were derived from the analysis of 6 CSF samples from clinically diagnosed AD patients with dementia and 5 CSF samples from clinically diagnosed non-AD patients with dementia.

[0124] Samples in both groups were from a diverse population of individuals, ranging in age, ethnicity, weight, occupation, and displaying varying non-dementia-related health-states. All samples were single time-point collections. The metabolites contained within the 136 serum samples and 11 CSF samples used in this application were separated into polar and non-polar extracts through sonication and vigorous mixing (vortex mixing).

[0125] ***Mass Spectrometry Analysis.*** Analysis of serum extracts collected from 136 individuals (75 clinically diagnosed AD, 30 clinically diagnosed non-AD, and 31 non-demented healthy controls) and 11 CSF extracts (6 clinically-diagnosed AD and 5 clinically diagnosed non-AD patients) was performed by direct injection into a FTMS and ionization by either ESI or atmospheric pressure chemical ionization (APCI) in both positive and negative modes. Sample extracts were diluted either three or six-fold in methanol:0.1%(v/v) ammonium hydroxide (50:50, v/v) for negative ionization modes, or in methanol:0.1% (v/v) formic acid (50:50, v/v) for positive ionization modes. For APCI, sample extracts were

directly injected without diluting. All analyses were performed on a Bruker Daltonics APEX III Fourier transform ion cyclotron resonance mass spectrometer equipped with a 7.0 T actively shielded superconducting magnet (Bruker Daltonics, Billerica, MA). Samples were directly injected using electrospray ionization (ESI) and/or APCI at a flow rate of 1200 μL per hour. Ion transfer/detection parameters were optimized using a standard mix of serine, tetra-alanine, reserpine, Hewlett-Packard tuning mix and the adrenocorticotrophic hormone fragment 4-10. In addition, the instrument conditions were tuned to optimize ion intensity and broad-band accumulation over the mass range of 100-1000 amu according to the instrument manufacturer's recommendations. A mixture of the abovementioned standards was used to internally calibrate each sample spectrum for mass accuracy over the acquisition range of 100-1000 amu.

[0126] In total, six separate analyses comprising combinations of extracts and ionization modes were obtained for each sample:

Aqueous Extract

1. Positive ESI (analysis mode 1101)
2. Negative ESI (analysis mode 1102)

Organic Extract

3. Positive ESI (analysis mode 1201)
4. Negative ESI (analysis mode 1202)
5. Positive APCI (analysis mode 1203)
6. Negative APCI (analysis mode 1204)

[0127] *Mass Spectrometry **Data** Processing.* Using a linear least-squares regression line, mass axis values were calibrated such that each internal standard mass peak had a mass error of <1 p.p.m. compared with its theoretical mass. Using XMASS software from Bruker Daltonics Inc., data file sizes of 1 megaword were acquired and zero-filled to 2 megawords. A sinm data transformation was performed prior to Fourier transform and magnitude calculations. The mass spectra from each analysis were integrated, creating a peak list that contained the accurate mass and absolute intensity of each peak. Compounds in the range of 100-2000 m/z were analyzed. In order to compare and summarize data across different ionization modes and polarities, all detected mass peaks were converted to their corresponding neutral masses assuming hydrogen adduct formation. A self-generated two-dimensional (mass vs. sample intensity) array was then created using DISCOVAmetrics™ software (Phenomenome Discoveries Inc., Saskatoon, SK, Canada). The data from multiple files were integrated and this combined file was then processed to determine the unique masses. The average of each unique mass was determined, representing the y axis. This value represents the average of all of the detected accurate masses that were statistically determined to be equivalent. Considering that the mass accuracy of the instrument for the calibration standards is approximately 1 ppm, a person skilled in the art will recognize that these average masses may include individual masses that fall within +/- 5 ppm of this average mass. A column was created for each file that was originally selected to be analyzed, representing the x axis. The intensity for each mass found in each of the files selected was then filled into its representative x,y coordinate. Coordinates that did not contain an intensity value were left blank. Once in the array, the data were further processed, visualized and interpreted, and putative chemical identities were assigned. Each of the spectra were then peak picked to obtain the mass and intensity of all metabolites detected. These data from all of the modes were then merged to create one data file per sample. The data from all 136 samples was then merged and aligned to create a two-dimensional metabolite array in which each sample is represented by a column and each unique metabolite is represented by a single row. In the cell corresponding to a given metabolite sample combination, the intensity of the metabolite in that sample is displayed. When the data is represented in this format, metabolites showing differences between groups of samples were determined. The same procedure was utilized to combine the 11 CSF samples in a two-dimensional metabolite array.

A. Serum Biomarkers

[0128] A student's T-test was used to select for metabolites which differed significantly between the following different clinical groups in serum. Metabolites that were less than $p<0.05$ were considered significant.

[0129] A1- Clinically diagnosed AD patients (n=75) vs. non-demented controls (n=31). This comparison yielded 262 metabolites (see Table 1).

[0130] A2 - Clinically diagnosed AD patients with a significant cognitive impairment (n=32) vs. non-demented controls (n=31). This comparison yielded 292 metabolites (see Table 2).

[0131] A3 - Clinically diagnosed AD patients with a significant cognitive impairment (n=32) vs. clinically diagnosed non-AD patients with a significant cognitive impairment (n=30); this comparison yielded 118 metabolites markers (see

Table 3).

[0132] A4 - Clinically diagnosed AD patients with significant cognitive impairment (n=32) vs. clinically diagnosed AD patients without significant cognitive impairment (n=43). This comparison yielded 97 metabolites markers (see Table 4).

[0133] A5 - Clinically diagnosed non-AD patients (n=30) vs. non-demented controls (n=31); this comparison yielded 199 metabolites markers (see Table 5).

[0134] A6 - Clinically diagnosed AD patients with mild cognitive impairment (n=43) vs. non-demented controls (n=31). This comparison yielded 136 metabolites (see Table 6).

[0135] A7 - Patients with significant cognitive impairment (n=42) and patients with a mild cognitive impairment (n=43). This comparison yielded 81 metabolites (Table 7).

[0136] Tables 1-7 show biochemical markers whose concentrations or amounts in serum are significantly different ($p<0.05$) between the tested populations and therefore have potential diagnostic utility for identifying each of the aforesaid populations. The features are described by their accurate mass and analysis mode, which together are sufficient to provide the putative molecular formulas and chemical characteristics (such as polarity and putative functional groups) for each metabolite.

[0137] From the initial lists of several hundred possible metabolites, it was determined that a combination of 8 metabolites fulfills the criteria for a serum dementia test: the combination can differentiate AD dementia from non-AD dementia, the early stages of AD and healthy controls. The best combination of 8 metabolites included the metabolites with neutral masses (measured in Daltons) 541.3432, 569.3687, 699.5198, 723.5195, 723.5197, 751.5555, 803.568, 886.5582. Although these are the actual masses, a person skilled in the art of this technology would recognize that +/- 5 ppm difference would indicate the same metabolite.

[0138] In analyzing the present results, a person of skill in the art would understand that the following clinical groups are of interest: non-AD with significant cognitive impairment, AD with significant cognitive impairment, AD without significant cognitive impairment and non-demented controls. Bar graphs representing the mean +/-SEM of the 8 biomarkers for the four different clinical groups are shown in Figure 1. Relative to control, non-demented individuals, the three non-control states can be described as follows:

1. Non-AD with significant cognitive impairment vs. control:

    a. Biomarker 541.3432 - decreased
    b. Biomarker 569.3687 - decreased
    c. Biomarker 699.5198 - no difference
    d. Biomarker 723.5195 - no difference
    e. Biomarker 723.5197 - no difference
    f. Biomarker 751.5555 - no difference
    g. Biomarker 803.568 - decreased
    h. Biomarker 886.5582 - decreased

2. Clinically diagnosed AD with significant cognitive impairment vs. control

    a. Biomarker 541.3432 - decreased

    b. Biomarker 569.3687 - decreased

    c. Biomarker 699.5198 - decreased

    d. Biomarker 723.5195 - decreased

    e. Biomarker 723.5197 - decreased

    f. Biomarker 751.5555 - decreased

    g. Biomarker 803.568 - decreased

    h. Biomarker 886.5582 - decreased

3. Clinically diagnosed AD without significant cognitive impairment vs. control

    a. Biomarker 541.3432 - decreased

b. Biomarker 569.3687 - no difference

c. Biomarker 699.5198 - decreased

d. Biomarker 723.5195 - decreased

e. Biomarker 723.5197 - decreased

f. Biomarker 751.5555 - decreased

g. Biomarker 803.568 - no difference

h. Biomarker 886.5582 - no difference

[0139] In each of the three non-control cases described above, a unique subset of markers was decreased.

[0140] Bar graphs representing the mean +/- SEM of the 8 biomarkers for the two different clinical groups with a significant cognitive impairment are shown in Figure 2. Relative to non-AD dementia with significant cognitive impairment, AD patients with significant cognitive impairment can be described as:

a. Biomarker 541.3432 - no difference
b. Biomarker 569.3687 - no difference
c. Biomarker 699.5198 - decreased
d. Biomarker 723.5195 - decreased
e. Biomarker 723.5197 - decreased
f. Biomarker 751.5555 - decreased
g. Biomarker 803.568 - no difference
h. Biomarker 886.5582 - no difference

[0141] The results of this invention show a clear distinction between the serum of individuals with clinically diagnosed AD WITH a significant cognitive impairment, individuals with clinically diagnosed AD WITHOUT a significant cognitive impairment (this could be early stage AD), individuals with non-AD dementia WITH a significant cognitive impairment, and non-demented controls. These findings are capable of identifying and distinguishing the different types of dementia from one another and from the early stages of cognitive impairment as described in this application. From the above results, it can be further concluded that the metabolite markers with masses 699.5198, 723.5195,723.5997,751.5555 are specific for AD pathology, while markers with masses of 541.3432, 569.3687, 803.568, 886.5582 are specific for cognitive impaired based on ADAS-cog testing.

[0142] A second neuropsychological test, Folstein's Mini-Mental State Exam (MMSE), which measures cognitive impairment, was applied to all 136 patients. The MMSE is widely used and is an extensively validated test of orientation, short and long-term memory, praxis, language and comprehension. In the clinically diagnosed AD patients that had no significant cognitive impairment (n=43), 15 of those patients had a score on MMSE that would indicate normal cognition (MMSE $\geq$ 28), whereas the remaining 28 patients had MMSE scores that indicated a mild impairment (score 18-23, n=11) or severe cognitive impairment (score 9-17, n=17). A F-test was used to select for metabolites which differed significantly between the MMSE scores (normal, mild or severe cognitive impairment) for 43 clinically diagnosed AD patients with no significant cognitive impairment on the ADAS-cog test ($p<0.05$). 23 metabolites met this criterion (shown in Table 8). These are all features which differ statistically between the two populations and therefore have potential diagnostic utility. The features are described by their accurate mass and analysis mode, which together are sufficient to provide the putative molecular formulas and chemical characteristics (such as polarity and putative functional groups) of each metabolite.

[0143] An optimal subset of 4 metabolites, all of which were observed to decrease, from the 23 metabolites was selected using Principal Components Analysis (PCA). The 4 metabolites able to produce the greatest separation between the groups were 565.3394, 569.369, 801.555, 857.6186. The metabolites are indicated by asterisks on Table 8 and represent a 4-metabolite biomarker panel associated with cognitive impairment on MMSE. The fact that a second set of metabolites were associated cognitive impairment suggests that the MMSE must be specific to one or several other cognitive states that the ADAS-cog is not specifically measuring.

[0144] Therefore, a total of three 4-biomarker panels can be applied to the 136 patients to classify them into one of 8 categories which will simultaneously indicate the presence of AD pathology (biomarkers 699.5198, 723.5195, 723.5997, 751.5555), cognitive impaired on ADAS-cog (541.3432, 569.3687, 803.568, 886.5582) and cognitive impaired on MMSE (565.3394, 569.369, 801.555, 857.6186). Using a 0/1 binary model, each patient can be labeled using a 3 digit code

from "000" indicating no cognitive impairment and no AD pathology to "111" indicating both MMSE and ADAS-cog impairment and AD pathology. Table 9 indicates the separation of the patient samples into the 8 categories.

[0145] The three 4-biomaker panels were applied individually to the metabolite array and the patients that showed the best separation on the PCA plot were selected. These patients were selected because they represented the best discriminator between the 3 different groups [AD (n=20) vs. non-AD pathology (n=20), high ADAS score (n=20) vs. low ADAS score (n=12), impaired cognition on the MMSE score (n=20) vs. normal cognition on the MMSE score (n=20)]. A student's t-test was performed between the different clinical groups ($p<0.05$). The 116 metabolites that met the p-value criteria for AD vs. non-AD pathology are listed in Table 10. Table 11 lists the 124 metabolites that met the p-value criteria for high ADAS score vs. low ADAS score, and Table 12 contains the list of 344 metabolites that met the p-value criteria for impaired score on MMSE and normal cognition on MMSE.

[0146] Both the ADAS-cog and MMSE neuropsychological tests measure cognitive errors related to praxis, orientation, memory and language ability. Therefore, it would be reasonable to suggest biomarkers associated with ADAS-cog score and/or MMSE are related to the ability to conceive of, organize and initiate unfamiliar sequences, the awareness of one's self and environment, as well as memory and language ability. As such, these biomarkers are not exclusive to cognitive impairment associated with dementia; rather any condition that results in any type of praxis, orientation, memory and/or language deficit would show a similar reduction within a biological sample.

[0147] The sample set (136 individuals) used for this discovery was not trivial, and was comprised of individuals of various ethnic and geographical backgrounds, and of varying age and health status. Therefore, there is sound reason to expect that the findings are representative of the general dementia population.

B. CSF Biomarkers.

[0148] A student's T-test was used to select for metabolites which differ between the clinically diagnosed AD patients and clinically diagnosed non-AD patients in CSF samples ($p<0.05$). 42 metabolites met this criterion (shown in Table 13). These metabolites differed statistically between the two populations and therefore have potential diagnostic utility. The metabolites are described by their accurate mass and analysis mode, which together are sufficient to provide the putative molecular formulas and chemical characteristics (such as polarity and putative functional groups) of each metabolite.

[0149] An optimal subset of 12 metabolites from the 42 metabolites described above was selected. These metabolites had the greatest statistical difference between the two groups ($p<0.01$). Metabolites were excluded if they were not detected in at least 60% of the samples in each group (4/6 clinically diagnosed AD and 3/5 clinically diagnosed non-AD). The panel comprises masses 207.0822, 275.8712, 371.7311, 373.728, 432.1532, 485.5603, 487.6482, 562.46, 622.2539, 640.2637, 730.6493, 742.2972. Although these are the actual masses, a person skilled in the art of this technology would recognize that an +/- 5 ppm difference would indicate the same metabolite.

[0150] The 12 biomarker panel was tested using 5 CSF samples from undiagnosed patients. The only information available on the samples was the subject's age, gender, and whether an individual had a co gnitive deficit. If the 12 biomarker panel was correct, the subject could be diagnosed as having AD dementia, non-AD dementia, or normal. From the 5 CSF samples provided by undiagnosed patients, 1 was diagnosed with non-AD dementia, 2 with AD dementia, and 2 as normal. The two normal subjects did not have a cognitive impairment as indicated by the Mini Mental State Examination (MMSE) score. Therefore, using a 12 metabolite feature set it was possible to both diagnose AD and non-AD dementia.

[0151] Bar graphs representing the mean +/- SEM of the 12 biomarkers for the two different clinical groups are shown in Figure 3. Relative to non-AD dementia with significant cognitive impairment, AD patients with a significant cognitive impairment can be described as:

a. Biomarker 207.0822 - increased
b. Biomarker 275.8712 - decreased
c. Biomarker 371.7311 - decreased
d. Biomarker 373.728 - decreased
e. Biomarker 432.1532 - increased
f. Biomarker 485.5603 - decreased
g. Biomarker 487.6482 - decreased
h. Biomarker 562.46 - increased
i. Biomarker 622.2539 - increased
j. Biomarker 640.2637 - increased
k. Biomarker 730.6493 - increased
l. Biomarker 742.2972 -increased

[0152] Based on these results, a clear distinction was made between the CSF of clinically diagnosed non-AD and AD patients. Therefore, such findings are capable of identifying and distinguishing AD dementia from non-AD dementia and can form the basis of a dementia diagnostic test in CSF as described in this application. It is expected that the finding are representative of the general dementia population.

[0153] Although a non-targeted FTMS-based platform was used in the identification and selection of the optimal metabolites in serum and CSF, other methods of subsequently detecting the molecules, including other MS-based platforms, ELISAs, colorimetric assays, etc can used to detect the molecules.

Example 2: Independent Method Confirmation of Discovered Metabolites

A. Serum Biomarkers

[0154] An independent mass spectrometry method was used to verify the intensity differences between non-demented normal and clinically-diagnosed AD serums of the eight diagnostic metabolites discovered using the FTMS method. Eight representative clinically-diagnosed AD sample extracts and eight representative non-demented control sample extracts were analyzed by LC-MS using an HP 1100 high-performance liquid chromatography interfaced to an ABI Q-Star mass spectrometer.

[0155] Aqueous fractions from five clinically-diagnosed AD and five non-demented control sample extracts were evaporated under nitrogen gas and reconstituted in 100 uL of methanol:water:formic acid (5:94.9:0.1). Five μL of the reconstituted sample was subjected to HPLC (Agilent Technologies) (HP 1100 with Metasil AQ 3u, 100 x 2 mm column) for full scan and 10 μL for MS/MS at a flow rate of 0.2 ml/min.

[0156] Eluate from the HPLC was analyzed using an ABI Q-Star XL mass spectrometer fitted with a Turboion spray ion (ESI) source in negative mode. The scan type in full scan mode was time-of-flight (TOF) with an accumulation time of 1.0000 seconds, mass range between 50 and 1500 Da, and duration time of 70 min. Source parameters were as follows: Ion source gas 1 (GS1) 55; Ion source gas 2 (GS2) 90; Curtain gas (CUR) 40; Nebulizer Current (NC) 0; Temperature 450°C; Declustering Potential (DP) -55; Focusing Potential (FP) -265; Declustering Potential 2 (DP2) -15. In MS/MS mode, scan type was product ion, accumulation time was 1.0000 seconds, scan range between 50 and 1000 Da and duration time 70 min. All source parameters are the same as above, with a collision energy of (CE) of -50 V and collision gas (CAD, nitrogen) of 5 psi.

[0157] Six of the eight metabolite masses previously discovered on the FTMS were verified on the ABI Q-Star mass spectrometer. The metabolites with the accurate masses of 723.5195 and 723.5197 were determined to be the same metabolite, and the metabolite with accurate mass of 886.5582 was not detected. Therefore, only six metabolites (699.5198, 723.5195, 751.5555, 541.3432, 569.3687, 803.568) were used for the remaining analyses.

[0158] The extracted ion chromatograms (EICs) for the sixbiomarkers are shown in Figure 4 The top panel shows the eight non-demented control EICs, and the bottom panel of each shows the eight clinically-diagnosed AD EICs. The sensitivity of the Q-star is superior to the FTMS, resulting in a greater magnitude in intensity difference between the non-demented control subjects and clinically diagnosed AD population for the selected biomarkers. Figure 5 shows the average raw intensity of the six biomarkers of the eight non-demented control and eight clinically-diagnosed AD samples as detected on the FTMS and Q-Star.

B. CSF Biomarkers

[0159] The metabolites and their associations with the clinical variables described in this invention are further confirmed using an independent mass spectrometry system. Representative sample extracts from each variable group are re-analyzed by LC-MS using an HP 1050 high-performance liquid chromatography, or equivalent interfaced to an ABI Q-Star, or equivalent mass spectrometer to obtain mass and intensity information for the purpose of identifying metabolites that differ in intensity between the clinical variables under investigation.

Example 3: Structure Elucidation of the Primary Metabolite Biomarkers

[0160] Characteristics that can be used for structure elucidation of metabolites include accurate mass and molecular formula determination, polarity, acid/base properties, NMR spectra, and MS/MS or MSn spectra. These data, and in particular theMS/MS spectrum, can be used as fingerprints of a particular metabolite and are unique identifiers of a particular metabolite regardless of whether the complete structure has been determined.

A. Serum Biomarkers - Structural Elucidation

[0161]

1. *LC retention time.* The extracts containing the metabolites of interest were subjected to reverse phase LC-MS using a C18 column and analysis by MS as described in Example 2 above. Table 14 lists the resulting retention times and detected masses for each of the six serum metabolite markers. The retention time for all six of the biomarkers is approximately 29-42 minutes under these HPLC conditions.

2. *Extraction conditions.* The conditions of extraction also provide insights about the chemical properties of the biomarkers. All eight metabolites in the serum (from Example 1) were ionized in negative mode (3 in APCI and 5 in ESI), which is indicative of a molecule containing an acidic moiety such as a carboxylic acid or phosphate. Any moiety capable of losing a hydrogen atom can be detected in negative ionization mode. Three of the metabolite markers were extracted into an organic ethyl acetate fraction (plasmalogen metabolites), indicating that these metabolites are non-polar under acidic condition; one was extracted into an organic ethyl acetate fraction dried down and resuspended in butanol, indicating that this metabolite (plasmalogen metabolite) is non-polar under acidic conditions. Four of the metabolites (phosphatidyl choline related metabolites) did not extract into the organic fraction, but rather remained in the aqueous methanol/ammonium hydroxide fraction, indicating that these metabolites are very polar.

3. *MS/MS spectra.* The six serum metabolites identified as having the best diagnostic ability were subj ect to MS/MS fragmentation using collision induced dissociation (CID). The structure of a given molecule will dictate a specific fragmentation pattern under defined conditions that is specific for that molecule (equivalent to a person's fingerprint). Even slight changes to the molecule's structure can result in a different fragmentation pattern. In addition to providing a fingerprint of the molecule's identity, the fragments generated by CID can be used to gain insights about the structure of a molecule, and for generating a very specific high-throughput quantitative detection method (see [30-33] for examples). Figures 6 through 11 show the MS/MS spectra for each of the six markers at -50V collision energy (CE) voltages.

[0162] The masses resulting from CID MS/MS of each parent mass were then used to calculate putative formulas for each of the fragment ions for the metabolites specific to the ADAS-cog scores, as shown in the tables for each marker (Tables 15 to 17). The information inherent in the fragmentation data is highly specific and descriptive for each metabolite, which can be used to gain structural insights about each molecule. MS/MS was carried out on the ABI-Q Star XL with all parameters as previously mentioned using Nitrogen as the collision gas at 5 psi and collision energy (CE) settings of -50 volts.

[0163] Based on the fragmentation pattern and masses, the metabolite markers specific to the ADAS-cog scores have been assigned structures having a phosphatidylcholine-related backbone. From the CID MS/MS, the molecular formulae of 3 metabolites specific to the ADAS-cog scores (accurate neutral masses of 541.3432, 569.3687, 803.568) were determined to be $C_{25}H_{51}NO_9P$, $C_{27}H_{55}NO_9P$, and $C_{43}H_{81}NO_{10}P$, respectively. Their structures are shown in Figures 12-14. The putative structures of additional markers are shown in Figure 15.

[0164] The 3 metabolites specific to AD pathology, with accurate neutral masses of 751.5555, 699.5198, and 723.5195, were analyzed using FT-ICRMS and LC/MS techniques, and by HRAPCI-MS, and MS/MS spectral analysis. Daughter ions determined from the fragmentation pattern for each metabolite marker are shown in figures 16-18. The molecular formulae were determined to be $C_{43}H_{78}NO_7P$, $C_{39}H_{74}NO_7P$, and $C_{41}H_{74}NO_7P$, respectively. Based on the fragmentation pattern and masses, the metabolite markers specific to AD patehology have been assigned structures having an ethanolamine plasmalogen backbone.

[0165] For the 751.5555 metabolite ($C_{43}H_{78}NO_7P$), and due to negative ionization conditions, the HRAPCI-MS m/z measured was 750.5482 ([M - H]-, calcd. 750.5477 for $C_{43}H_{77}NO_7P$). The relative intensity of the MS/MS fragment masses (MS/MS m/z) were measured as follows: 750 ([M-H]-, 25%), 482 (1%), 464 (12%), 446 (5%), 329 (8%), 303 (100%), 259 (12%), 205 (8%), 140 (8%). The MS/MS fragments are shown in Figure 16. The strong MS/MS fragment ion at m/z 303 and other fragment ions due to loss of sn-2 acyl group (m/z 464) as a ketone, loss of the sn-1 vinyl ether side chain (m/z 482) though small, and the fragment ion due to phosphoethanolamine (m/z 140) indicated the metabolite to be aplasmenyl phosphatidylethanolamine-type molecule with arachidonic acid at the sn-2 position. Based on these results, the structure of the 751.5555 metabolite was elucidated as 1-O-1'-(Z)-octadecenyl-2-arachidoyl-sn-glycero-3-phosphoethanolamine. This was confirmed by comparison of their LC/MS and MS/MS spectral data (Figure 19)

[0166] The two remaining metabolites with molecular formulae $C_{39}H_{74}NO_7P$ (neutral mass 699.5198) and $C_{41}H_{74}NO_7P$ (neutral mass 723.5195) were found to co-elute with the 751.5555 metabolite in LC/MS. The metabolites' MS/MS fragment ions and fragmentation patterns were similar to those of the 751.5555 metabolite.

[0167] For the 699.5198 metabolite, the HRAPCI-MS m/z measured was 698.5125 ([M - H]-, calcd. 698.5130 for $C_{39}H_{73}NO_7P$). The relative intensity of the MS/MS m/z were measured as follows: 698 ($[M-H]^-$, 8%), 536 (4%), 279 (100%), 255 (15%), 119 (10%). The MS/MS fragments are shown in Figure 17. Based on these results and on its structural similarity to the 751.5555 metabolite, the structure of the 699.5198 metabolite was determined to be 1-O-

1'-(Z)-hexadecenyl-2-linoleyl-sn-glycero-3-phosphoethanolamine.

[0168] For the 723.5195 metabolite, the HRAPCI-MS m/z measured was 722.5124 ($[M-H]^-$, calcd. 722.5130 for $C_{41}H_{73}NO_7P$). The relative intensity of the MS/MS m/z were measured as follows: 722 ($[M - H]^-$, 12%), 482 (1%), 436 (15%), 418 (6%), 303 (100%), 279 (6%), 259 (15%), 255 (10%), 205 (4%), 140 (5%). The MS/MS fragments are shown in Figure 18. Based on these results and on its structural similarity to the 751.5555 metabolite, the structure of the 723.5195 metabolite was proposed as 1-O-1'-(Z)-hexadecenyl-2-arachidoyl-sn-glycero-3-phosphoethanolamine.

[0169] 4. *NMR spectra.* The MS/MS fragmentation provides highly specific descriptive information about a metabolite. However, nuclear magnetic resonance (NMR) can assist in solving and confirming the structures of the metabolites. As NMR analysis techniques are typically less sensitive than mass spectrometry techniques, multiple injections are performed on the HPLC and the retention time window corresponding to the metabolites of interest collected and combined. The combined extract is then evaporated to dryness and reconstituted in the appropriate solvent for NMR analysis.

[0170] Multiple NMR techniques and instruments are available, for example, NMR spectral data are recorded on Bruker Avance 600 MHz spectrometer with cryogenic probe after the chromatographic separation and purification of the metabolites of interest. 1H NMR, 13C NMR, noe-difference spec, as well as 2-D NMR techniques like heteronuclear multiple quantum correlation (HMQC), and heteronuclear multiple bond correlation (HMBC) are used for structure elucidation work on the biomarkers.

B. CSF Biomarkers

[0171] The structural characteristics (LC retention time, extraction conditions, MS/MS fragments) for the 12 CSF metabolite markers are determined in the same manner as detailed above.

Example 4: Characterization of Ethanolamine Phospholipid in Serum

[0172] Based on the fact that the metabolite markers specific to AD pathology have an ethanolamine plasmalogen backbone, it was further investigated whether other serum plasmalogens could be indicative of AD. This characterization of ethanolamine phospholipids in serum was made using a chromatographic method combined with a mass spectrometric detector.

[0173] For MS/MS applications and experiments involving chromatography, an Agilent 1100 HPLC system was used in combination with an Applied Biosystems QSTAR XL mass spectrometer. An Agilent Zorbax RX-SIL (4.6 x 150mm, 5μm) column was used for normal phase chromatography. Conditions included an isocratic mobile phase (55:40:5 isopropanol:hexane:H2O) at a flow rate of 1.0mL/min for a total run time of 15min. The column was heated to 35°C. The sample injection volume was 10μL. Organic solvent extracts (ethyl acetate) of samples were evaporated to dryness under nitrogen gas and the residue was reconstituted in 100μL of 55:40:5 isopropanol:hexane:H2O solution prior to injection.

[0174] The QSTAR XL instrument was equipped with an APCI (Heated Nebulizer) source operating in negative mode. Values of major instrument parameters were DP, -60; FP, -265; DP2, -15; GS1, 75; GS2,15; CUR, 30; NC, -3; TEM, 400°C; Scan range, 50-1500amu; Accumulation time, 1 sec.

[0175] The three classes of ethanolamine phospholipids are described as diacyl (also referred to herein as PtdEt), alkyl-acyl (also referred to herein as plasmanyl) or alkenyl-acyl (also referred to herein as EtnPl or plasmenyl). Various basic structures of ethanolamine phospholipids are shown in Figure 20, along with the standard naming convention used herein. Table 18 shows a list of plasmanyl and plasmenyl ethanolamine phospholipids (M5-M24) that are presently identified and are of particular interest.

[0176] Figures 21-32 show structural information pertaining to selected metabolites detected in serum. These figures illustrate the retention time, MS/MS fragmentation patterns, and putative structures for selected molecules. Due to the conserved MS/MS fragmentation mechanism between these molecules, the theoretical MS/MS transition can be determined for any ethanolamine phospholipid by using a combination of the parent ion mass and the fragment mass of the moiety at either the sn-1 or sn-2 position.

Example 5: High Throughput Commercial Method Development

[0177] A high throughput method for differential diagnosis of AD dementia and non-AD dementia states was established.

[0178] High throughput screening (HTS) was performed with a linear ion trap mass spectrometer (Q-trap 4000, Applied Biosystem) coupled with Agilent 1100 LC system. Sample was prepared by adding 15uL of internal standard (5 μg/mL of (24-13C)-Cholic Acid in methanol) to 120uL ethyl acetate fraction of each sample.100 ul sample was injected by flow injection analysis (FIA), and monitored under negative APCI mode. The method was based on multiple reaction monitoring (MRM) scan mode of one parent/daughter transition for each metabolite and one internal standard. Each transition was

scanned for 70 ms for a total cycle time of 2.475 sec. The isocratic 10% EtOAc in MeOH elution was performed with a flow rate at 360 μl/min for 1min. The source parameters were set as follows: CUR: 10.0, CAD: 8, NC: -4.0, TEM: 400, GS1:30, GS2: 50, interface heater on. The compound parameters were set as follows: DP: -120.0, EP:-10, NC: -4.0, CE: -40, CXP: -15. Figure 33 illustrates a representative standard curve for this method for EtnPls 16:0/22:6 generated by diluting a normal serum sample while maintaining a constant concentration of internal standard (24-13C)-Cholic Acid).

Example 6: Effect of Aging and Severity of Dementia on Serum Levels of Ethanolamine Phospholipids

[0179] The effect of aging and severity of dementia on serum levels of ethanolamine phospholipids in 752 subjects aged 40-95 with various levels of dementia was investigated. The clinical data on the subject cohorts is shown in Table 19.

[0180] The effect of age was evaluated using a set of aged 30 to 95 subjects of untested cognitive status who did not suffer from dementia. Subjects were divided into one of five subgroups based upon their decade of life (30's, 40's, 50's, 60's, and ≥70). The 40-49 cohort was used as the pre-dementia reference group due to the low incidence of dementia at this age. The metabolites of interest (see Table 18) were measured using the high throughput method described in Example 5.

[0181] The effect of dementia severity was determined in subjects aged 56 to 95, comprised of 68 cognitively confirmed non-demented subjects (MMSE ≥ 28); 256 subjects currently diagnosed with SDAT (ADAS-cog 6-70, MMSE 0-26); 20 post-mortem confirmed SDAT and 20 post-mortem confirmed controls. Subjects were grouped into one of four dementia subgroups based upon either their MMSE score [≥ 28 = Cognitively Normal] or their ADAS-cog score [5-19 = low cognitive impairment); 20-39 = moderate; 40-70 = severe].

6A. Absolute levels of Ethanolamine Phospholipids

[0182] A significant gender bias was observed in that only females exhibited an age-related decrease in EtnPls. Free docosohexanoic acid (DHA, Free 22:6, M25) in both males and females was significantly increased in the 50-59, 60-69, and 70+ cohorts relative to the 40-49 cohorts. However, only males exhibited a concomitant increase in both 16:0/22:6-EtnPl (M19) and 18:0/22:6-EtnPl (M24) (see Tables 20-21 for males; Tables 22-23 for females). These data indicate that, in females, there may be an age-related dysfunction in the packaging of DHA into EtnPls. This gender difference may explain the increased incidence of dementia in very old females (19).

[0183] In both males and females, the majority of EtnPls in all dementia subgroups were significantly reduced relative to cognitive controls. In both males and females, free DHA (M25) was significantly decreased only in severely demented subjects. In females, a dementia effect was observed for three EtnPls (16:0/18:2 (M16), 18:0/18:2 (M21), and 16:0/20:4 (M17)) in that both 18:2-containing EtnPls were significantly lower in severely demented subjects versus either low or moderately demented females, and 16:0/20:4 (M17) was lower in the severe group versus the low group (see Tables 24-26). In males, a dementia effect was observed for DHA (M25) and 16:0/22:6 (M19) in that free DHA (M25) was reduced in the moderate group versus the low group and in the severe group versus the moderate group and 16:0/22:6 (M19) was reduced in the severe group versus the low group (see Tables 27-29). These results indicate that the progressive cognitive deterioration in AD manifests slightly differently in the two sexes.

[0184] Brain white matter contains primarily 18:1- and 18:2-containing EtnPls with low levels of 20:4-containing and 22:6-containing EtnPls, whereas gray matter contains significantly higher levels of 20:4-containing and 22:6-containing EtnPls [34]. In females, increasing dementia appears to affect both white (18:2) and gray (20:4) matter EtnPls equally, whereas in males predominantly gray (22:6) matter EtnPls appear to be affected to a greater extent.

[0185] Post-mortem collected serum samples from 20 pathologically confirmed AD subjects and 20 subjects containing minimal amyloid deposition were also analyzed. Both gray and white matter EtnPls were significantly decreased in post-mortem confirmed AD relative to age matched controls (see Tables 30 and 31).

6B. Relative levels of Ethanolamine Phospholipids

[0186] The data collected above was re-analyzed to obtain a ratio between the levels of each ethanolamine phospholipids with 16:0/18:0 PtdEt (M01). Measurement of the ethanolamine phospholipid levels in this manner is more stable and reproducible than measurement of the absolute levels. Furthermore, because the 16:0/18:0 PtdEt (M01) is naturally present in all samples and does not appear to vary significantly over disease states, this approach minimizes the sample-to-sample variability (due to handling, extraction, etc).

[0187] The results obtained further support the observations and conclusions made in 6A. The gender bias was with respect to an age-related decrease in EtnPls was evident in data where ratios to M01 were measured (see Tables 32-33 for males; Tables 34-35 for females). The same trends with respect to the severity of cognitive impairment were also observed (see Tables 36-38 for males; Tables 39-41 for females). In addition, pathology results on post-mortem serum samples show similar trends (Tables 42 and 43).

[0188] Both the absolute EtnPls levels and the EtnPls to M01 ratio exhibited a significant dementia effect. The EtnPls to M01 ratios of all eight EtnPls (16:0/18:1 (M15), 16:0/18:2 (M16), 16:0/20:4 (M17), 16:0/22:6 (M19), 18:0/18:1 (M20), 18:0/18:2 (M21), 18:0/20:4 (M22), 18:0/22:6 (M24)) were significantly lower in the severely demented group relative to the low group while six of the eight were significantly lower in the severe group relative to the moderate group

Example 7: The Grey and White Matter Score Distribution

[0189] A white and gray matter specific EtnPl scoring system was developed whereby each EtnPl in each subject was normalized to their respective gender-specific cognitively normal mean, log2 transformed and mean centered. Each subject's white matter score was taken as the lowest such value of plasmenyl 16:0/18:1 (M15), 16:0/18:2 (M16), 18:0/18:1 (M20), and 18:0/18:2 (M21) EtnPls, and their gray matter score as the lowest of plasmenyl 16:0/20:4 (M17), 16:0/22:6 (M19), 18:0/20:4 (M22), and 18:0/22:6 (M24) EtnPls.

[0190] These simplified scores revealed that both gray and white matter EtnPls were decreased at all stages of AD (Figure 39) and that the levels in post-mortem confirmed AD closely matched levels in severely demented subjects of both sexes (Tables 44-45). The cross-sectional white and gray matter score distributions in subjects of various levels of dementia clearly showed a dementia dependent shift in the population means (Tables 46-47). The effect of age on the white and gray matter scores was also determined (Tables 48-49). This also indicated that changes in serum levels of gray matter EtnPls may precede white matter changes and potentially be an early risk factor for AD. Such cross-sectional data does not account for baseline variability among subjects. Individual longitudinal trajectories of these scores may be more accurate at detecting early risk of AD in otherwise healthy, non-demented subjects.

[0191] Based on these scores, risk prediction can be performed on both male and female subjects (Tables 49-50) where a cut-off value that results in approximately 20-30% of cognitively normal subj ects being classified as either intermediate or high risk is used. Using this cut-off value, a subject's white and gray matter score is evaluated. If the subject tests normal on both scores, the subject is deemed to be at low risk. If the subject tests positive on one of the scores, the subjects is deemed to be at intermediate risk and if the subject tests positive on both scores, the subject is deemed to be at high risk.

Example 8. Effect of Dementia Severity and AD Pathology on Serum EtnPls Levels in combined male and female subjects

[0192] The effect of dementia severity was determined using 324 subjects (176 female, 148 male) aged 56 to 95, comprised of 68 cognitively confirmed non-demented subjects (MMSE $\geq$ 28) and 256 subjects currently diagnosed with AD (ADAS-cog 6-70, MMSE 0-26). The effect of AD pathology was determined using serum samples collected from 20 post-mortem confirmed AD and 19 control subjects (Table 19). Subjects were grouped into one of four dementia severity cohorts based upon either their MMSE score [$\geq$ 28 = Cognitively Normal] or their ADAS-cog score [5-19 = low cognitive impairment; 20-39 = moderate; 40-70 = severe].

[0193] Mean serum levels of 16:0/18:1 (M15), 16:0/18:2 (M16), 16:0/20:4 (M17), 16:0/22:6 (M19), 18:0/18:1 (M20), 18:0/18:2 (M21), 18:0/20:4(M22), 18:0/22:6 (M24) EtnPls; free docosahexaenoic acid (DHA, Free 22:6, M25); and phosphatidylethanolamine (PtdEt) 16:0/18:0 (D16:0/18:0; M01) were determined for each group (Figure 34). All eight EtnPls in all dementia subgroups were observed to be significantly reduced relative to cognitive controls (24 pair-wise comparisons, t-test p-values 2.6e-2 to 2.0e-10, median = 3.9e-5). Free DHA (M25) was significantly decreased in both moderately and severely demented subjects ($p<0.05$). All eight EtnPls were also significantly decreased in post-mortem confirmed SDAT relative to age matched controls. D16:0/18:0 (M01) levels, a non-plasmalogen phoshopholipid remained unchanged across the different dementia cohorts.

Example 9. Population Distributions as a Function of Dementia Severity

[0194] The EtnPls 16:0/22:6 (M19) to PtdEt 16:0/18:0 ratio (M01) (DHA-EtnPls) showed the strongest overall sex-independent dementia effect (Tables 38, 41) and was used for all subsequent population distributions and comparisons. A summary of the key comparisons using this ratio are listed in Table 52. This ratio was then log(2) transformed and used to create a population histogram for each cohort of increasing cognitive impairment (Figure 35). A cut-off value was selected based upon the findings of Bennett et al [35], (i.e. ~30% of the CN group being detected as AD) (Figure 35, dotted line). Using this cut-off, 63%, 79% and 83% of low, moderate and severely demented subjects, respectively, were subsequently classified as AD.

[0195] To compare these distributions with the known distributions of Aβ pathology in AD, the results of four prospective pathology studies [8, 35-37] were combined to generate the theoretical population distributions of Aβ pathology in demented and non-demented populations, assuming that Aβ is normally distributed in each population (Figure 36A). These studies reported that only 71% (140/198) of clinically diagnosed AD subjects have AD pathology at death and that 32% (87/268) of cognitively normal subjects meet neuropathological criteria for AD at death. When the data from

all of our cognitively tested subjects were combined, 32% (22/68) of our non-demented population and 75% (192/256) of our demented population were classified as AD positive based upon their serum EtnPls level (Figure 36B). This comparison revealed that the observed distribution of depleted 22:6-containing EtnPls perfectly matched the theoretical distribution of AD pathology in demented and non-demented subjects.

Example 10. Linear Extrapolation of Disease Progression and Serum EtnPls Depletion

[0196] To investigate whether a correlation between the decrease in EtnPls and increasing dementia in the clinically diagnosed AD population exists, a linear regression analysis was performed using the mean 22:6-containing EtnPls level (normalized to CN) of each of the dementia cohorts and the average ADAS-cog score for each of these three cohorts (Figure 37). A very high correlation was observed between the mean 22:6-containing EtnPls level and the mean ADAS-cog scores of the three dementia cohorts (r^2=0.99). However, this linear decrease did not extrapolate back to the CN group (X vs. CN). Assuming a clinical AD progression of 7.5 ADAS-cog units per year, this extrapolation predicts that that 22:6-containing EtnPls levels begin to decline approximately seven years before clinical cognitive impairment (ADAS-cog = 15) is evident.

Example 11. The Effect of Chronological Age on Serum DHA-EtnPls Levels

[0197] To investigate whether the above prediction could be verified experimentally, the serum 22:6-containing EtnPls levels in 209 subjects (110 male, 99 female, Table 19) of unknown cognitive status but currently not diagnosed with dementia was determined and compared to the clinical AD and CN cohorts (Figure 38). The results of this analysis revealed a significant drop in serum 22:6-containing EtnPls in the aged 60-69 cohort versus the aged 50-59 cohort (Figure 38A). This cohort also had significantly lower levels versus the CN group even though the CN group was, on average, 13 years older. Interestingly, the aged 70-95 cohort was not significantly different from either the aged 50-59 cohort or the CN cohort, but had significantly higher levels than the SDAT cohort.

Example 12. Sub-Populations Identified by Serum DHA-EtnPls Levels

[0198] The distribution of serum DHA-EtnPls within each age group, as shown in Figure 38B, was also examined. The population distributions of the five groups (three age groups, CN and AD) differentiated by age and dementia status reveal the presence of three distinct populations (P1-P3, Figure 38B). The populations were assigned as: P1 - subjects with AD pathology and no remaining reserve capacity; P3 - subjects with little or no AD pathology; P2 - subjects that are transitioning from P3 to P1. These P2 subjects are hypothesized to have AD pathology and some level of reserve remaining.

[0199] Since AD subjects have a life expectancy of less than 10 years from diagnosis [38, 39] and low 22:6-containing EtnPls are highly associated with AD severity, the decreased number of P1 subjects observed in the aged 70-95 cohort is most likely due to differences in life expectancy between P1 and P2 or P3. The transitory nature of P2 is best illustrated by examining the different ratios between the percentages of subj ects present in P3 compared to P2, as observed in the lower three panels of Figure 7B. These three cohorts differ only in dementia status. The P3 to P2 ratio changes from 3:1 (68% versus 22%) in the confirmed cognitive normal group to an intermediate ratio of 1:1 (43% versus 46%) in the normal healthy elderly group of unknown cognitive status, to 0.6:1 (25% versus 40%) in the confirmed demented AD cohort.

[0200] All citations are hereby incorporated by reference.

[0201] The present invention has been described with regard to one or more embodiments. However, it will be apparent to persons skilled in the art that a number of variations and modifications can be made without departing from the scope of the invention as defined in the claims.

Table 1: Accurate mass features differing between clinically diagnosed AD patients and non-demented controls ($p<0.05$, log2 transformed).

Detected Mass	Analysis Mode	AVG (log2) AD	SEM AD	AVG (log2) Normal	SEM Normal	Ratio	p-value
723.5197	1204	3.576	0.039	4.350	0.056	0.822	5.09E-19
723.5195	1202	2.186	0.040	2.892	0.052	0.756	4.86E-17
724.5257	1204	2.866	0.032	3.463	0.055	0.828	4.15E-16
749.5367	1202	3.176	0.034	3.714	0.041	0.855	3.82E-15
751.5555	1204	4.575	0.041	5.248	0.060	0.872	1.07E-14
751.5529	1202	3.335	0.036	3.920	0.050	0.851	1.14E-14
752.5564	1202	2.251	0.038	2.836	0.050	0.794	3.13E-14
752.5583	1204	3.472	0.042	4.094	0.061	0.848	6.47E-13
699.5198	1204	2.216	0.038	2.775	0.054	0.799	6.76E-13
750.544	1204	3.279	0.038	3.858	0.063	0.850	1.07E-12
749.5407	1204	4.426	0.039	5.012	0.064	0.883	1.33E-12
541.3432	1102	3.315	0.033	3.798	0.048	0.873	1.42E-12
750.5402	1202	2.192	0.038	2.704	0.044	0.811	2.76E-12
725.5385	1204	2.884	0.043	3.417	0.054	0.844	1.28E-10
569.3687	1102	2.262	0.039	2.724	0.048	0.830	6.22E-10
727.5568	1204	3.518	0.038	3.986	0.060	0.882	1.70E-09
804.5713	1102	4.207	0.042	4.610	0.033	0.913	3.88E-08
803.568	1102	5.432	0.043	5.838	0.035	0.930	7.10E-08
726.5461	1204	2.808	0.032	3.150	0.050	0.892	7.50E-08
827.57	1102	4.151	0.048	4.630	0.062	0.897	9.42E-08
803.5445	1101	5.123	0.055	5.655	0.059	0.906	1.01E-07
555.3102	1102	1.818	0.045	2.240	0.046	0.812	1.27E-07
565.3394	1102	3.480	0.050	3.958	0.055	0.879	1.28E-07
804.5476	1101	4.169	0.056	4.703	0.060	0.887	1.33E-07
828.5737	1102	3.138	0.046	3.590	0.061	0.874	1.89E-07
567.3547	1102	2.822	0.041	3.218	0.054	0.877	2.89E-07
728.5627	1204	2.935	0.033	3.281	0.060	0.895	5.16E-07
817.5377	1102	2.282	0.048	2.712	0.057	0.842	8.85E-07
779.5444	1101	6.433	0.053	6.874	0.043	0.936	1.06E-06
780.5474	1101	5.437	0.053	5.875	0.043	0.925	1.28E-06
812.5762	1202	1.659	0.050	2.084	0.058	0.796	2.24E-06
832.6026	1102	3.455	0.041	3.795	0.040	0.910	2.48E-06
811.5732	1202	2.705	0.036	3.027	0.055	0.893	3.40E-06
871.5528	1102	3.068	0.042	3.408	0.040	0.900	3.47E-06
831.5997	1102	4.564	0.042	4.903	0.040	0.931	3.48E-06
793.5386	1102	3.604	0.043	3.950	0.039	0.912	3.50E-06
782.5085	1204	3.401	0.045	3.780	0.055	0.900	3.81E-06
805.5832	1102	4.075	0.047	4.485	0.068	0.909	3.87E-06
781.5617	1101	6.109	0.061	6.610	0.072	0.924	5.14E-06
813.5885	1202	3.012	0.030	3.276	0.048	0.919	6.23E-06
794.5421	1102	2.523	0.042	2.853	0.040	0.885	6.30E-06
814.5917	1202	2.041	0.026	2.289	0.051	0.892	7.46E-06
747.5245	1204	3.473	0.043	3.886	0.090	0.894	9.55E-06
837.5027	1101	3.578	0.045	3.933	0.050	0.910	1.02E-05
782.565	1101	5.083	0.063	5.589	0.078	0.909	1.09E-05
746.5717	1204	3.085	0.031	3.362	0.061	0.918	1.82E-05
829.5856	1102	4.043	0.048	4.398	0.046	0.919	1.85E-05
784.5237	1204	3.310	0.040	3.603	0.037	0.919	1.91E-05
786.5416	1204	3.815	0.035	4.087	0.043	0.933	1.91E-05
760.5216	1204	4.075	0.036	4.347	0.039	0.938	2.11E-05
745.5658	1204	3.937	0.034	4.242	0.068	0.928	2.12E-05
744.5536	1204	4.322	0.034	4.605	0.058	0.939	2.46E-05
783.5672	1101	3.755	0.068	4.259	0.079	0.882	3.48E-05
807.5758	1101	5.736	0.052	6.102	0.047	0.940	3.69E-05
808.5792	1101	4.697	0.052	5.063	0.047	0.928	4.20E-05
743.5471	1204	5.286	0.036	5.579	0.063	0.947	4.94E-05
482.3215	1202	1.971	0.038	2.251	0.062	0.875	0.0001
755.486	1204	3.221	0.047	3.561	0.057	0.905	0.0001

758.5092	1204	4.574	0.033	4.808	0.042	0.951	0.0001
775.5533	1202	2.120	0.044	2.449	0.068	0.866	0.0001
787.5729	1202	1.847	0.040	2.145	0.057	0.861	0.0001
795.5181	1101	2.630	0.059	3.044	0.064	0.864	0.0001
795.555	1102	2.665	0.043	2.986	0.065	0.892	0.0001
805.5605	1101	5.414	0.057	5.785	0.048	0.936	0.0001
831.5759	1101	4.297	0.056	4.677	0.060	0.919	0.0001
855.6016	1102	3.538	0.045	3.873	0.065	0.914	0.0001
517.314	1101	5.470	0.038	5.755	0.069	0.951	0.0002
541.3139	1101	4.091	0.053	4.494	0.096	0.910	0.0002
542.3173	1101	2.284	0.055	2.687	0.089	0.850	0.0002
747.5201	1202	1.937	0.051	2.313	0.088	0.838	0.0002
757.4991	1101	3.644	0.065	4.073	0.070	0.895	0.0002
775.5528	1204	3.197	0.045	3.537	0.085	0.904	0.0002
806.5639	1101	4.423	0.057	4.779	0.049	0.926	0.0002
832.5791	1101	3.357	0.055	3.723	0.061	0.902	0.0002
915.5191	1101	2.376	0.051	2.717	0.063	0.874	0.0002
755.5468	1101	2.326	0.064	2.753	0.085	0.845	0.0003
777.553	1202	1.859	0.072	2.384	0.130	0.780	0.0003
829.5604	1101	3.535	0.053	3.875	0.058	0.912	0.0003
518.3174	1101	3.438	0.038	3.717	0.073	0.925	0.0004
731.5464	1101	1.945	0.096	2.600	0.157	0.748	0.0004
757.5626	1101	6.655	0.074	7.108	0.079	0.936	0.0004
758.5656	1101	5.702	0.075	6.160	0.078	0.926	0.0004
759.5779	1101	5.547	0.069	5.997	0.099	0.925	0.0004
760.5811	1101	4.419	0.071	4.886	0.103	0.904	0.0004
768.5539	1204	3.964	0.046	4.279	0.077	0.927	0.0004
748.5287	1204	2.277	0.091	2.820	0.088	0.807	0.0005
783.5148	1204	3.284	0.047	3.574	0.056	0.919	0.0005
821.5712	1102	3.064	0.040	3.304	0.044	0.927	0.0005
523.4679	1203	3.252	0.121	4.011	0.165	0.811	0.0006
781.562	1201	7.364	0.040	7.638	0.071	0.964	0.0006
810.5399	1204	2.835	0.050	3.145	0.066	0.901	0.0006
732.4938	1204	4.249	0.042	4.511	0.057	0.942	0.0007
522.4635	1203	4.713	0.126	5.485	0.176	0.859	0.0008
810.5969	1101	3.957	0.072	4.370	0.080	0.905	0.0009
853.5854	1102	2.626	0.043	2.880	0.052	0.912	0.0009
819.5551	1102	2.394	0.046	2.654	0.046	0.902	0.001
828.5743	1202	5.243	0.058	5.598	0.085	0.936	0.001
478.254	1201	1.584	0.083	1.051	0.148	1.507	0.0011
579.5325	1203	4.102	0.089	4.636	0.127	0.885	0.0011
744.4956	1204	3.881	0.039	4.117	0.058	0.943	0.0011
761.5843	1101	2.422	0.065	2.829	0.106	0.856	0.0011
809.5936	1101	4.964	0.070	5.362	0.079	0.926	0.0011
886.5582	1102	3.041	0.037	3.250	0.041	0.936	0.0011
481.3172	1202	3.923	0.039	4.159	0.060	0.943	0.0012
767.5495	1204	5.063	0.049	5.369	0.082	0.943	0.0012
782.5653	1201	6.339	0.043	6.614	0.076	0.959	0.0012
827.5701	1202	6.306	0.063	6.684	0.092	0.943	0.0012
847.5316	1101	2.742	0.059	3.091	0.083	0.887	0.0012
789.5892	1202	1.723	0.036	1.952	0.065	0.883	0.0013
543.3296	1101	3.733	0.044	4.023	0.087	0.928	0.0014
575.2728	1101	2.470	0.043	2.739	0.074	0.902	0.0014
580.5351	1203	1.456	0.127	2.192	0.174	0.664	0.0014
521.4522	1203	2.302	0.131	3.028	0.158	0.760	0.0016
731.4916	1204	5.482	0.046	5.746	0.063	0.954	0.0016
759.5163	1204	4.724	0.042	4.954	0.048	0.954	0.0016
306.2569	1204	2.998	0.046	3.266	0.067	0.918	0.0017
771.5814	1204	4.164	0.036	4.367	0.046	0.954	0.0017
786.5967	1101	4.808	0.074	5.203	0.078	0.924	0.0019
458.2405	1101	1.736	0.040	1.986	0.077	0.874	0.0021
520.4499	1203	3.956	0.112	4.577	0.148	0.864	0.0021
748.5735	1202	3.918	0.035	3.722	0.050	1.053	0.0021
490.3641	1203	1.944	0.092	1.397	0.159	1.391	0.0023
545.3453	1101	3.606	0.051	3.898	0.078	0.925	0.0023

605.5457	1203	5.135	0.068	5.509	0.089	0.932	0.0023
769.5656	1204	3.963	0.038	4.174	0.054	0.950	0.0023
570.3725	1202	2.976	0.032	3.155	0.045	0.943	0.0024
785.5933	1101	5.884	0.074	6.271	0.080	0.938	0.0024
582.2473	1201	3.325	0.096	2.793	0.141	1.191	0.0026
569.369	1202	4.908	0.033	5.089	0.047	0.964	0.0027
784.5811	1101	4.405	0.079	4.817	0.089	0.915	0.0027
811.6096	1101	3.078	0.083	3.511	0.096	0.877	0.0027
590.343	1202	4.025	0.050	4.304	0.076	0.935	0.0028
856.672	1202	2.764	0.038	2.553	0.057	1.082	0.0028
833.5932	1101	3.276	0.068	3.608	0.056	0.908	0.003
506.2851	1201	3.142	0.077	2.656	0.165	1.183	0.0031
793.5681	1204	3.155	0.040	3.372	0.055	0.936	0.0031
546.3485	1101	1.999	0.050	2.287	0.089	0.874	0.0036
591.3542	1202	4.045	0.061	4.345	0.058	0.931	0.0037
741.5305	1204	2.931	0.056	3.250	0.102	0.902	0.0042
796.5876	1204	2.634	0.043	2.860	0.062	0.921	0.0042
804.7227	1203	1.842	0.145	2.611	0.220	0.705	0.0044
807.59	1202	2.463	0.045	2.718	0.082	0.906	0.0045
506.3213	1202	2.538	0.040	2.748	0.061	0.923	0.0046
552.5022	1203	3.164	0.088	3.643	0.147	0.869	0.0047
589.3403	1202	5.876	0.056	6.171	0.085	0.952	0.0048
806.5873	1202	4.366	0.047	4.635	0.092	0.942	0.0048
550.4957	1203	6.898	0.096	7.415	0.160	0.930	0.0049
604.5433	1203	6.554	0.069	6.901	0.089	0.950	0.005
805.5839	1202	5.562	0.048	5.841	0.097	0.952	0.0052
551.4986	1203	5.480	0.095	5.988	0.158	0.915	0.0053
743.5469	1202	3.061	0.055	3.348	0.086	0.914	0.0056
541.3435	1202	5.669	0.059	5.974	0.094	0.949	0.0058
183.0661	1101	2.590	0.091	3.015	0.094	0.859	0.006
858.6212	1202	2.707	0.059	2.994	0.074	0.904	0.0061
614.4914	1203	2.779	0.060	2.448	0.114	1.135	0.0062
787.5465	1204	2.675	0.077	3.017	0.054	0.887	0.0062
772.5862	1204	3.287	0.031	3.437	0.042	0.956	0.007
837.5881	1202	2.429	0.027	2.577	0.053	0.942	0.007
509.3493	1202	2.403	0.035	2.579	0.055	0.931	0.0071
529.3167	1202	3.032	0.048	3.265	0.069	0.928	0.0075
564.5134	1203	2.706	0.075	3.075	0.111	0.880	0.0075
566.3434	1202	5.203	0.049	5.436	0.062	0.957	0.0075
833.7571	1203	2.962	0.109	3.507	0.170	0.845	0.0077
631.628	1203	1.795	0.127	2.391	0.161	0.751	0.008
857.6186	1202	3.773	0.058	4.049	0.076	0.932	0.008
858.6861	1202	2.943	0.040	2.756	0.052	1.068	0.0081
519.3321	1101	3.964	0.084	4.382	0.133	0.905	0.0083
685.26	1202	1.771	0.048	1.998	0.063	0.886	0.0083
757.5014	1204	3.755	0.048	3.971	0.052	0.946	0.0085
744.55	1202	1.968	0.051	2.222	0.083	0.886	0.0086
671.5723	1204	2.231	0.084	2.604	0.087	0.857	0.0087
304.241	1204	4.887	0.041	5.088	0.066	0.961	0.0092
536.4794	1203	2.320	0.101	2.799	0.143	0.829	0.0093
542.3461	1202	3.873	0.049	4.106	0.074	0.943	0.0095
675.6377	1204	3.953	0.043	4.160	0.066	0.950	0.0098
520.3354	1101	2.240	0.085	2.646	0.130	0.846	0.01
832.7523	1203	3.859	0.107	4.374	0.169	0.882	0.0103
409.0208	1202	2.806	0.035	2.980	0.063	0.942	0.0106
768.5503	1202	1.942	0.076	2.277	0.090	0.853	0.0111
303.1079	1202	5.648	0.034	5.802	0.047	0.973	0.0113
592.3571	1202	2.291	0.063	2.560	0.062	0.895	0.0115
837.718	1204	2.888	0.176	3.662	0.217	0.788	0.0121
832.7492	1204	3.286	0.119	3.848	0.190	0.854	0.0125
832.6037	1202	5.066	0.047	5.274	0.062	0.961	0.013
411.3212	1202	2.868	0.038	3.033	0.048	0.946	0.0134
838.7226	1204	2.313	0.148	2.973	0.206	0.778	0.0136
670.569	1204	3.239	0.061	3.515	0.093	0.921	0.0141
795.5838	1204	3.566	0.046	3.769	0.063	0.946	0.0141

767.547	1202	3.073	0.064	3.358	0.092	0.915	0.0143
305.2438	1204	2.519	0.044	2.719	0.067	0.926	0.0146
505.3229	1202	3.994	0.051	4.222	0.076	0.946	0.0156
803.5677	1202	7.196	0.070	7.502	0.098	0.959	0.0157
711.2577	1202	2.250	0.049	2.454	0.056	0.917	0.0159
827.5448	1101	3.549	0.077	3.873	0.095	0.916	0.016
548.4815	1203	7.094	0.072	7.405	0.103	0.958	0.0174
568.3573	1202	4.008	0.035	4.167	0.060	0.962	0.0175
578.5277	1203	4.301	0.303	5.548	0.355	0.775	0.0175
601.5164	1203	7.640	0.038	7.463	0.069	1.024	0.0185
549.4845	1203	5.666	0.077	5.994	0.110	0.945	0.0187
743.5466	1203	1.987	0.064	2.266	0.099	0.877	0.0189
772.5278	1204	3.324	0.039	3.488	0.055	0.953	0.019
765.5334	1204	3.269	0.060	3.540	0.104	0.923	0.0193
440.3532	1204	1.417	0.096	0.975	0.180	1.453	0.0205
495.332	1101	5.251	0.073	5.565	0.112	0.944	0.0205
804.5718	1202	5.877	0.057	6.117	0.080	0.961	0.0206
340.2976	1203	1.597	0.082	1.937	0.112	0.825	0.0208
856.6061	1202	4.565	0.056	4.805	0.086	0.950	0.0212
584.2646	1204	3.136	0.115	2.649	0.172	1.184	0.0218
733.6426	1204	2.978	0.049	2.718	0.126	1.096	0.0219
588.4731	1203	2.387	0.064	2.031	0.179	1.175	0.0223
765.5313	1202	1.802	0.073	2.098	0.095	0.859	0.0226
523.3634	1101	3.466	0.082	3.791	0.103	0.914	0.0235
830.5894	1202	4.847	0.051	5.051	0.064	0.960	0.0236
887.7352	1204	6.295	0.082	5.963	0.113	1.056	0.0244
598.5124	1204	2.094	0.134	1.513	0.233	1.385	0.0249
616.5052	1203	4.205	0.062	3.957	0.084	1.062	0.025
916.7743	1204	5.894	0.081	5.571	0.107	1.058	0.025
430.3818	1204	4.938	0.075	5.253	0.122	0.940	0.0262
855.6023	1202	5.552	0.056	5.784	0.087	0.960	0.0266
684.5489	1204	2.523	0.055	2.745	0.080	0.919	0.0269
831.6001	1202	6.192	0.053	6.404	0.074	0.967	0.0269
826.7069	1204	2.482	0.089	2.819	0.099	0.880	0.0275
915.7681	1204	6.304	0.085	5.972	0.116	1.056	0.0293
615.3539	1202	2.463	0.043	2.629	0.058	0.937	0.0296
431.386	1204	3.491	0.075	3.795	0.118	0.920	0.0298
942.7879	1204	3.487	0.078	3.195	0.092	1.091	0.0302
665.501	1204	3.388	0.071	3.074	0.142	1.102	0.0305
861.7806	1203	2.531	0.099	2.902	0.119	0.872	0.0306
618.4829	1201	1.791	0.120	1.310	0.185	1.367	0.0309
830.7352	1204	4.252	0.096	4.638	0.150	0.917	0.031
801.555	1202	2.660	0.056	2.881	0.082	0.923	0.0311
739.5143	1204	2.754	0.087	3.121	0.158	0.883	0.0317
492.3816	1203	3.513	0.055	3.302	0.077	1.064	0.0339
741.5319	1202	1.106	0.080	1.424	0.125	0.777	0.0339
914.7583	1204	5.082	0.083	4.763	0.118	1.067	0.0339
507.3316	1202	2.940	0.035	3.094	0.071	0.950	0.034
504.3814	1203	1.701	0.070	1.413	0.124	1.204	0.0341
496.3355	1101	3.442	0.074	3.736	0.119	0.921	0.0347
521.3477	1101	3.717	0.075	4.021	0.127	0.925	0.0351
829.5859	1202	5.976	0.056	6.181	0.070	0.967	0.0353
686.4877	1204	2.700	0.051	2.881	0.052	0.937	0.0358
888.7394	1204	5.702	0.080	5.400	0.110	1.056	0.0358
825.6926	1203	1.840	0.110	2.235	0.124	0.823	0.0369
746.557	1202	2.166	0.030	2.057	0.037	1.053	0.0378
757.5625	1201	7.728	0.046	7.909	0.077	0.977	0.0391
615.4798	1204	2.647	0.049	2.827	0.067	0.936	0.0396
831.7408	1203	4.104	0.085	4.425	0.130	0.928	0.0405
761.5846	1201	3.155	0.051	3.357	0.091	0.940	0.0414
581.3344	1202	1.927	0.076	2.207	0.110	0.873	0.0423
1098.9739	1204	2.955	0.090	2.606	0.152	1.134	0.0427
380.3096	1204	1.650	0.070	1.899	0.090	0.869	0.0434
565.3394	1202	7.001	0.052	7.186	0.068	0.974	0.0439
478.3664	1203	1.493	0.068	1.212	0.143	1.232	0.0475

835.7006	1204	2.799	0.115	3.214	0.167	0.871	0.0485
320.2356	1204	1.447	0.070	1.686	0.085	0.858	0.0486
493.385	1203	1.979	0.066	1.722	0.124	1.149	0.049
512.4082	1204	2.415	0.121	1.954	0.215	1.236	0.0493
610.3686	1201	5.156	0.083	4.771	0.223	1.081	0.0495
760.5811	1201	5.225	0.052	5.422	0.091	0.964	0.0495
600.5127	1203	8.858	0.044	8.692	0.074	1.019	0.0496
715.5167	1204	2.592	0.082	2.902	0.141	0.893	0.0498
759.5779	1201	6.347	0.051	6.541	0.090	0.970	0.0499

Table 2: Accurate mass features differing between clinically diagnosed AD patients with a significant cognitive impairment and non-demented controls ($p<0.05$, log2 transformed).

Detected m/z	Charge state	FC (log2) AD / Ctrl	SEM	AD mean (log2)	SEM	FC (2)	p-Value
541.3432	1102	3.138	0.034	3.798	0.048	1.210	3.45E-17
569.3687	1102	2.063	0.042	2.724	0.048	1.320	1.67E-15
723.5197	1204	3.581	0.053	4.350	0.056	1.215	1.04E-14
803.568	1102	5.238	0.048	5.838	0.035	1.115	2.00E-14
804.5713	1102	4.017	0.048	4.610	0.033	1.148	2.02E-14
723.5195	1202	2.193	0.056	2.892	0.052	1.319	4.37E-13
749.5367	1202	3.187	0.044	3.714	0.041	1.165	2.12E-12
555.3102	1102	1.634	0.053	2.240	0.046	1.371	3.10E-12
565.3394	1102	3.265	0.058	3.958	0.055	1.212	3.23E-12
724.5257	1204	2.850	0.048	3.463	0.055	1.215	4.54E-12
699.5198	1204	2.129	0.055	2.775	0.054	1.303	9.18E-12
871.5528	1102	2.885	0.049	3.408	0.040	1.181	2.08E-11
567.3547	1102	2.629	0.050	3.218	0.054	1.224	2.92E-11
751.5555	1204	4.591	0.056	5.248	0.060	1.143	3.18E-11
780.5474	1101	5.241	0.064	5.875	0.043	1.121	3.70E-11
752.5564	1202	2.281	0.049	2.836	0.050	1.244	4.78E-11
779.5444	1101	6.239	0.065	6.874	0.043	1.102	5.01E-11
829.5856	1102	3.806	0.059	4.398	0.046	1.156	9.29E-11
794.5421	1102	2.364	0.048	2.853	0.040	1.206	1.01E-10
793.5386	1102	3.435	0.052	3.950	0.039	1.150	1.05E-10
831.5997	1102	4.372	0.055	4.903	0.040	1.121	1.61E-10
832.6026	1102	3.268	0.055	3.795	0.040	1.161	1.67E-10
751.5529	1202	3.369	0.052	3.920	0.050	1.163	1.89E-10
749.5407	1204	4.423	0.047	5.012	0.064	1.133	1.93E-10
827.57	1102	3.984	0.059	4.630	0.062	1.162	1.95E-10
725.5385	1204	2.815	0.058	3.417	0.054	1.214	2.58E-10
804.5476	1101	3.987	0.073	4.703	0.060	1.180	2.67E-10
837.5027	1101	3.402	0.050	3.933	0.050	1.156	2.76E-10
803.5445	1101	4.941	0.074	5.655	0.059	1.144	3.46E-10
752.5583	1204	3.484	0.056	4.094	0.061	1.175	3.59E-10
828.5737	1102	2.982	0.056	3.590	0.061	1.204	3.85E-10
750.544	1204	3.258	0.054	3.858	0.063	1.184	6.22E-10
750.5402	1202	2.210	0.052	2.704	0.044	1.224	1.19E-09
805.5832	1102	3.874	0.056	4.485	0.068	1.158	1.95E-09
727.5568	1204	3.445	0.055	3.986	0.060	1.157	7.95E-09
807.5758	1101	5.531	0.069	6.102	0.047	1.103	8.66E-09
805.5605	1101	5.184	0.074	5.785	0.048	1.116	9.26E-09
808.5792	1101	4.488	0.071	5.063	0.047	1.128	1.11E-08
806.5639	1101	4.199	0.075	4.779	0.049	1.138	3.65E-08
915.5191	1101	2.189	0.058	2.717	0.063	1.241	5.21E-08
817.5377	1102	2.175	0.064	2.712	0.057	1.247	5.29E-08
781.5617	1101	5.928	0.084	6.610	0.072	1.115	8.47E-08
819.5551	1102	2.198	0.058	2.654	0.046	1.208	9.28E-08

726.5461	1204	2.759	0.044	3.150	0.050	1.141	1.31E-07
783.5672	1101	3.535	0.092	4.259	0.079	1.205	1.69E-07
886.5582	1102	2.911	0.041	3.250	0.041	1.117	2.03E-07
782.565	1101	4.901	0.088	5.589	0.078	1.140	2.35E-07
784.5237	1204	3.211	0.056	3.603	0.037	1.122	4.12E-07
853.5854	1102	2.449	0.056	2.880	0.052	1.176	4.56E-07
795.555	1102	2.520	0.054	2.986	0.065	1.185	5.49E-07
855.6016	1102	3.386	0.060	3.873	0.065	1.144	6.32E-07
821.5712	1102	2.919	0.053	3.304	0.044	1.132	6.68E-07
795.5181	1101	2.458	0.082	3.044	0.064	1.238	7.57E-07
832.5791	1101	3.184	0.076	3.723	0.061	1.169	9.68E-07
786.5416	1204	3.729	0.049	4.087	0.043	1.096	1.02E-06
831.5759	1101	4.123	0.080	4.677	0.060	1.134	1.03E-06
728.5627	1204	2.875	0.047	3.281	0.060	1.141	1.07E-06
757.4991	1101	3.450	0.089	4.073	0.070	1.181	1.08E-06
760.5216	1204	4.008	0.048	4.347	0.039	1.084	1.13E-06
829.5604	1101	3.360	0.075	3.875	0.058	1.153	1.41E-06
847.5316	1101	2.564	0.060	3.091	0.083	1.205	1.84E-06
755.5468	1101	2.115	0.086	2.753	0.085	1.302	1.88E-06
782.5085	1204	3.369	0.056	3.780	0.055	1.122	2.13E-06
755.486	1204	3.146	0.061	3.561	0.057	1.132	5.93E-06
833.5932	1101	3.045	0.095	3.608	0.056	1.185	7.05E-06
758.5656	1101	5.511	0.107	6.160	0.078	1.118	1.11E-05
758.5092	1204	4.504	0.047	4.808	0.042	1.068	1.24E-05
757.5626	1101	6.470	0.106	7.108	0.079	1.099	1.48E-05
760.5811	1101	4.216	0.099	4.886	0.103	1.159	1.48E-05
744.5536	1204	4.260	0.047	4.605	0.058	1.081	1.55E-05
759.5779	1101	5.352	0.096	5.997	0.099	1.121	1.60E-05
811.6096	1101	2.801	0.116	3.511	0.096	1.253	1.84E-05
731.5464	1101	1.634	0.139	2.600	0.157	1.591	1.89E-05
812.5762	1202	1.752	0.045	2.084	0.058	1.190	1.95E-05
743.5471	1204	5.227	0.047	5.579	0.063	1.067	2.40E-05
784.5811	1101	4.161	0.112	4.817	0.089	1.158	3.03E-05
632.5762	1203	0.925	0.149	1.830	0.132	1.979	3.07E-05
761.5843	1101	2.241	0.084	2.829	0.106	1.262	4.28E-05
517.314	1101	5.399	0.050	5.755	0.069	1.066	0.0001
518.3174	1101	3.358	0.051	3.717	0.073	1.107	0.0001
591.3542	1202	3.870	0.092	4.345	0.058	1.123	0.0001
732.4938	1204	4.186	0.056	4.511	0.057	1.078	0.0001
745.5658	1204	3.881	0.052	4.242	0.068	1.093	0.0001
746.5717	1204	3.047	0.043	3.362	0.061	1.103	0.0001
747.5245	1204	3.433	0.058	3.886	0.090	1.132	0.0001
777.553	1202	1.720	0.100	2.384	0.130	1.386	0.0001
783.5148	1204	3.217	0.063	3.574	0.056	1.111	0.0001
785.5933	1101	5.687	0.112	6.271	0.080	1.103	0.0001
786.5967	1101	4.611	0.112	5.203	0.078	1.128	0.0001
809.5936	1101	4.786	0.104	5.362	0.079	1.120	0.0001
810.5969	1101	3.779	0.108	4.370	0.080	1.157	0.0001
811.5732	1202	2.729	0.047	3.027	0.055	1.109	0.0001
858.6212	1202	2.533	0.080	2.994	0.074	1.182	0.0001
306.2569	1204	2.878	0.070	3.266	0.067	1.135	0.0002
482.3215	1202	1.940	0.050	2.251	0.062	1.160	0.0002
522.4635	1203	4.489	0.181	5.485	0.176	1.222	0.0002
523.4679	1203	3.035	0.180	4.011	0.165	1.322	0.0002
579.5325	1203	3.962	0.112	4.636	0.127	1.170	0.0002
759.5163	1204	4.645	0.061	4.954	0.048	1.066	0.0002
787.5729	1202	1.834	0.054	2.145	0.057	1.170	0.0002
810.5399	1204	2.760	0.071	3.145	0.066	1.140	0.0002
814.5917	1202	2.054	0.035	2.289	0.051	1.114	0.0002
857.6186	1202	3.614	0.081	4.049	0.076	1.121	0.0002
458.2405	1101	1.632	0.054	1.986	0.077	1.217	0.0003
481.3172	1202	3.866	0.050	4.159	0.060	1.076	0.0003
541.3139	1101	4.022	0.081	4.494	0.096	1.117	0.0003
545.3453	1101	3.500	0.071	3.898	0.078	1.114	0.0003
592.3571	1202	2.113	0.095	2.560	0.062	1.212	0.0003

757.5014	1204	3.642	0.067	3.971	0.052	1.091	0.0003
833.7551	1204	2.061	0.223	3.140	0.161	1.524	0.0003
543.3296	1101	3.652	0.055	4.023	0.087	1.102	0.0004
605.5457	1203	5.025	0.091	5.509	0.089	1.096	0.0004
731.4916	1204	5.419	0.060	5.746	0.063	1.060	0.0004
775.5533	1202	2.106	0.063	2.449	0.068	1.163	0.0004
813.5885	1202	3.034	0.043	3.276	0.048	1.080	0.0004
542.3173	1101	2.234	0.087	2.687	0.089	1.203	0.0005
722.5335	1101	2.406	0.062	2.717	0.056	1.129	0.0005
744.55	1202	1.842	0.064	2.222	0.083	1.206	0.0005
769.5656	1204	3.889	0.055	4.174	0.054	1.073	0.0005
807.59	1202	2.348	0.061	2.718	0.082	1.158	0.0005
828.5743	1202	5.181	0.076	5.598	0.085	1.081	0.0005
521.4522	1203	2.124	0.191	3.028	0.158	1.425	0.0007
604.5433	1203	6.440	0.091	6.901	0.089	1.072	0.0007
744.4956	1204	3.851	0.049	4.117	0.058	1.069	0.0007
748.5287	1204	2.249	0.127	2.820	0.088	1.254	0.0007
771.5814	1204	4.118	0.051	4.367	0.046	1.061	0.0007
827.5701	1202	6.245	0.082	6.684	0.092	1.070	0.0007
747.5201	1202	1.886	0.083	2.313	0.088	1.226	0.0008
775.5528	1204	3.176	0.061	3.537	0.085	1.114	0.0008
787.5465	1204	2.543	0.116	3.017	0.054	1.187	0.0008
827.5448	1101	3.373	0.104	3.873	0.095	1.148	0.0008
546.3485	1101	1.890	0.073	2.287	0.089	1.210	0.0009
520.4499	1203	3.775	0.176	4.577	0.148	1.212	0.001
570.3725	1202	2.926	0.047	3.155	0.045	1.078	0.001
781.562	1201	7.334	0.054	7.638	0.071	1.041	0.001
632.5032	1203	1.435	0.112	0.795	0.154	0.554	0.0011
743.5469	1202	2.976	0.070	3.348	0.086	1.125	0.0012
768.5539	1204	3.928	0.069	4.279	0.077	1.089	0.0012
806.5873	1202	4.280	0.057	4.635	0.092	1.083	0.0012
575.2728	1101	2.419	0.061	2.739	0.074	1.132	0.0013
550.4957	1203	6.766	0.117	7.415	0.160	1.096	0.0014
805.5839	1202	5.470	0.060	5.841	0.097	1.068	0.0014
183.0661	1101	2.412	0.147	3.015	0.094	1.250	0.0015
551.4986	1203	5.350	0.117	5.988	0.158	1.119	0.0015
741.5305	1204	2.825	0.080	3.250	0.102	1.150	0.0015
541.3435	1202	5.595	0.072	5.974	0.094	1.068	0.0018
552.5022	1203	3.055	0.110	3.643	0.147	1.193	0.0018
506.3213	1202	2.487	0.054	2.748	0.061	1.105	0.0019
569.369	1202	4.867	0.049	5.089	0.047	1.046	0.0019
782.5653	1201	6.310	0.058	6.614	0.076	1.048	0.002
490.3641	1203	2.028	0.121	1.397	0.159	0.689	0.0021
542.3461	1202	3.803	0.061	4.106	0.074	1.080	0.0021
566.3434	1202	5.130	0.071	5.436	0.062	1.060	0.0022
833.7571	1203	2.853	0.122	3.507	0.170	1.229	0.0022
837.718	1204	2.593	0.250	3.662	0.217	1.412	0.0023
549.4845	1203	5.510	0.107	5.994	0.110	1.088	0.0025
793.5681	1204	3.116	0.058	3.372	0.055	1.082	0.0025
478.254	1201	1.629	0.116	1.051	0.148	0.645	0.0027
536.4794	1203	2.188	0.134	2.799	0.143	1.279	0.0027
548.4815	1203	6.949	0.103	7.405	0.103	1.066	0.0027
832.6037	1202	4.981	0.069	5.274	0.062	1.059	0.0028
830.5894	1202	4.738	0.076	5.051	0.064	1.066	0.0029
1098.9739	1204	3.097	0.070	2.606	0.152	0.842	0.0031
767.5495	1204	5.033	0.074	5.369	0.082	1.067	0.0034
675.6377	1204	3.875	0.066	4.160	0.066	1.074	0.0035
564.5134	1203	2.641	0.093	3.075	0.111	1.164	0.0036
789.5892	1202	1.703	0.053	1.952	0.065	1.147	0.0036
832.7523	1203	3.734	0.131	4.374	0.169	1.171	0.0036
748.5735	1202	3.940	0.052	3.722	0.050	0.945	0.0037
801.555	1202	2.543	0.077	2.881	0.082	1.133	0.0037
856.672	1202	2.777	0.048	2.553	0.057	0.919	0.0037
858.6861	1202	2.982	0.055	2.756	0.052	0.924	0.0043
803.5677	1202	7.101	0.095	7.502	0.098	1.057	0.0045

838.7226	1204	2.127	0.200	2.973	0.206	1.398	0.0046
685.26	1202	1.708	0.074	1.998	0.063	1.169	0.0047
826.7069	1204	2.279	0.148	2.819	0.099	1.237	0.0047
582.2473	1201	3.332	0.122	2.793	0.141	0.838	0.0049
590.343	1202	4.005	0.069	4.304	0.076	1.075	0.005
832.7492	1204	3.163	0.146	3.848	0.190	1.217	0.0051
829.5859	1202	5.864	0.082	6.181	0.070	1.054	0.0053
772.5862	1204	3.263	0.043	3.437	0.042	1.053	0.0054
409.0208	1202	2.753	0.050	2.980	0.063	1.082	0.0055
509.3493	1202	2.358	0.054	2.579	0.055	1.094	0.0056
589.3403	1202	5.847	0.076	6.171	0.085	1.056	0.0057
430.3818	1204	4.790	0.109	5.253	0.122	1.097	0.0061
804.5718	1202	5.801	0.078	6.117	0.080	1.054	0.0066
505.3229	1202	3.931	0.071	4.222	0.076	1.074	0.0068
523.3634	1101	3.365	0.111	3.791	0.103	1.127	0.0072
671.5723	1204	2.131	0.140	2.604	0.087	1.222	0.0073
830.7352	1204	4.091	0.130	4.638	0.150	1.134	0.0073
431.386	1204	3.354	0.108	3.795	0.118	1.132	0.0074
631.628	1203	1.746	0.166	2.391	0.161	1.369	0.0075
825.6926	1203	1.644	0.169	2.235	0.124	1.359	0.0079
614.4914	1203	2.821	0.080	2.448	0.114	0.868	0.008
831.6001	1202	6.109	0.077	6.404	0.074	1.048	0.0081
615.3539	1202	2.394	0.063	2.629	0.058	1.098	0.0083
568.3573	1202	3.959	0.049	4.167	0.060	1.053	0.0088
767.547	1202	2.992	0.097	3.358	0.092	1.122	0.0088
768.5503	1202	1.849	0.125	2.277	0.090	1.231	0.0089
831.7408	1203	3.971	0.109	4.425	0.130	1.114	0.0089
411.3212	1202	2.838	0.054	3.033	0.048	1.069	0.0099
796.5876	1204	2.633	0.059	2.860	0.062	1.087	0.0099
863.6876	1204	4.853	0.087	5.188	0.092	1.069	0.0104
492.3816	1203	3.588	0.076	3.302	0.077	0.920	0.0105
772.5278	1204	3.282	0.056	3.488	0.055	1.063	0.0107
825.5544	1202	2.644	0.112	3.084	0.126	1.167	0.0108
320.2356	1204	1.302	0.114	1.686	0.085	1.295	0.011
380.3096	1204	1.580	0.083	1.899	0.090	1.202	0.0112
519.3321	1101	3.914	0.122	4.382	0.133	1.119	0.0116
711.2577	1202	2.205	0.075	2.454	0.056	1.113	0.0118
493.385	1203	2.083	0.073	1.722	0.124	0.827	0.0119
565.3394	1202	6.924	0.073	7.186	0.068	1.038	0.0119
670.569	1204	3.179	0.090	3.515	0.093	1.106	0.012
856.6061	1202	4.500	0.081	4.805	0.086	1.068	0.0121
340.2976	1203	1.502	0.124	1.937	0.112	1.290	0.0124
287.2824	1101	1.958	0.180	1.265	0.202	0.646	0.0126
495.332	1101	5.196	0.094	5.565	0.112	1.071	0.0137
304.241	1204	4.876	0.053	5.088	0.066	1.044	0.0138
305.2438	1204	2.492	0.061	2.719	0.067	1.091	0.0145
616.5052	1203	4.260	0.086	3.957	0.084	0.929	0.0145
746.5119	1204	2.615	0.165	3.137	0.119	1.200	0.0152
861.7806	1203	2.533	0.092	2.902	0.119	1.146	0.0152
686.4877	1204	2.617	0.088	2.881	0.052	1.101	0.0155
830.7363	1203	4.834	0.111	5.263	0.135	1.089	0.0162
835.7006	1204	2.651	0.155	3.214	0.167	1.212	0.0165
867.7579	1204	2.654	0.185	3.308	0.189	1.246	0.0167
870.7307	1203	3.361	0.074	2.985	0.142	0.888	0.0169
246.1465	1202	3.761	0.084	4.072	0.096	1.083	0.017
507.3316	1202	2.891	0.047	3.094	0.071	1.070	0.0173
855.6023	1202	5.497	0.079	5.784	0.087	1.052	0.0173
578.5277	1203	4.183	0.420	5.548	0.355	1.326	0.0176
615.4938	1203	1.386	0.133	0.902	0.148	0.651	0.0177
808.5803	1201	5.667	0.029	5.784	0.039	1.021	0.0177
860.7752	1204	3.643	0.124	4.070	0.125	1.117	0.0185
518.4345	1203	1.584	0.180	2.199	0.178	1.388	0.0186
520.3354	1101	2.215	0.123	2.646	0.130	1.195	0.0188
765.5313	1202	1.717	0.123	2.098	0.095	1.222	0.0195
777.5287	1201	2.793	0.063	3.020	0.072	1.082	0.0198

887.8005	1203	2.948	0.118	3.306	0.086	1.122	0.0198
739.5143	1204	2.602	0.149	3.121	0.158	1.200	0.0199
831.7387	1204	3.193	0.121	3.648	0.150	1.142	0.02
521.3477	1101	3.643	0.099	4.021	0.127	1.104	0.0203
584.2646	1204	3.154	0.130	2.649	0.172	0.840	0.0207
661.6233	1204	2.430	0.088	2.715	0.079	1.117	0.0209
715.5167	1204	2.449	0.131	2.902	0.141	1.185	0.0218
529.3167	1202	3.031	0.071	3.265	0.069	1.077	0.0221
544.4481	1203	2.105	0.067	2.333	0.071	1.108	0.0234
866.7532	1204	4.149	0.145	4.693	0.189	1.131	0.0235
581.3344	1202	1.844	0.111	2.207	0.110	1.197	0.0245
795.5838	1204	3.569	0.060	3.769	0.063	1.056	0.0246
807.5768	1201	6.720	0.030	6.829	0.037	1.016	0.0256
854.5902	1202	3.801	0.070	4.031	0.073	1.060	0.0266
865.7487	1204	4.895	0.152	5.445	0.193	1.112	0.0268
496.3355	1101	3.396	0.095	3.736	0.119	1.100	0.027
755.5467	1201	3.507	0.072	3.755	0.084	1.071	0.0274
1019.3838	1102	3.035	0.036	2.919	0.037	0.962	0.0291
684.5489	1204	2.508	0.071	2.745	0.080	1.094	0.0294
774.0316	1204	1.789	0.192	1.167	0.203	0.652	0.0294
765.5334	1204	3.218	0.101	3.540	0.104	1.100	0.0299
630.5587	1203	3.126	0.072	3.344	0.064	1.070	0.0301
488.3873	1203	2.241	0.069	1.986	0.096	0.886	0.0321
302.2255	1204	3.506	0.085	3.765	0.081	1.074	0.0322
757.5625	1201	7.689	0.066	7.909	0.077	1.029	0.0325
617.5089	1203	2.978	0.089	2.698	0.092	0.906	0.0328
829.7239	1204	2.802	0.120	3.185	0.131	1.137	0.0344
303.1079	1202	5.656	0.048	5.802	0.047	1.026	0.0348
826.5581	1202	1.648	0.107	2.032	0.149	1.233	0.0362
506.2851	1201	3.080	0.117	2.656	0.165	0.862	0.0363
504.3814	1203	1.746	0.098	1.413	0.124	0.809	0.0366
691.1957	1102	2.130	0.060	1.938	0.068	0.910	0.0373
626.5278	1203	3.820	0.064	4.009	0.060	1.049	0.0375
522.3511	1101	1.753	0.091	2.069	0.121	1.180	0.0385
759.5779	1201	6.294	0.076	6.541	0.090	1.039	0.0386
625.5161	1203	2.856	0.057	3.045	0.070	1.066	0.0387
760.5811	1201	5.173	0.077	5.422	0.091	1.048	0.0395
484.3794	1204	2.181	0.092	1.776	0.178	0.815	0.0396
819.5642	1202	2.811	0.080	3.104	0.120	1.104	0.0404
853.5862	1202	4.775	0.069	4.985	0.075	1.044	0.0423
700.552	1101	2.278	0.124	2.617	0.102	1.149	0.0426
709.2594	1202	2.152	0.092	2.382	0.053	1.107	0.0426
662.5175	1204	3.806	0.120	3.420	0.145	0.899	0.0432
761.5846	1201	3.118	0.074	3.357	0.091	1.077	0.0436
743.5466	1203	2.011	0.077	2.266	0.099	1.127	0.0442
478.3664	1203	1.545	0.088	1.212	0.143	0.785	0.0447
784.5811	1201	5.585	0.073	5.809	0.082	1.040	0.0448
860.7756	1203	4.383	0.087	4.653	0.100	1.061	0.0448
601.5164	1203	7.642	0.056	7.463	0.069	0.976	0.0453
758.5655	1201	6.637	0.074	6.860	0.084	1.034	0.0488
371.3542	1203	3.253	0.055	3.435	0.074	1.056	0.0489
783.5778	1201	6.661	0.074	6.883	0.083	1.033	0.049
921.8145	1204	2.716	0.211	3.255	0.155	1.198	0.0494
824.6892	1203	2.657	0.108	2.964	0.108	1.116	0.0497

Table 3: Accurate mass features differing between clinically diagnosed AD patients with a significant cognitive impairment and clinically diagnosed non-AD patients with a significant cognitive impairment ($p<0.05$, log2 transformed).

723.5197	1204	3.581	0.053	4.571	0.070	0.783	1.07E-17
723.5195	1202	2.193	0.056	3.033	0.049	0.723	2.70E-17
749.5367	1202	3.187	0.044	3.812	0.045	0.836	5.25E-15
724.5257	1204	2.850	0.048	3.630	0.066	0.785	1.68E-14
752.5564	1202	2.281	0.049	2.975	0.056	0.767	5.71E-14
751.5555	1204	4.591	0.056	5.427	0.071	0.846	6.78E-14
751.5529	1202	3.369	0.052	4.055	0.054	0.831	1.46E-13
752.5583	1204	3.484	0.056	4.284	0.070	0.813	2.38E-13
749.5407	1204	4.423	0.047	5.185	0.073	0.853	5.02E-13
750.5402	1202	2.210	0.052	2.804	0.044	0.788	9.50E-13
750.544	1204	3.258	0.054	4.004	0.074	0.814	7.49E-12
725.5385	1204	2.815	0.058	3.543	0.078	0.794	1.10E-10
699.5198	1204	2.129	0.055	2.825	0.079	0.754	3.41E-10
727.5568	1204	3.445	0.055	4.039	0.076	0.853	1.48E-08
728.5627	1204	2.875	0.047	3.301	0.056	0.871	1.21E-07
726.5461	1204	2.759	0.044	3.175	0.057	0.869	1.35E-07
775.5528	1204	3.176	0.061	3.712	0.075	0.856	3.75E-07
813.5885	1202	3.034	0.043	3.369	0.049	0.901	2.08E-06
775.5533	1202	2.106	0.063	2.524	0.056	0.834	4.26E-06
747.5245	1204	3.433	0.058	3.933	0.088	0.873	8.18E-06
814.5917	1202	2.054	0.035	2.355	0.055	0.872	1.16E-05
747.5201	1202	1.886	0.083	2.357	0.062	0.800	2.25E-05
811.5732	1202	2.729	0.047	3.041	0.055	0.897	4.54E-05
789.5892	1202	1.703	0.053	2.013	0.061	0.846	0.0002
810.5399	1204	2.760	0.071	3.111	0.064	0.887	0.0004
795.5838	1204	3.569	0.060	3.845	0.050	0.928	0.0007
856.6061	1202	4.500	0.081	4.894	0.078	0.919	0.0008
783.5148	1204	3.217	0.063	3.512	0.061	0.916	0.0011
855.6023	1202	5.497	0.079	5.876	0.079	0.935	0.0011
858.6212	1202	2.533	0.080	2.917	0.080	0.868	0.0011
787.5465	1204	2.543	0.116	2.964	0.045	0.858	0.0013
857.6186	1202	3.614	0.081	3.989	0.081	0.906	0.0015
773.537	1202	1.581	0.066	1.875	0.065	0.843	0.002
784.5237	1204	3.211	0.056	3.464	0.056	0.927	0.002
748.5287	1204	2.249	0.127	2.811	0.123	0.800	0.0021
828.5743	1202	5.181	0.076	5.517	0.075	0.939	0.0023
827.5701	1202	6.245	0.082	6.608	0.083	0.945	0.0026
786.5416	1204	3.729	0.049	3.961	0.058	0.941	0.0029
871.5934	1202	1.841	0.085	2.189	0.076	0.841	0.0031
744.5536	1204	4.260	0.047	4.473	0.054	0.952	0.0037
787.5729	1202	1.834	0.054	2.081	0.065	0.881	0.0042
755.486	1204	3.146	0.061	3.395	0.059	0.927	0.0044
796.5876	1204	2.633	0.059	2.868	0.056	0.918	0.0048
812.5762	1202	1.752	0.045	2.034	0.088	0.861	0.0049
817.5377	1102	2.175	0.064	2.427	0.060	0.896	0.0053
383.3284	1204	1.263	0.120	1.722	0.107	0.733	0.0055
840.6063	1202	2.746	0.042	2.927	0.050	0.938	0.0065
544.397	1204	2.998	0.111	2.235	0.255	1.342	0.0066
570.3725	1202	2.926	0.047	3.115	0.049	0.939	0.0071
782.5085	1204	3.369	0.056	3.596	0.062	0.937	0.0077
847.5954	1202	2.317	0.089	2.662	0.090	0.870	0.0079
855.6016	1102	3.386	0.060	3.619	0.062	0.936	0.0082
769.5656	1204	3.889	0.055	4.103	0.057	0.948	0.0084
819.5642	1202	2.811	0.080	3.149	0.099	0.893	0.0089
828.5737	1102	2.982	0.056	3.197	0.058	0.933	0.009

590.343	1202	4.005	0.069	4.261	0.066	0.940	0.0091
719.6231	1204	4.528	0.074	4.158	0.119	1.089	0.0092
589.3403	1202	5.847	0.076	6.129	0.075	0.954	0.0098
768.5539	1204	3.928	0.069	4.189	0.071	0.938	0.0102
839.6031	1202	3.723	0.041	3.895	0.051	0.956	0.0102
821.5712	1102	2.919	0.053	3.120	0.056	0.936	0.0106
1226.097	1203	3.278	0.092	2.921	0.105	1.122	0.0122
664.5323	1204	4.909	0.126	4.391	0.161	1.118	0.0126
733.6426	1204	2.981	0.074	2.625	0.120	1.135	0.0126
771.5814	1204	4.118	0.051	4.313	0.057	0.955	0.0126
809.5937	1201	6.453	0.060	6.677	0.065	0.966	0.0126
720.6258	1204	3.565	0.076	3.215	0.117	1.109	0.0127
667.5475	1204	3.516	0.124	3.013	0.157	1.167	0.0132
665.5354	1204	3.705	0.121	3.182	0.170	1.164	0.0133
666.5456	1204	4.713	0.126	4.232	0.146	1.114	0.0142
793.5386	1102	3.435	0.052	3.632	0.061	0.946	0.015
810.5971	1201	5.436	0.063	5.665	0.068	0.959	0.015
832.6037	1202	4.981	0.069	5.231	0.074	0.952	0.0151
663.5216	1204	2.566	0.145	1.946	0.210	1.319	0.0159
743.5471	1204	5.227	0.047	5.417	0.062	0.965	0.0162
767.5495	1204	5.033	0.074	5.287	0.074	0.952	0.017
796.5292	1204	2.928	0.063	3.142	0.062	0.932	0.017
671.5723	1204	2.131	0.140	2.568	0.113	0.830	0.0173
758.5092	1204	4.504	0.047	4.670	0.051	0.964	0.0188
509.3493	1202	2.358	0.054	2.542	0.056	0.927	0.0192
827.57	1102	3.984	0.059	4.191	0.064	0.951	0.0194
569.369	1202	4.867	0.049	5.033	0.049	0.967	0.02
831.6001	1202	6.109	0.077	6.380	0.085	0.958	0.02
638.5149	1204	3.530	0.120	3.086	0.150	1.144	0.0224
768.5503	1202	1.849	0.125	2.190	0.080	0.845	0.0249
313.1153	1204	3.859	0.102	3.338	0.209	1.156	0.025
592.3571	1202	2.113	0.095	2.375	0.065	0.890	0.0262
794.5421	1102	2.364	0.048	2.536	0.061	0.932	0.0276
662.5175	1204	3.806	0.120	3.377	0.153	1.127	0.0292
670.569	1204	3.179	0.090	3.474	0.101	0.915	0.0312
870.7307	1203	3.361	0.074	3.012	0.144	1.116	0.0312
1098.974	1204	3.097	0.070	2.739	0.151	1.131	0.0313
694.6161	1204	2.845	0.080	2.437	0.173	1.168	0.0324
541.3432	1102	3.138	0.034	3.255	0.043	0.964	0.0335
581.3344	1202	1.844	0.111	2.147	0.087	0.859	0.0351
691.596	1204	2.394	0.098	1.999	0.159	1.198	0.0351
803.5677	1202	7.101	0.095	7.405	0.108	0.959	0.0364
591.3542	1202	3.870	0.092	4.110	0.064	0.942	0.0367
705.6093	1204	3.137	0.072	2.823	0.132	1.111	0.0367
847.5316	1101	2.564	0.060	2.815	0.104	0.911	0.0367
854.5902	1202	3.801	0.070	4.027	0.082	0.944	0.0376
215.9153	1101	4.405	0.297	5.221	0.247	0.844	0.0379
569.3687	1102	2.063	0.042	2.217	0.062	0.931	0.0404
640.5294	1204	3.725	0.127	3.313	0.154	1.124	0.0407
853.5862	1202	4.775	0.069	4.993	0.081	0.956	0.0413
830.5894	1202	4.738	0.076	4.968	0.082	0.954	0.0415
760.5216	1204	4.008	0.048	4.156	0.053	0.964	0.0417
530.3821	1204	2.614	0.172	2.016	0.240	1.296	0.0441
1225.092	1203	3.451	0.135	3.011	0.170	1.146	0.0445
819.5551	1102	2.198	0.058	2.369	0.062	0.928	0.0456
743.5469	1202	2.976	0.070	3.200	0.087	0.930	0.0464
444.2717	1202	1.304	0.083	1.577	0.109	0.827	0.0471
678.5477	1204	3.874	0.101	3.523	0.145	1.099	0.0485
741.5305	1204	2.825	0.080	3.086	0.104	0.916	0.0489
759.5163	1204	4.645	0.061	4.811	0.057	0.966	0.0493
820.568	1202	1.757	0.128	2.102	0.117	0.836	0.0497

Table 4: Accurate mass features differing between clinically diagnosed AD patients with a significant cognitive impairment and clinically diagnosed AD patients without a significant cognitive impairment ($p<0.05$, log2 transformed).

[illegible] Mass	[illegible] Mode	[illegible] (log2) AD	[illegible] AD	[illegible] (log2) [illegible]	[illegible] [illegible]	[illegible] Score	[illegible] Value
541.3432	1102	3.138	0.034	3.518	0.039	0.892	3.47E-10
569.3687	1102	2.063	0.042	2.479	0.045	0.832	3.90E-09
829.5856	1102	3.806	0.059	4.301	0.048	0.885	1.30E-08
567.3547	1102	2.629	0.050	3.031	0.045	0.868	1.02E-07
831.5997	1102	4.372	0.055	4.774	0.042	0.916	1.93E-07
832.6026	1102	3.268	0.055	3.662	0.042	0.892	2.67E-07
804.5713	1102	4.017	0.048	4.426	0.054	0.908	3.40E-07
803.568	1102	5.238	0.048	5.656	0.057	0.926	3.97E-07
871.5528	1102	2.885	0.049	3.279	0.054	0.880	8.30E-07
565.3394	1102	3.265	0.058	3.728	0.064	0.876	1.14E-06
805.5832	1102	3.874	0.056	4.292	0.055	0.903	1.41E-06
819.5551	1102	2.198	0.058	2.604	0.053	0.844	2.52E-06
555.3102	1102	1.634	0.053	2.033	0.059	0.803	3.32E-06
853.5854	1102	2.449	0.056	2.824	0.051	0.867	5.09E-06
805.5605	1101	5.184	0.074	5.665	0.065	0.915	6.42E-06
808.5792	1101	4.488	0.071	4.925	0.057	0.911	9.48E-06
793.5386	1102	3.435	0.052	3.799	0.057	0.904	1.17E-05
807.5758	1101	5.531	0.069	5.961	0.059	0.928	1.20E-05
806.5639	1101	4.199	0.075	4.669	0.066	0.899	1.28E-05
837.5027	1101	3.402	0.050	3.781	0.064	0.900	1.45E-05
794.5421	1102	2.364	0.048	2.703	0.059	0.875	2.79E-05
780.5474	1101	5.241	0.064	5.661	0.070	0.926	3.62E-05
779.5444	1101	6.239	0.065	6.654	0.070	0.938	4.37E-05
821.5712	1102	2.919	0.053	3.221	0.048	0.906	0.0001
827.57	1102	3.984	0.059	4.337	0.063	0.919	0.0001
886.5582	1102	2.911	0.041	3.189	0.053	0.913	0.0001
915.5191	1101	2.189	0.058	2.592	0.073	0.845	0.0001
722.5335	1101	2.406	0.062	2.735	0.057	0.880	0.0002
828.5737	1102	2.982	0.056	3.313	0.063	0.900	0.0002
833.5932	1101	3.045	0.095	3.522	0.077	0.865	0.0002
855.6016	1102	3.386	0.060	3.704	0.055	0.914	0.0002
755.5468	1101	2.115	0.086	2.563	0.082	0.825	0.0003
795.555	1102	2.520	0.054	2.818	0.057	0.894	0.0003
803.5445	1101	4.941	0.074	5.324	0.070	0.928	0.0003
811.6096	1101	2.801	0.116	3.370	0.096	0.831	0.0003
804.5476	1101	3.987	0.073	4.370	0.073	0.912	0.0004
829.5604	1101	3.360	0.075	3.728	0.063	0.901	0.0004
783.5672	1101	3.535	0.092	3.993	0.085	0.885	0.0005
832.5791	1101	3.184	0.076	3.541	0.067	0.899	0.0008
847.5316	1101	2.564	0.060	2.955	0.095	0.868	0.0008
784.5811	1101	4.161	0.112	4.668	0.093	0.891	0.0009
831.5759	1101	4.123	0.080	4.485	0.066	0.919	0.0009
757.4991	1101	3.450	0.089	3.866	0.083	0.892	0.0011
781.5617	1101	5.928	0.084	6.305	0.075	0.940	0.0014
795.5181	1101	2.458	0.082	2.823	0.073	0.871	0.0015
782.565	1101	4.901	0.088	5.279	0.080	0.928	0.0022
760.5811	1101	4.216	0.099	4.632	0.089	0.910	0.0027
759.5779	1101	5.352	0.096	5.752	0.085	0.930	0.0028
591.3542	1202	3.870	0.092	4.224	0.068	0.916	0.0031
592.3571	1202	2.113	0.095	2.472	0.070	0.855	0.0035
761.5843	1101	2.241	0.084	2.609	0.088	0.859	0.0035
858.6212	1202	2.533	0.080	2.870	0.078	0.883	0.0037
458.2405	1101	1.632	0.054	1.858	0.054	0.878	0.0042
785.5933	1101	5.687	0.112	6.096	0.083	0.933	0.0047
786.5967	1101	4.611	0.112	5.018	0.084	0.919	0.005

758.5656	1101	5.511	0.107	5.915	0.094	0.932	0.0061
306.2569	1204	2.878	0.070	3.125	0.053	0.921	0.0066
857.6186	1202	3.614	0.081	3.925	0.076	0.921	0.0066
757.5626	1101	6.470	0.106	6.861	0.094	0.943	0.0075
809.5936	1101	4.786	0.104	5.150	0.081	0.929	0.0077
810.5969	1101	3.779	0.108	4.144	0.083	0.912	0.0095
807.59	1202	2.348	0.061	2.574	0.062	0.912	0.0113
383.3284	1204	1.263	0.120	1.659	0.095	0.761	0.012
786.5416	1204	3.729	0.049	3.903	0.046	0.955	0.012
744.55	1202	1.842	0.064	2.093	0.074	0.880	0.0124
827.5448	1101	3.373	0.104	3.751	0.105	0.899	0.0128
784.5237	1204	3.211	0.056	3.405	0.052	0.943	0.0133
746.5119	1204	2.615	0.165	3.058	0.057	0.855	0.0145
817.5377	1102	2.175	0.064	2.405	0.066	0.905	0.0155
699.5198	1204	2.129	0.055	2.309	0.047	0.922	0.0161
757.5014	1204	3.642	0.067	3.869	0.063	0.941	0.0161
826.7069	1204	2.279	0.148	2.684	0.086	0.849	0.0215
758.5092	1204	4.504	0.047	4.652	0.043	0.968	0.0235
546.3485	1101	1.890	0.073	2.115	0.064	0.894	0.0236
801.555	1202	2.543	0.077	2.788	0.077	0.912	0.0272
829.7239	1204	2.802	0.120	3.161	0.105	0.886	0.0272
748.5721	1102	3.795	0.067	3.996	0.060	0.950	0.0288
518.3174	1101	3.358	0.051	3.523	0.054	0.953	0.0296
826.5581	1202	1.648	0.107	1.983	0.108	0.831	0.0309
830.5894	1202	4.738	0.076	4.956	0.064	0.956	0.0317
430.3818	1204	4.790	0.109	5.108	0.096	0.938	0.0322
313.1153	1204	3.859	0.102	3.311	0.233	1.166	0.0327
755.5467	1201	3.507	0.072	3.728	0.072	0.941	0.0327
545.3453	1101	3.500	0.071	3.713	0.069	0.943	0.0353
320.2356	1204	1.302	0.114	1.590	0.070	0.819	0.0363
183.0661	1101	2.412	0.147	2.779	0.096	0.868	0.0416
825.5544	1202	2.644	0.112	2.968	0.109	0.891	0.0418
549.4845	1203	5.510	0.107	5.818	0.103	0.947	0.0424
829.5859	1202	5.864	0.082	6.087	0.070	0.963	0.0433
431.386	1204	3.354	0.108	3.651	0.099	0.919	0.0463
784.5811	1201	5.585	0.073	5.782	0.064	0.966	0.0463
777.5287	1201	2.793	0.063	2.986	0.072	0.935	0.0466
278.2254	1204	4.828	0.056	4.996	0.062	0.966	0.0467
548.4815	1203	6.949	0.103	7.233	0.096	0.961	0.0472
777.553	1202	1.720	0.100	2.002	0.098	0.859	0.0483
517.314	1101	5.399	0.050	5.547	0.055	0.973	0.0488
661.6233	1204	2.430	0.088	2.638	0.054	0.921	0.0489

Table 5: Accurate mass features differing between clinically diagnosed non-AD patients and non-demented controls ($p<0.05$, log2 transformed).

541.3432	1102	3.255	0.043	3.679	0.048	0.885	3.43E-12
567.3547	1102	2.621	0.052	3.117	0.054	0.841	2.78E-11
805.5605	1101	5.159	0.072	5.604	0.048	0.921	1.08E-09
806.5639	1101	4.150	0.073	4.630	0.049	0.896	1.51E-09
804.5713	1102	4.159	0.056	4.466	0.033	0.931	3.79E-09
783.5672	1101	3.515	0.077	4.126	0.079	0.852	4.13E-09
781.5617	1101	5.919	0.072	6.403	0.072	0.924	4.19E-09
780.5474	1101	5.276	0.075	5.691	0.043	0.927	4.35E-09
803.568	1102	5.379	0.056	5.656	0.035	0.951	4.43E-09
779.5444	1101	6.291	0.073	6.659	0.043	0.945	5.24E-09
760.5811	1101	4.034	0.079	4.733	0.103	0.852	6.28E-09
805.5832	1102	3.897	0.057	4.344	0.068	0.897	6.49E-09
759.5779	1101	5.166	0.082	5.810	0.099	0.889	1.04E-08
782.565	1101	4.878	0.077	5.415	0.078	0.901	1.14E-08
829.5856	1102	3.952	0.051	4.261	0.046	0.927	1.44E-08
569.3687	1102	2.217	0.062	2.639	0.048	0.840	1.99E-08
755.5468	1101	1.974	0.089	2.667	0.085	0.740	2.63E-08
757.4991	1101	3.368	0.086	3.945	0.070	0.854	2.69E-08
871.5528	1102	2.960	0.059	3.301	0.040	0.897	4.58E-08
804.5476	1101	4.125	0.073	4.556	0.060	0.906	6.76E-08
803.5445	1101	5.084	0.072	5.478	0.059	0.928	7.46E-08
758.5656	1101	5.440	0.089	5.968	0.078	0.912	8.14E-08
565.3394	1102	3.359	0.081	3.834	0.055	0.876	8.59E-08
757.5626	1101	6.417	0.087	6.886	0.079	0.932	1.74E-07
808.5792	1101	4.527	0.078	4.904	0.047	0.923	2.30E-07
795.5181	1101	2.491	0.071	2.948	0.064	0.845	2.65E-07
807.5758	1101	5.569	0.080	5.911	0.047	0.942	3.99E-07
731.5464	1101	1.460	0.132	2.519	0.157	0.580	4.14E-07
837.5027	1101	3.437	0.071	3.810	0.050	0.902	4.34E-07
761.5843	1101	2.053	0.092	2.740	0.106	0.749	5.01E-07
784.5811	1101	4.092	0.095	4.666	0.089	0.877	5.41E-07
831.5997	1102	4.512	0.057	4.749	0.040	0.950	6.07E-07
832.6026	1102	3.409	0.056	3.677	0.040	0.927	6.72E-07
555.3102	1102	1.792	0.066	2.170	0.046	0.826	8.11E-07
833.5932	1101	3.038	0.087	3.495	0.056	0.869	1.09E-06
829.5604	1101	3.381	0.077	3.754	0.058	0.901	3.91E-06
811.6096	1101	2.826	0.097	3.401	0.096	0.831	4.19E-06
785.5933	1101	5.629	0.100	6.075	0.080	0.927	5.08E-06
786.5967	1101	4.566	0.101	5.041	0.078	0.906	5.43E-06
827.57	1102	4.191	0.064	4.486	0.062	0.934	6.39E-06
828.5737	1102	3.197	0.058	3.478	0.061	0.919	1.44E-05
810.5969	1101	3.785	0.100	4.234	0.080	0.894	2.51E-05
809.5936	1101	4.804	0.094	5.194	0.079	0.925	2.81E-05
517.314	1101	5.339	0.065	5.575	0.069	0.958	3.58E-05
495.332	1101	5.003	0.083	5.391	0.112	0.928	0.0001
518.3174	1101	3.325	0.062	3.601	0.073	0.923	0.0001
793.5386	1102	3.632	0.061	3.827	0.039	0.949	0.0001
794.5421	1102	2.536	0.061	2.763	0.040	0.918	0.0001
832.5791	1101	3.305	0.080	3.607	0.061	0.916	0.0001
853.5854	1102	2.527	0.065	2.790	0.052	0.906	0.0001
915.5191	1101	2.278	0.083	2.632	0.063	0.866	0.0001
183.0661	1101	2.324	0.143	2.920	0.094	0.796	0.0002
521.3477	1101	3.406	0.099	3.895	0.127	0.875	0.0002
523.3634	1101	3.221	0.102	3.673	0.103	0.877	0.0002
543.3296	1101	3.579	0.072	3.898	0.087	0.918	0.0002
795.555	1102	2.608	0.069	2.893	0.065	0.902	0.0002
831.5759	1101	4.272	0.080	4.531	0.060	0.943	0.0002

886.5582	1102	2.998	0.049	3.149	0.041	0.952	0.0002
496.3355	1101	3.200	0.086	3.620	0.119	0.884	0.0004
827.5448	1101	3.340	0.105	3.752	0.095	0.890	0.0004
819.5551	1102	2.369	0.062	2.571	0.046	0.922	0.0005
522.3511	1101	1.480	0.111	2.005	0.121	0.738	0.0006
817.5377	1102	2.427	0.060	2.627	0.057	0.924	0.001
545.3453	1101	3.512	0.082	3.776	0.078	0.930	0.0011
575.2728	1101	2.381	0.076	2.653	0.074	0.897	0.0012
700.552	1101	2.150	0.094	2.535	0.102	0.848	0.0012
722.5335	1101	2.437	0.062	2.632	0.056	0.926	0.0014
520.3354	1101	2.075	0.117	2.564	0.130	0.809	0.0016
458.2405	1101	1.664	0.064	1.924	0.077	0.865	0.0017
542.3173	1101	2.268	0.092	2.603	0.089	0.871	0.0017
519.3321	1101	3.807	0.121	4.245	0.133	0.897	0.0019
546.3485	1101	1.931	0.069	2.216	0.089	0.872	0.0021
541.3139	1101	4.077	0.092	4.353	0.096	0.937	0.0025
1019.384	1102	3.095	0.042	2.828	0.037	1.094	0.0026
804.7227	1203	1.612	0.233	2.530	0.220	0.637	0.0027
831.7408	1203	3.839	0.137	4.286	0.130	0.896	0.0028
303.1079	1202	5.575	0.057	5.621	0.047	0.992	0.0032
549.4845	1203	5.480	0.127	5.807	0.110	0.944	0.0033
548.4815	1203	6.917	0.122	7.174	0.103	0.964	0.0034
746.5717	1204	3.115	0.058	3.257	0.061	0.957	0.0046
830.7363	1203	4.694	0.139	5.098	0.135	0.921	0.0046
306.2569	1204	3.015	0.059	3.164	0.067	0.953	0.0058
760.5216	1204	4.156	0.053	4.211	0.039	0.987	0.0058
732.4938	1204	4.274	0.060	4.370	0.057	0.978	0.0059
855.6016	1102	3.619	0.062	3.752	0.065	0.965	0.0059
523.4679	1203	3.249	0.212	3.886	0.165	0.836	0.0065
522.4635	1203	4.717	0.208	5.313	0.176	0.888	0.0066
1227.107	1203	3.235	0.116	3.547	0.100	0.912	0.0074
833.7551	1204	2.396	0.213	3.042	0.161	0.788	0.0075
520.4499	1203	3.898	0.194	4.434	0.148	0.879	0.0076
1228.111	1203	2.587	0.203	3.131	0.105	0.826	0.0077
521.4522	1203	2.319	0.204	2.933	0.158	0.790	0.0083
591.3542	1202	4.110	0.064	4.209	0.058	0.976	0.0085
856.672	1202	2.741	0.042	2.473	0.057	1.108	0.0086
777.553	1202	1.958	0.096	2.309	0.130	0.848	0.009
552.5022	1203	3.097	0.142	3.529	0.147	0.878	0.0092
777.5287	1201	2.781	0.055	2.926	0.072	0.951	0.0092
675.6377	1204	3.806	0.112	4.030	0.066	0.945	0.0098
748.5735	1202	3.883	0.036	3.606	0.050	1.077	0.0101
467.807	1101	1.408	0.134	0.863	0.144	1.631	0.0104
832.7523	1203	3.763	0.160	4.237	0.169	0.888	0.0104
837.718	1204	2.737	0.273	3.548	0.217	0.771	0.0107
745.5658	1204	4.005	0.060	4.109	0.068	0.975	0.0109
568.3573	1202	3.960	0.053	4.037	0.060	0.981	0.0113
550.4957	1203	6.848	0.150	7.184	0.160	0.953	0.0114
833.7571	1203	2.911	0.156	3.397	0.170	0.857	0.0115
838.7226	1204	2.158	0.237	2.880	0.206	0.749	0.0119
551.4986	1203	5.429	0.150	5.801	0.158	0.936	0.0121
585.2673	1202	1.612	0.153	1.034	0.148	1.558	0.0125
821.5712	1102	3.120	0.056	3.200	0.044	0.975	0.0133
835.7006	1204	2.553	0.198	3.113	0.167	0.820	0.0136
731.4916	1204	5.523	0.062	5.567	0.063	0.992	0.0138
867.7579	1204	2.503	0.252	3.205	0.189	0.781	0.0139
482.3215	1202	2.040	0.058	2.181	0.062	0.935	0.0145
858.6861	1202	2.935	0.050	2.670	0.052	1.099	0.0145
584.2646	1204	3.282	0.185	2.567	0.172	1.279	0.0148
829.7246	1203	4.743	0.119	4.973	0.101	0.954	0.015
828.7207	1203	5.497	0.121	5.716	0.107	0.962	0.0154
723.5197	1204	4.571	0.070	4.214	0.056	1.085	0.0167
864.738	1204	4.725	0.142	5.051	0.141	0.936	0.0171
691.1957	1102	2.168	0.067	1.878	0.068	1.155	0.0181
585.2664	1204	1.716	0.183	1.077	0.170	1.593	0.0187

749.5777	1202	2.879	0.034	2.659	0.046	1.083	0.0189
757.5014	1204	3.770	0.066	3.847	0.052	0.980	0.0197
863.7336	1204	5.458	0.146	5.763	0.147	0.947	0.02
830.7352	1204	4.133	0.151	4.493	0.150	0.920	0.0202
252.2095	1204	1.665	0.076	1.852	0.070	0.899	0.0206
860.7756	1203	4.306	0.109	4.507	0.100	0.955	0.0222
863.6876	1204	4.889	0.090	5.026	0.092	0.973	0.0227
861.7806	1203	2.435	0.158	2.811	0.119	0.866	0.0228
840.6063	1202	2.927	0.050	2.664	0.059	1.099	0.0229
632.5762	1203	1.325	0.170	1.773	0.132	0.747	0.0231
826.7069	1204	2.424	0.137	2.731	0.099	0.887	0.0242
419.8773	1101	1.946	0.176	1.305	0.194	1.491	0.0243
440.3532	1204	1.481	0.134	0.945	0.180	1.567	0.0247
831.7387	1204	3.137	0.164	3.534	0.150	0.888	0.0248
310.2883	1204	2.448	0.085	2.607	0.062	0.939	0.0256
481.3172	1202	3.978	0.053	4.029	0.060	0.987	0.0259
205.8865	1101	3.759	0.234	2.793	0.319	1.346	0.0271
513.4122	1204	1.142	0.153	0.623	0.163	1.833	0.0279
839.6031	1202	3.895	0.051	3.609	0.057	1.079	0.0286
865.7487	1204	4.847	0.188	5.275	0.193	0.919	0.029
579.5325	1203	4.188	0.154	4.491	0.127	0.933	0.0292
807.59	1202	2.477	0.072	2.633	0.082	0.941	0.0293
351.8903	1101	2.359	0.220	1.567	0.256	1.506	0.0296
782.5085	1204	3.596	0.062	3.662	0.055	0.982	0.0297
859.7696	1203	5.853	0.104	5.972	0.093	0.980	0.0298
409.8484	1101	2.107	0.192	1.437	0.210	1.466	0.0304
577.5137	1203	8.099	0.104	8.148	0.094	0.994	0.0305
1018.942	1203	3.468	0.142	3.767	0.126	0.921	0.0305
703.5709	1101	3.024	0.090	3.185	0.079	0.949	0.0314
484.3794	1204	2.234	0.118	1.721	0.178	1.298	0.0315
283.2602	1204	6.622	0.070	6.621	0.067	1.000	0.0316
401.8166	1101	1.696	0.161	1.139	0.177	1.489	0.0316
832.7492	1204	3.251	0.195	3.728	0.190	0.872	0.0316
190.033	1101	3.264	0.233	2.384	0.289	1.369	0.0317
806.5873	1202	4.367	0.082	4.490	0.092	0.973	0.032
282.2573	1204	9.088	0.073	9.019	0.071	1.008	0.0327
195.8577	1101	3.161	0.202	2.370	0.266	1.334	0.0328
744.4956	1204	3.941	0.058	3.988	0.058	0.988	0.0332
866.7532	1204	4.123	0.184	4.547	0.189	0.907	0.0334
215.9153	1101	5.221	0.247	4.183	0.346	1.248	0.0335
825.6926	1203	1.767	0.173	2.165	0.124	0.816	0.0339
469.8042	1101	1.617	0.150	1.096	0.170	1.475	0.0344
874.7645	1204	3.091	0.144	3.377	0.111	0.915	0.0345
494.4343	1203	2.119	0.275	2.809	0.232	0.754	0.0346
399.8196	1101	1.827	0.171	1.249	0.184	1.463	0.0348
802.7056	1204	1.701	0.206	2.248	0.202	0.756	0.0348
576.5098	1203	9.446	0.111	9.460	0.099	0.999	0.0355
382.1082	1101	2.222	0.229	1.494	0.220	1.487	0.0356
720.6438	1204	2.962	0.180	3.293	0.083	0.900	0.036
805.5839	1202	5.574	0.081	5.658	0.097	0.985	0.0365
779.5441	1201	7.096	0.041	7.010	0.053	1.012	0.0368
231.8893	1101	2.592	0.233	1.800	0.259	1.440	0.0372
686.4877	1204	2.721	0.054	2.791	0.052	0.975	0.0374
429.3749	1204	2.601	0.098	2.777	0.077	0.937	0.0378
265.8423	1101	2.499	0.220	1.743	0.252	1.433	0.0384
722.6424	1204	3.726	0.167	4.006	0.086	0.930	0.0385
780.5474	1201	6.022	0.043	5.972	0.054	1.008	0.0396
599.4936	1204	1.373	0.191	1.873	0.188	0.733	0.04
536.4794	1203	2.280	0.202	2.711	0.143	0.841	0.0422
244.0559	1101	3.574	0.126	3.098	0.132	1.153	0.0424
202.0453	1101	5.561	0.180	4.832	0.215	1.151	0.0425
535.7944	1101	1.480	0.143	1.018	0.153	1.455	0.0425
758.5092	1204	4.670	0.051	4.658	0.042	1.003	0.0426
626.5104	1204	2.100	0.135	2.391	0.114	0.878	0.0427
847.5316	1101	2.815	0.104	2.994	0.083	0.940	0.0432

592.3571	1202	2.375	0.065	2.480	0.062	0.958	0.0437
569.4784	1204	1.175	0.183	0.634	0.178	1.853	0.0447
721.639	1204	4.879	0.142	5.064	0.088	0.963	0.0447
752.5583	1204	4.284	0.070	3.966	0.061	1.080	0.0451
507.7055	1101	1.487	0.126	1.052	0.154	1.413	0.0454
827.7086	1203	3.916	0.119	4.098	0.096	0.956	0.046
784.5237	1204	3.464	0.056	3.490	0.037	0.993	0.0461
755.486	1204	3.395	0.059	3.450	0.057	0.984	0.0471
628.5237	1204	2.627	0.158	2.955	0.136	0.889	0.0472
218.0192	1101	3.591	0.258	2.716	0.302	1.322	0.049

Table 6: Accurate mass features differing between clinically diagnosed AD patients with a mild cognitive impairment and non-demented controls ($p<0.05$, log2 transformed).

723.5197	1204	3.576	0.058	4.350	0.056	0.822	6.42E-14
723.5195	1202	2.181	0.056	2.892	0.052	0.754	2.49E-13
751.5529	1202	3.293	0.050	3.920	0.050	0.840	1.39E-12
724.5257	1204	2.883	0.044	3.463	0.055	0.833	9.96E-12
749.5367	1202	3.168	0.051	3.714	0.041	0.853	1.33E-11
752.5564	1202	2.216	0.057	2.836	0.050	0.781	1.91E-11
751.5555	1204	4.553	0.060	5.248	0.060	0.868	1.96E-11
750.5402	1202	2.175	0.054	2.704	0.044	0.804	2.92E-10
752.5583	1204	3.453	0.063	4.094	0.061	0.844	6.11E-10
750.544	1204	3.299	0.052	3.858	0.063	0.855	3.31E-09
749.5407	1204	4.429	0.061	5.012	0.064	0.884	9.50E-09
699.5198	1204	2.309	0.047	2.775	0.054	0.832	1.20E-08
725.5385	1204	2.958	0.060	3.417	0.054	0.866	4.59E-07
727.5568	1204	3.588	0.050	3.986	0.060	0.900	3.00E-06
812.5762	1202	1.571	0.087	2.084	0.058	0.754	1.13E-05
541.3432	1102	3.518	0.039	3.798	0.048	0.926	2.42E-05
813.5885	1202	2.992	0.041	3.276	0.048	0.913	2.68E-05
811.5732	1202	2.683	0.055	3.027	0.055	0.886	3.92E-05
726.5461	1204	2.869	0.047	3.150	0.050	0.911	0.0001
814.5917	1202	2.028	0.040	2.289	0.051	0.886	0.0001
632.5762	1203	0.944	0.175	1.830	0.132	0.516	0.0002
728.5627	1204	2.998	0.045	3.281	0.060	0.914	0.0003
782.5085	1204	3.435	0.071	3.780	0.055	0.909	0.0003
569.3687	1102	2.479	0.045	2.724	0.048	0.910	0.0004
803.5445	1101	5.324	0.070	5.655	0.059	0.941	0.0007
804.5476	1101	4.370	0.073	4.703	0.060	0.929	0.0009
817.5377	1102	2.405	0.066	2.712	0.057	0.887	0.001
787.5729	1202	1.864	0.058	2.145	0.057	0.869	0.0011
747.5245	1204	3.521	0.063	3.886	0.090	0.906	0.0013
775.5533	1202	2.140	0.062	2.449	0.068	0.874	0.0013
746.5717	1204	3.117	0.043	3.362	0.061	0.927	0.0014
827.57	1102	4.337	0.063	4.630	0.062	0.937	0.0017
745.5658	1204	3.989	0.041	4.242	0.068	0.940	0.0018
828.5737	1102	3.313	0.063	3.590	0.061	0.923	0.0025
542.3173	1101	2.344	0.067	2.687	0.089	0.872	0.0027
760.5216	1204	4.140	0.052	4.347	0.039	0.952	0.0028
748.5287	1204	2.319	0.131	2.820	0.088	0.822	0.003
774.0316	1204	2.044	0.199	1.167	0.203	1.752	0.0031
784.5237	1204	3.405	0.052	3.603	0.037	0.945	0.0035
775.5528	1204	3.221	0.065	3.537	0.085	0.911	0.004
744.5536	1204	4.388	0.046	4.605	0.058	0.953	0.0042

482.3215	1202	2.001	0.057	2.251	0.062	0.889	0.0043
768.5539	1204	3.995	0.060	4.279	0.077	0.934	0.0044
506.2851	1201	3.210	0.100	2.656	0.165	1.209	0.0045
747.5201	1202	2.006	0.060	2.313	0.088	0.867	0.0045
755.486	1204	3.295	0.069	3.561	0.057	0.925	0.0047
781.5617	1101	6.305	0.075	6.610	0.072	0.954	0.005
786.5416	1204	3.903	0.046	4.087	0.043	0.955	0.0052
804.5713	1102	4.426	0.054	4.610	0.033	0.960	0.0064
743.5471	1204	5.349	0.054	5.579	0.063	0.959	0.0066
541.3139	1101	4.172	0.067	4.494	0.096	0.928	0.0069
767.5495	1204	5.085	0.063	5.369	0.082	0.947	0.0072
782.565	1101	5.279	0.080	5.589	0.078	0.945	0.0074
555.3102	1102	2.033	0.059	2.240	0.046	0.908	0.0086
567.3547	1102	3.031	0.045	3.218	0.054	0.942	0.0089
565.3394	1102	3.728	0.064	3.958	0.055	0.942	0.0094
582.2473	1201	3.346	0.151	2.793	0.141	1.198	0.0099
803.568	1102	5.656	0.057	5.838	0.035	0.969	0.0108
779.5444	1101	6.654	0.070	6.874	0.043	0.968	0.0113
796.5876	1204	2.630	0.063	2.860	0.062	0.919	0.0117
758.5092	1204	4.652	0.043	4.808	0.042	0.968	0.0126
783.5148	1204	3.344	0.068	3.574	0.056	0.936	0.0126
748.5735	1202	3.893	0.045	3.722	0.050	1.046	0.0135
529.3167	1202	3.028	0.064	3.265	0.069	0.927	0.0138
781.562	1201	7.406	0.060	7.638	0.071	0.970	0.0144
780.5474	1101	5.661	0.070	5.875	0.043	0.964	0.0145
810.5399	1204	2.905	0.069	3.145	0.066	0.923	0.0147
837.5881	1202	2.412	0.040	2.577	0.053	0.936	0.0147
590.343	1202	4.042	0.072	4.304	0.076	0.939	0.0149
580.5351	1203	1.531	0.200	2.192	0.174	0.699	0.0166
789.5892	1202	1.755	0.049	1.952	0.065	0.899	0.0167
887.7352	1204	6.359	0.115	5.963	0.113	1.066	0.0174
828.5743	1202	5.301	0.087	5.598	0.085	0.947	0.0178
916.7743	1204	5.952	0.113	5.571	0.107	1.068	0.0178
856.672	1202	2.753	0.058	2.553	0.057	1.078	0.0179
827.5701	1202	6.362	0.095	6.684	0.092	0.952	0.0187
942.7879	1204	3.531	0.102	3.195	0.092	1.105	0.019
523.4679	1203	3.471	0.153	4.011	0.165	0.865	0.0194
915.7681	1204	6.365	0.115	5.972	0.116	1.066	0.0194
517.314	1101	5.547	0.055	5.755	0.069	0.964	0.0195
777.553	1202	2.002	0.098	2.384	0.130	0.840	0.0204
744.4956	1204	3.916	0.061	4.117	0.058	0.951	0.0206
440.3532	1204	1.502	0.136	0.975	0.180	1.539	0.021
782.5653	1201	6.382	0.065	6.614	0.076	0.965	0.0222
494.4343	1203	2.145	0.226	2.900	0.232	0.740	0.0232
303.1079	1202	5.646	0.048	5.802	0.047	0.973	0.0233
771.5814	1204	4.208	0.050	4.367	0.046	0.964	0.0236
521.4522	1203	2.482	0.173	3.028	0.158	0.820	0.0242
793.5681	1204	3.191	0.055	3.372	0.055	0.946	0.0244
832.6026	1102	3.662	0.042	3.795	0.040	0.965	0.0252
589.3403	1202	5.900	0.084	6.171	0.085	0.956	0.026
732.4938	1204	4.319	0.061	4.511	0.057	0.957	0.0263
783.5672	1101	3.993	0.085	4.259	0.079	0.938	0.0265
569.369	1202	4.947	0.042	5.089	0.047	0.972	0.0273
522.4635	1203	4.938	0.167	5.485	0.176	0.900	0.0277
795.5181	1101	2.823	0.073	3.044	0.064	0.927	0.0287
888.7394	1204	5.759	0.115	5.400	0.110	1.066	0.0287
490.3641	1203	1.864	0.138	1.397	0.159	1.334	0.029
914.7583	1204	5.125	0.112	4.763	0.118	1.076	0.0294
520.4499	1203	4.141	0.131	4.577	0.148	0.905	0.03
805.5832	1102	4.292	0.055	4.485	0.068	0.957	0.0301
795.5838	1204	3.558	0.070	3.769	0.063	0.944	0.0305
575.2728	1101	2.532	0.060	2.739	0.074	0.925	0.0324
831.5997	1102	4.774	0.042	4.903	0.040	0.974	0.0325
518.3174	1101	3.523	0.054	3.717	0.073	0.948	0.0338
520.3354	1101	2.271	0.117	2.646	0.130	0.858	0.0354

573.4852	1203	4.919	0.063	4.740	0.053	1.038	0.0354
579.5325	1203	4.235	0.135	4.636	0.127	0.913	0.0355
570.3725	1202	3.021	0.043	3.155	0.045	0.958	0.0359
793.5386	1102	3.799	0.057	3.950	0.039	0.962	0.0359
481.3172	1202	3.980	0.058	4.159	0.060	0.957	0.0361
831.5759	1101	4.485	0.066	4.677	0.060	0.959	0.0365
913.7513	1204	5.358	0.113	5.006	0.120	1.070	0.037
772.5862	1204	3.306	0.045	3.437	0.042	0.962	0.0378
304.241	1204	4.898	0.062	5.088	0.066	0.963	0.0397
746.557	1202	2.177	0.042	2.057	0.037	1.058	0.0399
519.3321	1101	4.014	0.116	4.382	0.133	0.916	0.0405
833.7551	1204	2.611	0.191	3.140	0.161	0.831	0.0406
889.7492	1204	7.711	0.122	7.365	0.110	1.047	0.0415
614.4914	1203	2.747	0.091	2.448	0.114	1.122	0.0418
618.4829	1201	1.844	0.179	1.310	0.185	1.407	0.0429
601.5164	1203	7.639	0.052	7.463	0.069	1.024	0.0431
671.5723	1204	2.349	0.088	2.604	0.087	0.902	0.0435
794.5421	1102	2.703	0.059	2.853	0.040	0.948	0.0438
731.4916	1204	5.555	0.068	5.746	0.063	0.967	0.0444
512.4082	1204	2.523	0.180	1.954	0.215	1.292	0.0451
768.5503	1202	2.028	0.082	2.277	0.090	0.891	0.0453
665.501	1204	3.429	0.105	3.074	0.142	1.116	0.0454
890.7535	1204	7.055	0.116	6.731	0.106	1.048	0.0454
759.5163	1204	4.804	0.055	4.954	0.048	0.970	0.0455
605.5457	1203	5.235	0.100	5.509	0.089	0.950	0.0473
541.4425	1204	2.234	0.148	1.745	0.198	1.280	0.0488
572.4816	1203	6.271	0.061	6.108	0.052	1.027	0.049
743.5466	1203	1.977	0.103	2.266	0.099	0.873	0.0492

Table 7: Accurate mass features differing between dementia patients with a significant cognitive impairment (ADAS $\geq$ 16) and dementia patients with a mild cognitive impairment (ADAS $\leq$ 15) ($p<0.05$, log2 transformed).

541.3432	1102	3.155	0.038	3.581	0.054	0.881	6.71E-09
567.3547	1102	2.633	0.052	3.122	0.058	0.843	3.84E-08
569.3687	1102	2.079	0.053	2.526	0.054	0.823	2.41E-07
829.5856	1102	3.861	0.057	4.303	0.059	0.897	1.71E-06
565.3394	1102	3.268	0.064	3.784	0.081	0.864	3.73E-06
837.5027	1101	3.373	0.056	3.818	0.070	0.884	4.53E-06
804.5713	1102	4.022	0.051	4.414	0.060	0.911	5.01E-06
831.5997	1102	4.379	0.055	4.761	0.046	0.920	5.17E-06
832.6026	1102	3.278	0.055	3.658	0.046	0.896	5.66E-06
803.568	1102	5.252	0.052	5.640	0.065	0.931	1.42E-05
805.5832	1102	3.894	0.056	4.293	0.063	0.907	1.48E-05
871.5528	1102	2.886	0.051	3.244	0.059	0.890	2.25E-05
555.3102	1102	1.669	0.053	2.070	0.074	0.806	2.34E-05
853.5854	1102	2.473	0.058	2.824	0.040	0.876	2.85E-05
886.5582	1102	2.898	0.036	3.166	0.051	0.916	4.34E-05
808.5792	1101	4.475	0.071	4.922	0.068	0.909	4.77E-05
780.5474	1101	5.229	0.067	5.665	0.086	0.923	0.0001
805.5605	1101	5.210	0.072	5.655	0.078	0.921	0.0001
807.5758	1101	5.522	0.071	5.962	0.069	0.926	0.0001
543.3296	1101	3.594	0.055	3.948	0.075	0.910	0.0002
779.5444	1101	6.228	0.067	6.660	0.086	0.935	0.0002
806.5639	1101	4.213	0.074	4.656	0.079	0.905	0.0002
829.5604	1101	3.368	0.070	3.766	0.069	0.894	0.0002
755.5468	1101	2.034	0.091	2.551	0.098	0.797	0.0003

819.5551	1102	2.270	0.062	2.611	0.062	0.869	0.0003
915.5191	1101	2.209	0.066	2.603	0.082	0.849	0.0004
794.5421	1102	2.389	0.054	2.705	0.073	0.883	0.0007
832.5791	1101	3.221	0.066	3.564	0.066	0.904	0.0007
793.5386	1102	3.462	0.057	3.778	0.069	0.916	0.0008
803.5445	1101	4.995	0.065	5.351	0.078	0.933	0.0008
804.5476	1101	4.045	0.064	4.402	0.080	0.919	0.0008
731.5464	1101	1.574	0.132	2.200	0.109	0.716	0.0011
827.57	1102	4.055	0.057	4.341	0.062	0.934	0.0014
722.5335	1101	2.379	0.064	2.687	0.064	0.885	0.0015
831.5759	1101	4.163	0.072	4.510	0.070	0.923	0.0015
517.314	1101	5.343	0.057	5.631	0.068	0.949	0.0019
757.4991	1101	3.393	0.086	3.828	0.102	0.886	0.0019
783.5672	1101	3.547	0.087	3.974	0.097	0.893	0.002
545.3453	1101	3.457	0.072	3.795	0.073	0.911	0.0022
518.3174	1101	3.321	0.056	3.600	0.068	0.922	0.0023
760.5811	1101	4.181	0.092	4.609	0.101	0.907	0.003
784.5811	1101	4.155	0.104	4.630	0.111	0.897	0.0033
546.3485	1101	1.883	0.067	2.196	0.078	0.857	0.0034
759.5779	1101	5.313	0.091	5.727	0.098	0.928	0.0034
855.6016	1102	3.447	0.060	3.709	0.056	0.929	0.0034
847.5316	1101	2.627	0.075	3.004	0.106	0.874	0.0037
781.5617	1101	5.942	0.079	6.291	0.082	0.945	0.0039
575.2728	1101	2.359	0.070	2.663	0.069	0.886	0.0042
828.5737	1102	3.070	0.054	3.317	0.064	0.926	0.0047
795.555	1102	2.558	0.065	2.831	0.063	0.904	0.0053
821.5712	1102	2.952	0.058	3.195	0.057	0.924	0.0053
833.5932	1101	3.069	0.092	3.444	0.083	0.891	0.0053
782.565	1101	4.918	0.082	5.266	0.085	0.934	0.0056
795.5181	1101	2.462	0.075	2.793	0.090	0.882	0.0066
725.5527	1101	3.222	0.073	3.500	0.057	0.921	0.0068
761.5843	1101	2.194	0.095	2.580	0.098	0.850	0.0078
738.5448	1102	2.493	0.076	2.766	0.047	0.901	0.0083
811.6096	1101	2.869	0.106	3.277	0.096	0.876	0.0088
758.5656	1101	5.459	0.101	5.870	0.112	0.930	0.0092
785.5933	1101	5.643	0.108	6.049	0.097	0.933	0.0103
458.2405	1101	1.635	0.057	1.880	0.075	0.870	0.0104
757.5626	1101	6.418	0.100	6.815	0.112	0.942	0.0112
541.3139	1101	3.968	0.074	4.278	0.096	0.928	0.0116
786.5967	1101	4.570	0.109	4.973	0.099	0.919	0.012
748.5721	1102	3.811	0.069	4.050	0.055	0.941	0.0137
749.5761	1102	2.699	0.066	2.929	0.053	0.922	0.0156
501.3212	1201	1.903	0.052	2.108	0.066	0.903	0.0176
809.5936	1101	4.792	0.099	5.124	0.084	0.935	0.0194
810.5969	1101	3.785	0.102	4.126	0.086	0.917	0.0199
542.3173	1101	2.183	0.077	2.464	0.091	0.886	0.0228
724.5493	1101	4.493	0.076	4.734	0.059	0.949	0.0232
723.5197	1204	3.966	0.083	3.699	0.091	1.072	0.0362
521.3477	1101	3.545	0.086	3.863	0.130	0.918	0.0374
1098.974	1204	3.016	0.105	2.552	0.219	1.182	0.039
523.3634	1101	3.263	0.100	3.596	0.130	0.907	0.0433
807.5768	1201	6.721	0.033	6.816	0.031	0.986	0.0452
826.7069	1204	2.385	0.134	2.766	0.113	0.862	0.0462
931.7695	1203	2.852	0.090	2.495	0.169	1.143	0.0475
183.0661	1101	2.358	0.139	2.748	0.116	0.858	0.0485
504.3814	1203	1.818	0.065	1.573	0.113	1.156	0.0489

Table 8: Accurate mass features differing between patients with mild cognitive impairment (MMSE 18-23), severe cognitive impairment (MMSE ≤ 17) and normal cognitive ability (MMSE ≥ 28) as measured on the MMSE.

726.5461	1204	3.125	0.058	2.729	0.053	2.981	0.067	1.048	0.916	1.145	0.0002
675.6377	1204	4.131	0.049	3.856	0.082	4.124	0.061	1.002	0.935	1.071	0.0102
801.555*	1202	2.733	0.144	2.602	0.110	3.052	0.077	0.895	0.853	1.050	0.0108
570.3725	1202	3.071	0.067	2.895	0.054	3.130	0.054	0.981	0.925	1.061	0.0116
597.484	1203	2.915	0.146	2.582	0.101	3.046	0.110	0.957	0.848	1.129	0.0138
246.1472	1204	2.437	0.187	3.031	0.161	2.974	0.067	0.819	1.019	0.804	0.0161
565.3394*	1202	7.087	0.132	6.908	0.090	7.304	0.087	0.970	0.946	1.026	0.0171
596.4791	1203	4.125	0.172	3.792	0.112	4.283	0.111	0.963	0.886	1.088	0.0188
246.1465	1202	3.577	0.208	4.046	0.123	4.169	0.104	0.858	0.970	0.884	0.0199
432.3254	1204	2.540	0.059	2.325	0.058	2.495	0.047	1.018	0.932	1.092	0.0201
569.369*	1202	5.009	0.056	4.834	0.050	5.032	0.063	0.995	0.961	1.036	0.0285
661.6233	1204	2.783	0.091	2.448	0.090	2.683	0.079	1.037	0.912	1.137	0.0307
857.6186*	1202	3.923	0.122	3.699	0.104	4.090	0.101	0.959	0.904	1.061	0.0332
804.5718	1202	5.940	0.135	5.776	0.088	6.170	0.112	0.963	0.936	1.028	0.0334
803.5677	1202	7.274	0.174	7.084	0.116	7.570	0.131	0.961	0.936	1.027	0.0359
542.3461	1202	3.898	0.134	3.773	0.071	4.124	0.104	0.945	0.915	1.033	0.037
810.5399	1204	3.152	0.104	2.749	0.088	2.959	0.113	1.065	0.929	1.146	0.0374
728.5627	1204	3.233	0.078	2.954	0.065	3.054	0.071	1.059	0.967	1.094	0.0404
566.3434	1202	5.338	0.100	5.142	0.093	5.460	0.082	0.978	0.942	1.038	0.0417
481.3172	1202	3.940	0.088	3.875	0.069	4.136	0.077	0.953	0.937	1.017	0.0436
724.5257	1204	3.168	0.102	2.875	0.079	2.961	0.055	1.070	0.971	1.102	0.0447
825.5544	1202	2.933	0.173	2.605	0.144	3.160	0.171	0.928	0.824	1.126	0.0474
826.5581	1202	2.005	0.151	1.579	0.156	2.139	0.188	0.937	0.738	1.270	0.0488

Table 9: Grouping of patients into one of 8 groups based on the presence of AD pathology, ADAS score and MMSE score. A score of 1 was given for the presence of AD pathology, high ADAS score (≥ 16), or low MMSE score (≤ 23); a score of 0 was given in the absence of AD pathology, low ADAS score (≤ 15), or high MMSE score (≥ 28).

Patient ID	AD Pathology	ADAS	MMSE
7001	1	1	1
7002	0	1	1
7006	1	0	1
7007	1	1	1
7008	1	0	1
7009	1	0	1
7010	1	0	1
7011	1	0	1
7014	1	0	1
7015	0	1	1
7016	1	1	1
7017	1	1	1
7022	1	1	1
7023	1	1	1
7024	1	0	1
7025	1	0	1
7027	1	0	1
7028	1	1	1
7029	1	1	1
7030	1	0	1
7031	1	0	1
7033	0	1	1
7034	1	0	1
7035	0	1	1
7037	1	1	1
7039	1	0	1
7042	1	0	1
7043	0	1	1
7044	1	1	1
7045	1	0	1
7046	1	1	1
7047	0	1	1
7048	1	0	1
7049	1	0	1
7050	0	1	1
7051	1	0	1
7052	1	0	1
7053	1	0	1
7055	0	1	1
7056	1	1	1
7057	1	0	1
7058	1	0	1
7059	0	1	1
7062	0	0	0
7063	1	1	1
7064	0	0	0
7066	0	0	1
7067	1	1	1
7070	0	0	0

Patient ID	AD Pathology	ADAS	MMSE
7096	1	0	1
7097	1	0	1
7098	0	0	0
7101	0	0	0
7102	1	0	0
7103	0	1	0
7104	0	1	0
7105	0	1	0
7106	1	1	0
7108	0	0	0
7109	0	0	0
7110	0	1	0
7111	0	1	0
7112	1	1	0
7113	1	1	0
7114	1	1	0
7115	0	1	0
7116	1	1	0
7117	0	1	0
7118	0	0	0
7119	0	0	0
7120	0	0	0
7124	1	1	0
7125	1	1	0
7126	0	0	0
7127	0	0	0
7128	0	1	0
7129	1	0	0
7130	0	0	0
7131	0	0	0
7133	0	1	0
7134	0	1	0
7135	0	0	0
7136	1	0	0
7137	0	0	0
7138	0	0	0
7139	0	1	0
7140	1	0	0
7141	1	1	0
7142	1	1	0
7143	1	0	0
7144	1	0	0
7145	0	1	0
7146	0	1	0
7147	0	1	0
7150	1	0	0
7151	1	0	0
7152	0	1	0
7153	0	0	0

7074	0	1	1
7075	1	1	1
7076	0	1	1
7077	1	1	1
7078	1	0	1
7079	0	1	1
7080	0	1	1
7081	1	1	1
7082	1	1	1
7084	1	1	1
7085	1	0	1
7086	0	1	1
7087	0	1	1
7088	1	1	1
7089	1	1	1
7090	1	1	1
7091	0	1	1
7093	1	0	1
7094	0	1	1
7095	0	1	1

7154	1	1	0
7155	1	1	0
7156	0	0	0
7157	1	0	0
7158	1	0	0
7309	1	0	1
7310	1	0	0
7315	1	0	1
7802	0	0	0
7811	0	0	0
7814	1	0	0
7817	1	0	0
7818	0	0	0
7819	0	1	0
7823	1	0	0
7831	0	0	0
7832	1	0	0
7833	1	0	0

Table 10: Accurate mass features differing between patients showing the best discrimination between AD and non-AD pathology ($p<0.05$, log2 transformed).

699.5199	1204	1.985	0.043	2.956	0.067	0.672	1.24E-14
723.5195	1204	3.281	0.070	4.702	0.101	0.698	4.86E-14
723.5194	1202	2.039	0.077	3.191	0.069	0.639	1.59E-13
751.5553	1204	4.290	0.074	5.450	0.093	0.787	5.86E-12
724.5258	1204	2.667	0.062	3.750	0.092	0.711	6.50E-12
751.5529	1202	3.197	0.068	4.076	0.062	0.784	1.03E-11
752.5564	1202	2.126	0.069	3.010	0.061	0.706	1.16E-11
749.5367	1202	3.061	0.062	3.861	0.056	0.793	1.22E-11
752.5581	1204	3.170	0.072	4.292	0.094	0.739	1.52E-11
749.5406	1204	4.177	0.067	5.235	0.095	0.798	4.77E-11
750.5403	1202	2.081	0.074	2.886	0.051	0.721	6.77E-11
750.5438	1204	3.060	0.068	4.067	0.091	0.752	7.99E-11
727.5567	1204	3.305	0.074	4.064	0.053	0.813	4.71E-10
725.5385	1204	2.654	0.094	3.590	0.079	0.739	3.99E-09
728.5629	1204	2.813	0.063	3.345	0.057	0.841	2.54E-07
726.5462	1204	2.753	0.064	3.215	0.062	0.856	7.09E-06
768.5538	1204	3.755	0.060	4.250	0.084	0.884	2.34E-05
747.5244	1204	3.263	0.092	3.999	0.123	0.816	2.45E-05
744.5535	1204	4.147	0.050	4.492	0.053	0.923	3.13E-05
813.5885	1202	2.969	0.051	3.362	0.067	0.883	3.58E-05
743.547	1204	5.096	0.053	5.455	0.059	0.934	0.0001
767.5494	1204	4.835	0.065	5.337	0.092	0.906	0.0001
775.5527	1204	2.993	0.100	3.645	0.105	0.821	0.0001
775.5533	1202	1.993	0.078	2.525	0.088	0.789	0.0001
811.5732	1202	2.590	0.072	3.025	0.071	0.856	0.0001
812.5761	1202	1.599	0.064	2.057	0.084	0.777	0.0001
817.5376	1102	1.992	0.073	2.490	0.081	0.800	0.0001
747.5201	1202	1.829	0.090	2.412	0.110	0.758	0.0002
795.5837	1204	3.418	0.073	3.810	0.062	0.897	0.0002
796.5874	1204	2.468	0.051	2.839	0.074	0.869	0.0002
748.5286	1204	1.812	0.247	2.917	0.126	0.621	0.0003
810.54	1204	2.627	0.088	3.116	0.083	0.843	0.0003

782.5084	1204	3.308	0.060	3.687	0.078	0.897	0.0004
755.486	1204	3.069	0.080	3.477	0.073	0.883	0.0005
758.5092	1204	4.418	0.065	4.707	0.043	0.939	0.0007
771.5813	1204	3.965	0.074	4.288	0.046	0.925	0.0007
304.241	1204	4.716	0.057	5.013	0.062	0.941	0.0011
814.5919	1202	1.988	0.046	2.307	0.077	0.862	0.0011
786.5415	1204	3.671	0.074	3.979	0.050	0.923	0.0013
787.5728	1202	1.743	0.085	2.136	0.075	0.816	0.0013
793.5386	1102	3.337	0.086	3.690	0.057	0.904	0.0015
783.5147	1204	3.166	0.071	3.512	0.077	0.901	0.0022
828.5736	1102	2.906	0.080	3.292	0.087	0.883	0.0023
828.5743	1202	5.132	0.073	5.485	0.081	0.936	0.0024
743.5468	1203	1.812	0.118	2.235	0.061	0.811	0.0029
784.5235	1204	3.196	0.081	3.490	0.045	0.916	0.003
760.5215	1204	3.910	0.072	4.200	0.058	0.931	0.0032
787.5464	1204	2.617	0.090	2.937	0.050	0.891	0.0037
827.57	1102	3.933	0.078	4.313	0.096	0.912	0.0039
305.2438	1204	2.384	0.064	2.648	0.058	0.900	0.0041
794.5421	1102	2.275	0.090	2.601	0.058	0.875	0.0041
827.5701	1202	6.193	0.081	6.559	0.090	0.944	0.0046
590.343	1202	3.939	0.055	4.216	0.074	0.934	0.0047
589.3404	1202	5.769	0.061	6.076	0.085	0.950	0.0057
789.5893	1202	1.673	0.064	1.967	0.077	0.851	0.0057
670.5689	1204	3.048	0.095	3.510	0.127	0.868	0.006
855.6016	1102	3.325	0.079	3.646	0.079	0.912	0.0064
759.5162	1204	4.510	0.086	4.811	0.060	0.937	0.0065
671.5722	1204	2.157	0.123	2.635	0.111	0.819	0.0066
769.5654	1204	3.829	0.065	4.086	0.063	0.937	0.0069
856.6063	1202	4.446	0.076	4.777	0.087	0.931	0.007
409.0208	1202	2.638	0.057	2.899	0.073	0.910	0.0072
774.0313	1204	2.317	0.202	1.370	0.268	1.691	0.0076
804.5713	1102	3.964	0.086	4.276	0.071	0.927	0.008
855.6025	1202	5.437	0.074	5.749	0.085	0.946	0.0083
530.382	1204	2.991	0.089	2.097	0.309	1.426	0.0085
626.5278	1203	3.676	0.068	3.915	0.053	0.939	0.0087
731.4914	1204	5.281	0.086	5.589	0.073	0.945	0.0093
732.4937	1204	4.050	0.083	4.348	0.070	0.931	0.0093
517.3722	1204	2.189	0.112	1.465	0.241	1.494	0.0096
741.5307	1204	2.754	0.086	3.117	0.105	0.884	0.0109
803.5681	1102	5.187	0.087	5.491	0.073	0.945	0.0111
746.5714	1204	2.962	0.065	3.228	0.076	0.918	0.0113
627.5304	1203	2.544	0.068	2.783	0.058	0.914	0.0118
544.397	1204	3.249	0.120	2.323	0.341	1.399	0.0145
745.5656	1204	3.812	0.071	4.091	0.083	0.932	0.0148
739.5142	1204	2.576	0.105	3.009	0.137	0.856	0.0162
570.3725	1202	2.879	0.050	3.071	0.057	0.938	0.0164
686.4877	1204	2.527	0.068	2.757	0.064	0.917	0.0179
517.3136	1201	2.907	0.104	2.575	0.088	1.129	0.0193
744.4956	1204	3.741	0.073	3.988	0.070	0.938	0.0202
529.3167	1202	2.929	0.057	3.199	0.095	0.916	0.0203
821.5713	1102	2.825	0.089	3.091	0.065	0.914	0.0207
819.5641	1202	2.632	0.117	3.063	0.136	0.859	0.0209
667.5474	1204	3.336	0.118	2.882	0.150	1.158	0.0222
886.5582	1102	2.820	0.064	3.038	0.067	0.928	0.0232
796.529	1204	2.815	0.070	3.063	0.078	0.919	0.0234
306.2569	1204	2.848	0.083	3.103	0.074	0.918	0.0256
581.3344	1202	1.676	0.132	2.082	0.115	0.805	0.0261
817.584	1202	2.181	0.064	2.383	0.060	0.915	0.0261
685.5538	1204	1.862	0.132	2.222	0.083	0.838	0.0263
555.3101	1102	1.640	0.094	1.944	0.093	0.844	0.0277
666.5455	1204	4.533	0.128	4.059	0.168	1.117	0.0301
820.5677	1202	1.550	0.163	2.037	0.145	0.761	0.031
773.5368	1202	1.455	0.109	1.808	0.114	0.805	0.0324
541.3432	1102	3.148	0.073	3.377	0.073	0.932	0.0328
767.547	1202	2.917	0.095	3.237	0.111	0.901	0.0345

569.369	1202	4.824	0.048	4.987	0.057	0.967	0.0352
871.5935	1202	1.702	0.068	2.049	0.145	0.830	0.0362
1226.0968	1203	3.089	0.116	2.709	0.130	1.140	0.0365
793.5679	1204	3.022	0.067	3.237	0.075	0.934	0.0407
411.3211	1202	2.817	0.068	2.988	0.042	0.943	0.0408
684.5491	1204	2.304	0.087	2.600	0.110	0.886	0.041
768.5504	1202	1.786	0.141	2.160	0.106	0.827	0.041
743.5469	1202	2.894	0.076	3.173	0.109	0.912	0.0417
482.3215	1202	1.866	0.054	2.056	0.072	0.908	0.0424
574.4637	1202	1.059	0.201	1.653	0.204	0.640	0.0444
509.3493	1202	2.290	0.057	2.490	0.079	0.919	0.0446
772.586	1204	3.167	0.062	3.330	0.050	0.951	0.0458
383.3283	1204	1.280	0.142	1.662	0.119	0.770	0.0462
664.5322	1204	4.643	0.145	4.176	0.173	1.112	0.0465
312.2312	1204	2.771	0.059	2.583	0.070	1.073	0.0467
481.3172	1202	3.803	0.057	3.982	0.065	0.955	0.0468
765.5335	1204	3.065	0.107	3.418	0.137	0.897	0.0491
847.5953	1202	2.162	0.114	2.518	0.134	0.858	0.0492
624.5131	1203	3.900	0.068	4.084	0.061	0.955	0.0497

Table 11: Accurate mass features differing between patients showing the best discrimination between high ADAS score and low ADAS score ($p<0.05$, log2 transformed).

541.3435	1102	3.007	0.047	3.741	0.083	0.804	5.76E-09
569.3685	1102	1.862	0.065	2.686	0.070	0.693	9.27E-09
804.5713	1102	3.915	0.047	4.494	0.080	0.871	3.59E-07
803.5681	1102	5.145	0.046	5.720	0.084	0.899	5.31E-07
837.5027	1101	3.257	0.058	3.866	0.070	0.842	5.33E-07
807.5758	1101	5.318	0.076	6.045	0.065	0.880	5.92E-07
808.5792	1101	4.265	0.076	4.992	0.069	0.854	7.70E-07
832.6024	1102	3.129	0.065	3.740	0.063	0.837	1.34E-06
779.5444	1101	6.061	0.061	6.691	0.082	0.906	1.39E-06
780.5474	1101	5.073	0.063	5.714	0.083	0.888	1.42E-06
831.5995	1102	4.245	0.068	4.850	0.061	0.875	2.37E-06
546.3486	1101	1.593	0.073	2.250	0.084	0.708	5.48E-06
871.5529	1102	2.778	0.050	3.307	0.090	0.840	6.59E-06
567.3545	1102	2.637	0.079	3.305	0.081	0.798	8.54E-06
545.3453	1101	3.142	0.085	3.836	0.077	0.819	9.04E-06
805.5604	1101	5.013	0.074	5.685	0.099	0.882	9.51E-06
794.5422	1102	2.287	0.056	2.795	0.079	0.818	1.22E-05
886.5584	1102	2.853	0.053	3.354	0.081	0.851	1.32E-05
827.57	1102	3.893	0.063	4.438	0.079	0.877	1.41E-05
828.5737	1102	2.920	0.061	3.425	0.069	0.852	1.56E-05
805.5831	1102	3.821	0.058	4.385	0.100	0.871	1.61E-05
829.5856	1102	3.781	0.076	4.393	0.077	0.861	1.68E-05
915.5191	1101	2.144	0.053	2.621	0.078	0.818	1.99E-05
793.5387	1102	3.352	0.056	3.854	0.086	0.870	2.76E-05
806.5637	1101	4.001	0.078	4.667	0.107	0.857	2.85E-05
821.5713	1102	2.834	0.067	3.309	0.046	0.856	3.30E-05
565.3396	1102	3.216	0.096	3.992	0.121	0.806	3.57E-05
555.3098	1102	1.608	0.081	2.242	0.094	0.717	4.04E-05
757.4989	1101	3.119	0.086	3.849	0.148	0.810	0.0001
832.5792	1101	3.024	0.092	3.662	0.085	0.826	0.0001
855.6015	1102	3.274	0.068	3.795	0.093	0.862	0.0001

458.2404	1101	1.430	0.076	1.984	0.109	0.721	0.0002
783.5671	1101	3.275	0.105	4.025	0.141	0.813	0.0002
803.5445	1101	4.778	0.095	5.397	0.079	0.885	0.0002
804.5475	1101	3.844	0.095	4.459	0.075	0.862	0.0002
831.576	1101	3.924	0.100	4.575	0.095	0.858	0.0002
518.3174	1101	3.093	0.072	3.609	0.101	0.857	0.0003
781.5616	1101	5.679	0.096	6.315	0.110	0.899	0.0003
517.314	1101	5.122	0.077	5.642	0.104	0.908	0.0004
782.5649	1101	4.649	0.100	5.296	0.118	0.878	0.0004
785.5933	1101	5.333	0.121	6.107	0.132	0.873	0.0004
786.5967	1101	4.256	0.124	5.039	0.133	0.844	0.0004
833.5932	1101	2.746	0.113	3.494	0.134	0.786	0.0004
853.5855	1102	2.333	0.088	2.875	0.080	0.811	0.0004
755.5468	1101	1.879	0.101	2.593	0.157	0.725	0.0005
811.6096	1101	2.512	0.140	3.375	0.152	0.744	0.0006
809.5936	1101	4.448	0.126	5.177	0.119	0.859	0.0007
761.5843	1101	1.993	0.094	2.654	0.160	0.751	0.0008
810.5969	1101	3.451	0.128	4.183	0.115	0.825	0.0008
847.5316	1101	2.543	0.093	3.082	0.092	0.825	0.0008
757.5626	1101	6.144	0.104	6.825	0.155	0.900	0.0009
758.5656	1101	5.185	0.107	5.885	0.158	0.881	0.0009
543.3296	1101	3.486	0.084	4.025	0.125	0.866	0.001
759.5779	1101	5.080	0.100	5.759	0.169	0.882	0.0011
760.5811	1101	3.952	0.102	4.645	0.177	0.851	0.0012
795.5551	1102	2.493	0.075	2.937	0.092	0.849	0.0012
829.5604	1101	3.200	0.098	3.759	0.106	0.851	0.0012
523.3635	1101	2.882	0.117	3.595	0.163	0.801	0.0014
575.2728	1101	2.204	0.078	2.673	0.104	0.824	0.0014
784.581	1101	3.921	0.129	4.667	0.171	0.840	0.0018
819.5553	1102	2.210	0.089	2.665	0.085	0.829	0.0025
817.5378	1102	2.089	0.088	2.491	0.068	0.839	0.0047
731.5463	1101	1.373	0.174	2.218	0.197	0.619	0.0052
795.5183	1101	2.270	0.081	2.725	0.140	0.833	0.0058
722.5334	1101	2.190	0.085	2.598	0.111	0.843	0.0083
760.5217	1204	4.084	0.063	4.331	0.042	0.943	0.0118
833.757	1203	2.531	0.161	3.274	0.231	0.773	0.0132
429.3749	1204	2.703	0.080	3.137	0.167	0.861	0.0143
722.4789	1201	1.895	0.093	2.247	0.064	0.843	0.0145
1228.1111	1203	2.699	0.127	3.291	0.194	0.820	0.0146
541.3139	1101	3.909	0.116	4.412	0.152	0.886	0.0158
860.7753	1203	4.152	0.110	4.647	0.161	0.893	0.016
703.5709	1101	2.858	0.095	3.216	0.072	0.888	0.0163
579.5325	1203	3.776	0.177	4.492	0.191	0.841	0.0166
858.686	1202	3.030	0.064	2.781	0.057	1.090	0.0166
831.7408	1203	3.708	0.137	4.286	0.176	0.865	0.0175
484.3041	1203	2.257	0.120	1.475	0.348	1.530	0.0176
580.5352	1203	1.310	0.222	2.135	0.172	0.614	0.0181
830.7362	1203	4.568	0.137	5.156	0.187	0.886	0.0182
495.332	1101	4.769	0.114	5.305	0.195	0.899	0.0186
183.0662	1101	1.868	0.215	2.671	0.183	0.699	0.0191
702.5677	1101	4.033	0.104	4.409	0.074	0.915	0.0194
887.8001	1203	2.884	0.137	3.396	0.122	0.849	0.0199
886.7916	1203	4.153	0.131	4.631	0.120	0.897	0.0232
759.5164	1204	4.697	0.077	4.975	0.066	0.944	0.0236
725.5527	1101	3.123	0.108	3.499	0.079	0.892	0.0244
832.7522	1203	3.418	0.170	4.119	0.245	0.830	0.0255
828.7207	1203	5.336	0.130	5.867	0.187	0.909	0.0263
496.3355	1101	2.972	0.113	3.473	0.195	0.856	0.0264
604.5432	1203	6.338	0.149	6.863	0.137	0.924	0.0283
864.738	1204	4.641	0.166	5.295	0.232	0.876	0.0298
680.5623	1204	3.590	0.125	4.126	0.214	0.870	0.0305
627.5201	1204	3.756	0.157	4.380	0.227	0.858	0.0315
1019.3838	1102	3.116	0.042	2.950	0.063	1.056	0.0323
825.6927	1203	1.408	0.212	2.138	0.204	0.658	0.0331
863.7336	1204	5.382	0.170	6.035	0.237	0.892	0.0338

521.3477	1101	3.368	0.126	3.890	0.213	0.866	0.0349
731.4916	1204	5.513	0.065	5.746	0.076	0.959	0.0351
542.3173	1101	2.116	0.120	2.565	0.157	0.825	0.0352
829.7242	1204	2.575	0.161	3.185	0.221	0.809	0.0356
835.6998	1204	2.285	0.247	3.153	0.271	0.725	0.0356
276.2095	1204	2.479	0.091	2.885	0.179	0.859	0.0358
653.536	1204	4.096	0.154	4.679	0.218	0.875	0.0368
523.4678	1203	2.747	0.238	3.609	0.295	0.761	0.0372
829.7246	1203	4.606	0.121	5.065	0.173	0.909	0.0376
921.8142	1204	2.618	0.338	3.654	0.184	0.716	0.039
605.5456	1203	4.920	0.154	5.420	0.131	0.908	0.0392
549.4844	1203	5.315	0.129	5.753	0.137	0.924	0.0398
732.4939	1204	4.258	0.065	4.480	0.069	0.950	0.04
365.3159	1203	1.907	0.098	1.449	0.217	1.316	0.0402
867.7581	1204	2.358	0.280	3.299	0.284	0.715	0.0402
738.5445	1102	2.458	0.122	2.825	0.059	0.870	0.0409
859.7695	1203	5.769	0.102	6.185	0.179	0.933	0.0414
625.5075	1204	3.271	0.138	3.811	0.224	0.858	0.0422
512.3356	1203	2.602	0.095	2.151	0.223	1.210	0.0432
842.7387	1203	2.626	0.103	2.998	0.139	0.876	0.0432
552.5021	1203	2.742	0.161	3.315	0.213	0.827	0.0444
724.5493	1101	4.410	0.105	4.736	0.081	0.931	0.0447
626.5108	1204	2.117	0.159	2.677	0.209	0.791	0.0454
928.7505	1203	2.869	0.168	2.238	0.265	1.282	0.0473
894.781	1204	3.884	0.196	4.542	0.228	0.855	0.048
866.7533	1204	3.905	0.219	4.667	0.292	0.837	0.0492
278.2255	1204	4.693	0.070	5.006	0.156	0.937	0.0494
865.7486	1204	4.644	0.223	5.419	0.296	0.857	0.0497

Table 12: Accurate mass features differing between patients showing the best discrimination between high MMSE score and low MMSE score ($p<0.05$, log2 transformed).

505.3229	1202	3.585	0.045	4.514	0.053	0.794	3.90E-15
857.6186	1202	3.339	0.058	4.298	0.053	0.777	5.05E-14
803.5678	1202	6.747	0.056	7.962	0.082	0.847	5.19E-14
858.6211	1202	2.300	0.058	3.221	0.059	0.714	6.73E-13
566.3434	1202	4.856	0.055	5.682	0.055	0.855	1.90E-12
801.555	1202	2.220	0.057	3.128	0.064	0.710	2.89E-12
832.6036	1202	4.692	0.057	5.569	0.061	0.842	3.64E-12
804.5718	1202	5.516	0.047	6.475	0.080	0.852	4.63E-12
565.3393	1202	6.629	0.054	7.462	0.062	0.888	9.30E-12
506.3214	1202	2.237	0.051	2.908	0.044	0.769	1.26E-11
743.5467	1202	2.635	0.077	3.621	0.066	0.728	2.57E-11
831.6	1202	5.793	0.055	6.774	0.087	0.855	4.69E-11
744.55	1202	1.608	0.082	2.504	0.056	0.642	1.72E-10
570.3724	1202	2.702	0.042	3.289	0.052	0.821	4.09E-10
829.5859	1202	5.572	0.065	6.476	0.085	0.860	8.42E-10
830.5894	1202	4.477	0.061	5.311	0.078	0.843	1.01E-09
509.3494	1202	2.113	0.042	2.685	0.059	0.787	4.17E-09
542.3461	1202	3.562	0.047	4.292	0.082	0.830	6.29E-09
711.2577	1202	1.891	0.072	2.585	0.057	0.731	1.12E-08
709.2595	1202	1.864	0.079	2.546	0.047	0.732	1.49E-08
481.3172	1202	3.642	0.055	4.233	0.060	0.860	2.74E-08
569.369	1202	4.664	0.046	5.203	0.063	0.897	7.82E-08
805.5839	1202	5.216	0.051	5.867	0.082	0.889	1.16E-07

806.5873	1202	4.024	0.052	4.658	0.078	0.864	1.16E-07
856.6061	1202	4.179	0.069	5.099	0.121	0.819	1.81E-07
743.5469	1204	5.166	0.051	5.635	0.049	0.917	1.96E-07
793.5386	1102	2.966	0.065	3.468	0.043	0.855	2.63E-07
855.6023	1202	5.166	0.065	6.090	0.128	0.848	2.81E-07
482.3215	1202	1.742	0.057	2.291	0.066	0.761	4.15E-07
541.3433	1202	5.318	0.067	6.197	0.123	0.858	4.56E-07
744.5535	1204	4.203	0.048	4.631	0.048	0.908	4.68E-07
807.5899	1202	2.124	0.071	2.730	0.070	0.778	8.81E-07
827.5701	1202	5.937	0.077	6.931	0.147	0.857	1.20E-06
847.5954	1202	2.030	0.095	2.867	0.104	0.708	1.37E-06
828.5742	1202	4.908	0.074	5.818	0.137	0.844	1.67E-06
787.5464	1204	2.601	0.059	3.069	0.056	0.847	2.17E-06
591.3542	1202	3.749	0.081	4.387	0.078	0.855	3.05E-06
794.5422	1102	1.910	0.065	2.338	0.040	0.817	3.76E-06
804.5713	1102	3.619	0.065	4.092	0.056	0.885	4.94E-06
803.568	1102	4.829	0.068	5.317	0.057	0.908	5.22E-06
758.5094	1204	4.437	0.052	4.813	0.046	0.922	5.89E-06
592.3571	1202	2.013	0.084	2.634	0.079	0.764	7.14E-06
760.5216	1204	3.930	0.056	4.313	0.045	0.911	8.02E-06
759.5165	1204	4.558	0.067	5.001	0.050	0.911	9.01E-06
767.5469	1202	2.700	0.119	3.526	0.101	0.766	9.49E-06
786.5416	1204	3.664	0.051	4.093	0.064	0.895	1.12E-05
784.5239	1204	3.102	0.069	3.575	0.060	0.868	1.23E-05
821.5711	1102	2.415	0.067	2.863	0.055	0.843	1.25E-05
819.5641	1202	2.451	0.109	3.287	0.126	0.746	2.03E-05
777.5531	1202	1.473	0.133	2.257	0.083	0.653	2.21E-05
853.5862	1202	4.524	0.069	5.222	0.126	0.866	3.29E-05
507.3316	1202	2.653	0.056	3.061	0.064	0.867	3.70E-05
731.4917	1204	5.356	0.062	5.744	0.053	0.932	4.18E-05
831.5998	1102	3.958	0.081	4.429	0.057	0.894	4.26E-05
854.5902	1202	3.521	0.075	4.231	0.130	0.832	4.70E-05
630.5586	1203	2.845	0.054	3.242	0.069	0.877	0.0001
732.494	1204	4.127	0.062	4.492	0.050	0.919	0.0001
741.5307	1204	2.661	0.099	3.337	0.105	0.797	0.0001
771.5815	1204	4.036	0.064	4.423	0.055	0.913	0.0001
819.5552	1102	1.733	0.081	2.149	0.045	0.806	0.0001
832.6027	1102	2.864	0.081	3.318	0.056	0.863	0.0001
871.5527	1102	2.467	0.073	2.914	0.066	0.846	0.0001
871.5935	1202	1.550	0.108	2.224	0.110	0.697	0.0001
886.7917	1203	3.826	0.095	4.459	0.099	0.858	0.0001
910.7968	1203	3.257	0.083	3.757	0.079	0.867	0.0001
529.3166	1202	2.771	0.071	3.332	0.112	0.832	0.0002
589.3404	1202	5.578	0.072	6.318	0.155	0.883	0.0002
768.5503	1202	1.668	0.144	2.412	0.103	0.691	0.0002
884.7801	1203	6.076	0.082	6.639	0.104	0.915	0.0002
568.3574	1202	3.760	0.055	4.144	0.074	0.907	0.0003
685.2601	1202	1.483	0.102	2.052	0.093	0.723	0.0003
765.5313	1202	1.447	0.148	2.219	0.120	0.652	0.0003
772.5863	1204	3.177	0.051	3.466	0.050	0.917	0.0003
829.5856	1102	3.407	0.088	3.862	0.064	0.882	0.0003
911.8032	1203	2.388	0.077	2.794	0.064	0.855	0.0003
786.5967	1101	4.302	0.096	4.955	0.132	0.868	0.0004
885.7854	1203	5.116	0.080	5.615	0.095	0.911	0.0004
174.1409	1203	1.904	0.122	2.872	0.212	0.663	0.0005
590.3431	1202	3.790	0.071	4.415	0.142	0.858	0.0005
604.5432	1203	6.172	0.114	6.803	0.113	0.907	0.0005
757.5626	1101	6.170	0.099	6.804	0.129	0.907	0.0005
879.5999	1202	2.601	0.104	3.235	0.124	0.804	0.0005
605.5456	1203	4.762	0.115	5.393	0.118	0.883	0.0006
757.5016	1204	3.549	0.094	3.977	0.057	0.893	0.0006
581.3345	1202	1.572	0.124	2.253	0.131	0.698	0.0007
628.5421	1203	3.231	0.070	3.606	0.070	0.896	0.0007
723.5195	1202	2.196	0.085	2.730	0.110	0.805	0.0007
749.5365	1202	3.146	0.084	3.579	0.078	0.879	0.0007

785.5933	1101	5.382	0.098	6.025	0.137	0.893	0.0007
887.7999	1203	2.493	0.171	3.227	0.087	0.773	0.0007
886.8012	1204	3.209	0.117	3.782	0.096	0.849	0.0008
186.1408	1203	1.539	0.100	2.279	0.172	0.675	0.0009
200.1564	1203	2.724	0.075	3.280	0.129	0.830	0.0009
769.5655	1204	3.833	0.075	4.197	0.063	0.913	0.0009
817.5838	1202	2.041	0.086	2.452	0.070	0.833	0.0009
715.5169	1204	2.238	0.200	3.073	0.108	0.728	0.001
699.52	1204	2.223	0.082	2.690	0.099	0.826	0.0011
758.5656	1101	5.231	0.101	5.844	0.134	0.895	0.0011
795.5182	1101	2.324	0.087	2.800	0.098	0.830	0.0011
772.528	1204	3.202	0.075	3.531	0.053	0.907	0.0012
739.5164	1202	1.109	0.170	1.859	0.124	0.597	0.0014
779.5444	1101	6.186	0.098	6.639	0.083	0.932	0.0014
244.2187	1203	2.645	0.062	3.037	0.093	0.871	0.0015
508.3356	1202	0.969	0.088	1.386	0.078	0.700	0.0015
811.6096	1101	2.569	0.101	3.204	0.152	0.802	0.0017
882.766	1203	7.238	0.092	7.755	0.117	0.933	0.0017
744.4954	1204	3.832	0.067	4.118	0.049	0.930	0.0018
884.7877	1204	4.658	0.101	5.127	0.092	0.909	0.0018
262.2293	1203	2.639	0.059	2.992	0.084	0.882	0.002
784.5811	1101	3.896	0.100	4.493	0.143	0.867	0.002
817.5375	1102	1.715	0.076	2.148	0.101	0.798	0.002
723.5197	1204	3.643	0.087	4.211	0.143	0.865	0.0021
810.5401	1204	2.693	0.070	3.119	0.104	0.863	0.0021
880.6035	1202	1.837	0.084	2.351	0.126	0.782	0.0021
807.5757	1101	5.434	0.097	5.912	0.102	0.919	0.0022
883.7705	1203	6.396	0.085	6.870	0.111	0.931	0.0022
749.576	1102	2.516	0.057	2.174	0.084	1.157	0.0023
852.5738	1202	3.365	0.120	3.968	0.135	0.848	0.0025
752.5564	1202	2.277	0.101	2.730	0.092	0.834	0.0027
783.5672	1101	3.273	0.106	3.856	0.141	0.849	0.0027
808.5792	1101	4.393	0.099	4.868	0.104	0.902	0.0027
755.5468	1101	1.885	0.107	2.412	0.121	0.782	0.0031
780.5475	1101	5.202	0.096	5.629	0.089	0.924	0.0031
826.707	1204	2.266	0.118	2.743	0.086	0.826	0.0031
851.5698	1202	4.297	0.118	4.898	0.142	0.877	0.0031
631.5619	1203	1.475	0.132	1.956	0.066	0.754	0.0033
755.4861	1204	3.019	0.074	3.424	0.102	0.882	0.0034
188.1566	1203	2.272	0.134	2.926	0.154	0.777	0.0035
883.7765	1204	4.148	0.099	4.589	0.095	0.904	0.0035
726.5459	1204	2.790	0.064	3.090	0.069	0.903	0.0038
750.5403	1202	2.185	0.089	2.549	0.073	0.857	0.0038
627.5302	1203	2.497	0.080	2.845	0.075	0.878	0.0039
885.7922	1204	3.954	0.103	4.382	0.089	0.902	0.0039
675.6357	1203	1.815	0.210	0.815	0.240	2.228	0.0042
751.5529	1202	3.374	0.098	3.787	0.090	0.891	0.0043
882.7723	1204	4.984	0.102	5.422	0.096	0.919	0.0043
530.3213	1202	1.209	0.089	1.698	0.129	0.712	0.0044
380.3096	1204	1.432	0.107	1.867	0.092	0.767	0.0046
783.5148	1204	3.121	0.064	3.517	0.111	0.887	0.0048
202.172	1203	3.048	0.112	3.631	0.153	0.839	0.0049
748.5721	1102	3.632	0.058	3.325	0.082	1.092	0.0049
603.5317	1203	7.585	0.077	7.883	0.060	0.962	0.005
243.0718	1101	4.430	0.144	3.210	0.373	1.380	0.0052
582.2473	1201	3.377	0.132	2.673	0.191	1.264	0.0055
739.5141	1204	2.498	0.195	3.173	0.109	0.787	0.0056
879.7454	1204	3.291	0.124	3.749	0.088	0.878	0.0057
494.4342	1203	1.382	0.353	2.777	0.303	0.497	0.0059
782.5086	1204	3.266	0.073	3.662	0.110	0.892	0.0059
855.6016	1102	2.984	0.080	3.363	0.097	0.887	0.006
921.8153	1204	2.175	0.312	3.187	0.131	0.682	0.006
724.5256	1204	2.877	0.077	3.324	0.128	0.866	0.0061
183.0661	1101	2.155	0.151	2.748	0.130	0.784	0.0065
522.4634	1203	4.325	0.238	5.237	0.198	0.826	0.0067

853.7296	1204	3.607	0.109	4.012	0.083	0.899	0.0068
216.1877	1203	2.796	0.092	3.282	0.140	0.852	0.0076
779.5442	1201	7.005	0.079	7.301	0.065	0.959	0.0076
777.5288	1201	2.657	0.093	3.009	0.079	0.883	0.0077
523.468	1203	2.895	0.227	3.731	0.183	0.776	0.0083
569.3687	1102	1.734	0.098	2.075	0.067	0.836	0.0085
775.5535	1202	2.112	0.083	2.438	0.079	0.866	0.0087
632.5035	1204	4.858	0.122	5.325	0.110	0.912	0.0088
805.5604	1101	5.112	0.099	5.504	0.097	0.929	0.0089
313.269	1203	1.592	0.175	2.180	0.112	0.730	0.009
743.5464	1203	1.703	0.150	2.156	0.056	0.790	0.009
768.5539	1204	3.881	0.077	4.240	0.100	0.915	0.009
686.488	1204	2.671	0.054	2.872	0.047	0.930	0.0092
886.5582	1102	2.503	0.058	2.781	0.079	0.900	0.0092
602.5282	1203	8.833	0.081	9.116	0.059	0.969	0.0093
558.4667	1202	1.932	0.201	2.652	0.159	0.728	0.0095
809.5936	1101	4.523	0.112	5.054	0.155	0.895	0.0101
881.7616	1204	4.015	0.111	4.427	0.099	0.907	0.0101
833.7558	1204	1.919	0.311	2.863	0.138	0.670	0.0103
864.7596	1203	2.184	0.067	2.468	0.078	0.885	0.0103
613.3405	1202	3.422	0.124	3.963	0.150	0.863	0.0104
626.5277	1203	3.649	0.073	3.946	0.079	0.925	0.0105
629.5449	1203	2.015	0.088	2.370	0.093	0.850	0.0106
767.5494	1204	4.975	0.083	5.343	0.104	0.931	0.0106
517.3722	1204	2.176	0.149	1.408	0.235	1.545	0.0107
773.5347	1204	3.151	0.056	3.426	0.082	0.920	0.0108
806.5638	1101	4.113	0.100	4.498	0.097	0.914	0.0109
204.1876	1203	2.205	0.099	2.682	0.143	0.822	0.0113
837.5027	1101	3.439	0.075	3.734	0.078	0.921	0.0116
595.4932	1202	1.393	0.217	2.170	0.185	0.642	0.0117
915.5192	1101	2.301	0.087	2.588	0.060	0.889	0.0117
257.8105	1101	3.636	0.084	2.677	0.344	1.358	0.0121
541.343	1102	2.816	0.087	3.105	0.062	0.907	0.0121
745.5656	1204	3.838	0.051	4.054	0.062	0.947	0.0125
749.5408	1204	4.465	0.071	4.865	0.130	0.918	0.0126
725.5385	1204	2.932	0.068	3.293	0.115	0.890	0.0128
757.4993	1101	3.262	0.095	3.716	0.140	0.878	0.0128
852.725	1204	3.774	0.105	4.122	0.076	0.916	0.0128
780.5474	1201	5.941	0.081	6.223	0.067	0.955	0.0129
880.7516	1203	7.205	0.107	7.651	0.127	0.942	0.0129
881.7558	1203	6.471	0.103	6.883	0.116	0.940	0.0132
338.2821	1203	4.474	0.095	4.792	0.073	0.934	0.0135
827.5699	1102	3.597	0.089	3.987	0.116	0.902	0.0136
880.7566	1204	4.483	0.117	4.882	0.094	0.918	0.0138
572.4468	1204	1.726	0.131	2.213	0.129	0.780	0.014
336.2662	1203	3.181	0.097	3.518	0.083	0.904	0.0141
615.3539	1202	2.263	0.089	2.598	0.092	0.871	0.0146
544.4479	1203	1.928	0.085	2.273	0.100	0.848	0.0148
579.5325	1203	3.737	0.170	4.362	0.166	0.857	0.0148
520.45	1203	3.613	0.209	4.378	0.204	0.825	0.0149
633.5078	1204	3.891	0.128	4.347	0.118	0.895	0.0149
519.3321	1101	3.416	0.099	3.875	0.146	0.881	0.0151
547.6031	1101	2.454	0.114	1.714	0.259	1.432	0.0152
727.5569	1204	3.548	0.077	3.866	0.093	0.918	0.0152
339.285	1203	2.242	0.107	2.601	0.087	0.862	0.0154
746.5719	1204	3.004	0.054	3.196	0.050	0.940	0.0154
828.5736	1102	2.605	0.083	2.966	0.111	0.878	0.0154
798.6742	1203	1.685	0.154	2.329	0.192	0.723	0.0155
860.7753	1203	4.054	0.129	4.507	0.117	0.899	0.0156
521.4522	1203	1.837	0.271	2.786	0.244	0.660	0.0158
594.4878	1202	2.699	0.253	3.523	0.191	0.766	0.0158
781.5617	1101	5.737	0.110	6.187	0.134	0.927	0.0158
810.5969	1101	3.498	0.121	4.023	0.161	0.870	0.0158
631.4902	1204	2.690	0.150	3.208	0.132	0.839	0.0163
518.4346	1203	1.198	0.238	2.121	0.267	0.565	0.0164

244.0559	1101	3.875	0.099	3.359	0.174	1.153	0.0165
751.5556	1204	4.690	0.092	5.091	0.126	0.921	0.0165
825.5544	1202	2.647	0.146	3.202	0.159	0.827	0.017
520.3353	1101	1.661	0.103	2.114	0.144	0.786	0.0176
858.7632	1203	6.769	0.125	7.244	0.137	0.935	0.0178
861.7801	1203	2.123	0.171	2.681	0.138	0.792	0.0179
646.4837	1204	1.688	0.192	2.245	0.108	0.752	0.0184
489.6451	1101	2.555	0.109	1.822	0.269	1.402	0.0186
255.8135	1101	4.518	0.090	3.502	0.393	1.290	0.019
260.2135	1203	1.422	0.129	1.878	0.128	0.757	0.0193
833.5931	1101	2.952	0.114	3.347	0.109	0.882	0.0197
831.5759	1101	4.038	0.114	4.451	0.121	0.907	0.0201
544.3971	1204	3.313	0.158	2.377	0.342	1.394	0.0203
294.2207	1204	5.248	0.117	5.652	0.112	0.929	0.0205
724.5493	1101	4.674	0.050	4.395	0.101	1.063	0.0205
663.487	1204	1.733	0.223	2.369	0.128	0.731	0.0207
860.7753	1204	3.460	0.170	3.955	0.104	0.875	0.0207
246.1465	1202	3.707	0.141	4.188	0.134	0.885	0.0209
606.4869	1204	4.562	0.137	5.023	0.126	0.908	0.0215
576.5097	1203	9.304	0.133	9.756	0.127	0.954	0.0216
311.775	1101	2.594	0.152	1.849	0.264	1.403	0.022
566.413	1204	2.026	0.190	2.553	0.100	0.794	0.0221
577.5136	1203	7.959	0.125	8.392	0.124	0.948	0.0224
835.7001	1204	2.246	0.249	3.007	0.187	0.747	0.0226
665.501	1204	2.974	0.116	3.370	0.114	0.883	0.0227
675.6377	1204	3.825	0.077	4.086	0.075	0.936	0.023
600.5127	1203	8.597	0.082	8.866	0.075	0.970	0.0232
752.5583	1204	3.555	0.096	3.939	0.126	0.902	0.0241
161.1053	1101	4.011	0.148	2.977	0.402	1.347	0.0242
616.4673	1201	1.329	0.218	2.031	0.193	0.654	0.0245
253.8163	1101	4.184	0.090	3.283	0.364	1.274	0.0248
878.74	1204	3.665	0.118	4.001	0.074	0.916	0.025
580.535	1203	1.221	0.219	1.936	0.203	0.631	0.0252
859.7694	1203	5.668	0.122	6.076	0.119	0.933	0.0252
538.4224	1202	1.087	0.172	1.689	0.184	0.643	0.0256
804.723	1203	1.425	0.264	2.238	0.214	0.637	0.0256
833.7571	1203	2.599	0.192	3.201	0.165	0.812	0.0261
530.382	1204	2.988	0.204	2.114	0.305	1.413	0.0262
908.7832	1203	5.011	0.090	5.309	0.088	0.944	0.027
653.5361	1204	3.973	0.129	4.367	0.107	0.910	0.0273
559.47	1202	0.812	0.174	1.388	0.171	0.585	0.0274
748.5735	1202	3.935	0.071	3.726	0.054	1.056	0.0279
803.5445	1101	4.899	0.121	5.305	0.124	0.924	0.028
832.7521	1203	3.434	0.205	4.059	0.169	0.846	0.0283
320.2357	1204	1.225	0.148	1.609	0.071	0.761	0.0284
728.5626	1204	2.941	0.066	3.161	0.067	0.930	0.0284
795.555	1102	2.053	0.080	2.292	0.062	0.896	0.0285
838.7232	1204	2.011	0.253	2.753	0.191	0.730	0.0285
782.565	1101	4.709	0.114	5.143	0.147	0.916	0.0286
750.544	1204	3.351	0.066	3.678	0.124	0.911	0.0287
783.4315	1101	2.505	0.125	1.807	0.271	1.386	0.029
214.172	1203	3.549	0.090	3.910	0.126	0.908	0.0292
312.2663	1203	3.879	0.140	4.315	0.126	0.899	0.03
857.7531	1203	7.332	0.109	7.738	0.138	0.947	0.03
202.0453	1101	5.911	0.122	5.238	0.266	1.128	0.0305
763.5157	1202	1.570	0.175	2.098	0.147	0.748	0.0306
218.0192	1101	4.023	0.134	3.143	0.357	1.280	0.0307
856.7481	1203	8.173	0.118	8.608	0.151	0.949	0.032
795.5839	1204	3.545	0.061	3.800	0.093	0.933	0.0321
565.4104	1204	3.353	0.123	3.754	0.127	0.893	0.0332
313.7722	1101	3.080	0.178	2.250	0.319	1.369	0.0334
909.7882	1203	4.177	0.092	4.456	0.081	0.938	0.0337
429.6888	1101	2.475	0.093	1.833	0.268	1.351	0.0341
431.957	1202	1.847	0.154	2.312	0.136	0.799	0.0341
607.4919	1204	2.906	0.259	3.579	0.147	0.812	0.0341

294.1443	1201	2.449	0.210	1.795	0.201	1.364	0.0348
598.4965	1203	6.590	0.104	6.923	0.106	0.952	0.035
549.6005	1101	2.027	0.167	1.424	0.212	1.424	0.0351
283.9028	1101	3.018	0.076	2.397	0.267	1.259	0.0353
820.5679	1202	1.438	0.153	2.061	0.231	0.698	0.0353
574.4597	1204	3.354	0.210	3.994	0.196	0.840	0.0359
826.7048	1203	4.509	0.145	4.950	0.134	0.911	0.0361
805.5832	1102	3.502	0.085	3.742	0.066	0.936	0.0364
550.4956	1203	6.603	0.188	7.165	0.167	0.922	0.0365
630.4861	1204	3.807	0.132	4.238	0.142	0.898	0.0369
551.4985	1203	5.182	0.182	5.733	0.167	0.904	0.0371
549.4845	1203	5.363	0.140	5.765	0.115	0.930	0.0372
827.7083	1203	3.751	0.145	4.174	0.124	0.899	0.0374
306.2569	1204	2.821	0.075	3.051	0.072	0.925	0.0375
775.553	1204	3.272	0.071	3.577	0.119	0.915	0.0377
242.203	1203	4.260	0.087	4.573	0.113	0.932	0.0382
828.7202	1204	3.465	0.158	3.906	0.122	0.887	0.0385
232.2188	1203	3.156	0.098	3.499	0.122	0.902	0.0387
722.4789	1201	1.873	0.084	2.132	0.082	0.879	0.0389
530.3471	1202	2.566	0.117	2.910	0.103	0.882	0.0393
264.2452	1203	1.753	0.138	2.114	0.090	0.829	0.0397
858.7663	1204	5.791	0.140	6.169	0.100	0.939	0.0401
759.5779	1101	5.093	0.108	5.471	0.136	0.931	0.0404
559.469	1204	2.761	0.191	3.288	0.149	0.840	0.0406
593.4743	1204	2.069	0.240	2.728	0.184	0.758	0.0406
392.2938	1204	1.941	0.277	2.718	0.225	0.714	0.041
575.499	1203	7.133	0.096	7.452	0.112	0.957	0.0414
826.5581	1202	1.759	0.125	2.203	0.163	0.798	0.0417
719.6233	1204	4.578	0.094	4.279	0.102	1.070	0.0419
295.2287	1204	2.883	0.203	3.414	0.138	0.844	0.0422
555.3101	1102	1.310	0.070	1.541	0.080	0.850	0.0424
830.7355	1204	3.947	0.183	4.447	0.141	0.888	0.0427
474.3706	1203	0.868	0.128	1.234	0.112	0.704	0.0433
203.1157	1101	3.694	0.116	2.965	0.319	1.246	0.0437
295.2239	1204	3.109	0.123	3.476	0.119	0.894	0.0437
855.7417	1204	4.834	0.122	5.184	0.107	0.932	0.0438
760.5811	1101	3.973	0.109	4.349	0.138	0.913	0.0441
625.5076	1204	3.218	0.140	3.624	0.126	0.888	0.0443
270.2343	1203	1.714	0.106	2.018	0.095	0.850	0.0444
661.6233	1204	2.375	0.073	2.644	0.103	0.898	0.0445
446.3403	1202	0.751	0.166	1.275	0.181	0.589	0.0446
521.3474	1201	2.493	0.169	2.031	0.137	1.228	0.0451
837.718	1204	2.369	0.329	3.272	0.267	0.724	0.0451
228.1877	1203	2.954	0.108	3.313	0.131	0.892	0.0458
832.7495	1204	2.994	0.226	3.588	0.164	0.834	0.0458
576.477	1202	1.734	0.213	2.337	0.187	0.742	0.0459
1085.3294	1101	3.756	0.022	3.463	0.136	1.085	0.0467
444.2717	1202	1.195	0.096	1.496	0.105	0.799	0.0473
545.6062	1101	1.955	0.134	1.427	0.213	1.370	0.0477
651.5221	1204	3.677	0.131	4.039	0.111	0.910	0.0482
829.7244	1203	4.651	0.135	5.044	0.130	0.922	0.0482
859.7706	1204	4.962	0.145	5.331	0.100	0.931	0.0482
575.4632	1204	2.109	0.207	2.692	0.185	0.783	0.0485
804.5476	1101	3.984	0.119	4.353	0.130	0.915	0.0485
725.5527	1101	3.407	0.058	3.160	0.102	1.078	0.0486
350.2423	1202	2.544	0.227	1.901	0.207	1.338	0.0489
382.1083	1101	2.600	0.210	1.858	0.286	1.399	0.049
836.7076	1204	1.427	0.242	2.163	0.256	0.660	0.0493
671.5726	1204	2.055	0.138	2.458	0.136	0.836	0.0495
197.8549	1101	3.431	0.102	2.697	0.337	1.272	0.0499
773.537	1202	1.569	0.078	1.805	0.082	0.869	0.0499

Table 13: Accurate mass features differing between clinically diagnosed AD and non-AD patients in CSF ($p<0.05$, log2 transformed).

[illegible] Mass	[illegible] Mode	AVG [illegible]	SEM [illegible]	[illegible]	[illegible]	[illegible]	[illegible]
742.2972	1203	1.187	0.130	0.000	0.000	1.187	1.69E-05
562.46	1203	1.080	0.134	0.000	0.000	1.080	4.84E-05
731.653	1203	0.905	0.193	0.000	0.000	0.905	0.0022
432.1532	1203	1.445	0.125	0.880	0.053	0.609	0.0037
487.6482	1101	2.388	0.044	2.668	0.057	1.117	0.0037
275.8712	1101	2.362	0.057	2.664	0.058	1.128	0.0045
371.7311	1101	3.417	0.098	3.818	0.022	1.117	0.0053
622.2539	1203	2.667	0.110	2.166	0.074	0.812	0.0056
485.6503	1101	1.758	0.051	1.976	0.024	1.124	0.0058
207.0822	1203	1.010	0.126	0.198	0.198	0.196	0.006
640.2637	1203	3.557	0.152	2.876	0.106	0.809	0.0063
373.728	1101	3.013	0.086	3.358	0.037	1.114	0.0071
656.2587	1203	0.977	0.080	0.322	0.199	0.330	0.0097
730.6493	1203	1.888	0.139	0.948	0.278	0.502	0.0109
220.0798	1101	2.252	0.078	2.556	0.044	1.135	0.011
641.2661	1203	1.915	0.148	1.010	0.282	0.527	0.0152
779.4393	1101	3.612	0.032	3.728	0.022	1.032	0.0167
782.5647	1201	1.898	0.208	1.128	0.142	0.594	0.0172
313.7721	1101	4.045	0.096	4.350	0.031	1.075	0.0215
785.4288	1101	3.273	0.039	3.410	0.033	1.042	0.0253
777.4426	1101	2.495	0.017	2.614	0.044	1.048	0.0279
341.8614	1101	2.747	0.069	2.990	0.061	1.089	0.0305
250.0366	1101	3.122	0.115	3.462	0.049	1.109	0.0309
315.7693	1101	3.347	0.090	3.618	0.044	1.081	0.0311
253.8164	1101	4.237	0.108	4.542	0.030	1.072	0.033
369.7338	1101	2.713	0.148	3.132	0.035	1.154	0.034
781.5607	1201	2.728	0.234	2.048	0.095	0.751	0.0345
206.0789	1203	4.178	0.147	3.484	0.253	0.834	0.0357
429.689	1101	3.232	0.042	3.392	0.051	1.050	0.0358
638.2465	1203	1.927	0.188	1.372	0.095	0.712	0.0362
578.1574	1101	1.828	0.042	1.674	0.046	0.916	0.0368
262.0777	1101	4.738	0.114	5.072	0.052	1.070	0.0371
265.8423	1101	3.682	0.101	3.960	0.028	1.076	0.0395
582.6334	1101	1.702	0.051	1.526	0.052	0.897	0.0395
255.8135	1101	4.678	0.113	4.978	0.029	1.064	0.0418
321.8039	1101	3.190	0.098	3.480	0.062	1.091	0.0423
514.6879	1101	2.650	0.037	2.534	0.032	0.956	0.0424
262.0221	1101	3.633	0.126	3.964	0.026	1.091	0.0435
746.621	1101	1.015	0.225	0.306	0.190	0.301	0.0438
781.4354	1101	4.163	0.028	4.254	0.025	1.022	0.045
311.775	1101	3.457	0.111	3.764	0.053	1.089	0.0461
257.8105	1101	3.753	0.115	4.056	0.036	1.081	0.0472

Table 14. Retention Time of Six Biomarkers

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
541.3432	C25H52NO9P	541.3379	540.3616	29.4
569.3687	C27H56NO9P	569.3692	568.3979	31.0
699.5198	C39H74NO7P	699.5202	698.5392	40.5
723.5195	C41H74NO7P	723.5202	722.5331	40.2
751.5555	C43H78NO7P	751.5515	750.5667	41.9
803.568	C43H82NO10P	803.5676	802.5575	38.6

Table 15. Metabolite 541.3432 Fragments

C25H51NO9P	540.33014	540.3616	0.0315	-	-
C23H47NO7P	480.30901	480.3313	0.0223	60.02112	C2H4O2
C16H31O2	255.23240	255.2521	0.0197	292.15251	C9H27NO7P
C7H15NO5P	224.06878	224.0904	0.0216	300.26644	C18H36O3
O3P	78.95850	78.975	0.0165	461.37163	C25H51NO6

Legend:
frag formula: The putative computationally derived molecular formula of the fragment neutral mass.
theoretical: The theoretical mass of the formulas shown in the frag formula column.
Qstar-detected: The detected mass from the ABI Q-Star XL.
delta: The difference between the theoretical and neutral mass.
diff: The mass difference between the Qstar-detected parent ion mass and the Qstar-detected fragmant ion mass.
Loss: The putative molecular formulas of the *"diff"* column

Note: These are only predicted formulas for each fragment and are not necessarily the actual formulas.

Table 16. Metabolite 569.3687 Fragments

C27H55NO9P	568.3614	568.3979	0.0365	-	-
C25H51NO7P	508.34031	508.3612	0.0209	60.02112	C2H4O2
C18H35O2	283.26370	283.2900	0.0263	285.09773	C9H20NO7P
C7H15NO5P	224.06878	224.0899	0.0211	344.23266	C20H40O4
C4H11NO4P	168.04256	168.0668	0.0242	400.31887	C23H44O5
C3H6PO5	152.99528	153.0196	0.0243	446.33992	C24H49NO4P
O3P	78.95850	78.975	0.0165	489.40293	C27H55NO6

Legend:
frag formula: The putative computationally derived molecular formula of the fragment neutral mass.
theoretical: The theoretical mass of the formulas shown in the frag formula column.
Qstar-detected: The detected mass from the ABI Q-Star XL.
delta: The difference between the theoretical and neutral mass.
diff: The mass difference between the Qstar-detected parent ion mass and the Qstar-detected fragmant ion mass.
Loss: The putative molecular formulas of the *"diff"* column

Note: These are only predicted formulas for each fragment and are not necessarily the actual formulas.

Table 17. Metabolite 803.568 Fragments

C43H81NO10P	802.55980	802.5575	-0.0023	-	-
C41H77NO8P	742.53868	742.5526	0.0139	76.01604	C2H4O3
C23H47NO7P	480.30901	480.3248	0.0158	322.25079	C20H34O3
C18H32O2	279.23240	279.2485	0.0161	522.31957	C25H49NO8P
C16H31O2	255.23240	255.2469	0.0145	547.32740	C27H50NO8P
C7H15NO5P	224.06878	224.0853	0.0165	578.49102	C36H66O5
C4H11NO4P	168.04256	168.0629	0.0203	634.51724	C39H70O6

Legend:
frag formula: The putative computationally derived molecular formula of the fragment neutral mass.
theoretical: The theoretical mass of the formulas shown in the frag formula column.
Qstar-detected: The detected mass from the ABI Q-Star XL.
delta: The difference between the theoretical and neutral mass.
diff: The mass difference between the Qstar-detected parent ion mass and the Qstar-detected fragmant ion mass.
Loss: The putative molecular formulas of the *"diff"* column

Note: These are only predicted formulas for each fragment and are not necessarily the actual formulas.

Table 18. List of Preferred List of Metabolites

Metabolite Code	Metabolite Name	Molecular Formula	Parent Mass	M-H Mass	Diagnostic Fragment Mass	MS/MS Transition
M01	PtdEt 16:0/18:0	C39H78N1O8P1	719.54648	718.5	R1 (C16H31O2) - 255	718.0 / 255.0
M02	PtdEt 16:0/18:1	C39H76N1O8P1	717.53083	716.5	R1 (C16H31O2) - 255	716.0 / 255.0
M03	PtdEt 18:0/18:0	C41H82N1O8P1	747.57777	746.5	R1 (C18H35O2) - 283	746.0 / 283.0
M04	PtdEt 18:0/18:1	C41H80N1O8P1	745.56213	744.5	R1 (C18H35O2) - 283	744.0 / 283.0
M05	Plasmanyl 16:0/18:1	C39H78N1O7P1	703.55156	702.5	R2 (C18H33O2) - 281	702.0 / 281.0
M06	Plasmanyl 16:0/18:2	C39H76N1O7P1	701.53591	700.5	R2 (C18H31O2) - 279	700.0 / 279.0
M07	Plasmanyl 16:0/20:4	C41H76N1O7P1	725.53591	724.5	R2 (C20H31O2) - 303	724.0 / 303.0
M08	Plasmanyl 16:0/22:4	C43H80N1O7P1	753.56721	752.5	R2 (C22H35O2) - 331	752.0 / 331.0
M09	Plasmanyl 16:0122:6	C43H76N1O7P1	749.53591	748.5	R2 (C22H31O2) - 327	748.0 / 327.0
M10	Plasmanyl 18:0/18:1	C41H82N1O7P1	731.58286	730.5	R2 (C18H33O2) - 281	730.0 / 281.0
M11	Plasmanyl 18:0/18:2	C41H80N1O7P1	729.56721	728.5	R2 (C18H31O2) - 279	728.0 / 279.0
M12	Plasmanyl 18:0/20:4	C43H80N1O7P1	753.56721	752.5	R2 (C20H31O2) - 303	752.0 / 303.0
M13	Plasmanyl 18:0/22:4	C45H84N1O7P1	781.59851	780.5	R2 (C22H35O2) - 331	780.0 / 331.0

(continued)

Metabolite Code	Metabolite Name	Molecular Formula	Parent Mass	M-H Mass	Diagnostic Fragment Mass	MS/MS Transition
M14	Plasmanyl 18:0/22:6	C45H80N1O7P1	777.56721	776.5	R2 (C22H31O2) - 327	776.0 / 327.0
M15	Plasmenyl 16:0/18:1	C39H76N1O7P1	701.53591	700.5	R2 (C18H33O2) - 281	700.0 / 281.0
M16	Plasmenyl 16:0/18:2	C39H74N1O7P1	699.52026	698.5	R2 (C18H31O2) - 279	698.0 / 279.0
M17	Plasmenyl 16:0/20:4	C41H74N1O7P1	723.52026	722.5	R2 (C20H31O2) - 303	722.0 / 303.0
M18	Plasmenyl 16:0/22:4	C43H78N1O7P1	751.55156	750.5	R2 (C22H35O2) - 331	750.0 / 331.0
M19	Plasmenyl 16:0/22:6	C43H74N1O7P1	747.52026	746.5	R2 (C22H31O2) - 327	746.0 / 327.0
M20	Plasmenyl 18:0/18:1	C41H80N1O7P1	729.56721	728.5	R2 (C18H33O2) - 281	728.0 / 281.0
M21	Plasmenyl 18:0/18:2	C41H78N1O7P1	727.55156	726.5	R2 (C18H31O2) - 279	726.0 / 279.0
M22	Plasmenyl 18:0/20:4	C43H78N1O7P1	751.55156	750.5	R2 (C20H31O2) - 303	750.6 / 303.2
M23	Plasmenyl 18:0/22:4	C45H82N1O7P1	779.58286	778.5	R2 (C22H35O2) - 331	778.0 / 331.0
M24	Plasmenyl 18:0/22:6	C45H78N1O7P1	775.55156	774.5	R2 (C22H31O2) - 327	774.0 / 327.0
M25	Free 22:6	C22H3202	328.24022	327.2	(C21H31) - 283	327.2 / 283.0
M26	Free 20:4	C20H3202	304.24022	303.2	(C19H31) - 259	303.2 / 259.5

Table 19. Clinical Data on Subject Cohorts

Population	n	Age		MMSE		ADAS-cog	
		Mean	SEM	Mean	SEM	Mean	SEM
Age Ctl, 30-39, Female	14	36.4	0.9				
Age Ctl, 30-39, Male	11	35.2	1.0				
Age Ctl, 40-49, Female	44	44.8	0.5				
Age Ctl, 40-49, Male	27	44.7	0.6				
Age Ctl, 50-59, Female	107	54.2	0.3				
Age Ctl, 50-59, Male	59	54.1	0.4				
Age Ctl, 60-69, Female	55	63.4	0.3				
Age Ctl, 60-69, Male	34	64.4	0.5				
Age Ctl, 70+_Female	27	79.7	1.2				
Age Ctl, 70+_Male	35	75.5	0.7				
Cognitive Normal, Female	36	77.6	1.1	29.6	0.1		
Cognitive Normal, Male	32	76.8	1.1	29.3	0.1		
SDAT_all, Female	140	80.0	0.6	12.6	0.7	34.2	1.6
SDAT_all, Male	117	79.8	0.7	15.3	0.5	27.4	1.3
SDAT, ADAS 5-19, Female	38	79.6	1.2	17.6	0.7	15.2	0.6
SDAT, ADAS 20-39, Female	54	78.6	1.0	16.6	0.7	27.0	0.8
SDAT, ADAS 40-70, Female	48	81.9	1.1	4.2	0.7	57.3	1.5
SDAT, ADAS 5-19, Male	40	79.0	1.1	17.3	0.7	15.3	0.5

(continued)

Population	n	Age		MMSE		ADAS-cog	
		Mean	SEM	Mean	SEM	Mean	SEM
SDAT, ADAS 20-39, Male	58	79.6	0.9	16.8	0.6	27.5	0.7
SDAT, ADAS 40-70, Male	18	82.6	2.1	6.2	1.1	53.2	2.2
Post Mortem SDAT Male	10	80.1	1.4				
Post Mortem SDAT Female	10	77.6	1.5				
Post Mortem Ctl, Female	9	84.4	1.8				
Post Mortem Ctl, Male	10	77.9	1.4				

Table 20. Effect of Age on Serum Ethanolamine Phospholipid Levels in Males

	Age Ctl, 30-39, Male		Age Ctl, 40-49, Male		Age Ctl, 50-59, Male		Age Ctl, 60-69, Male		Age Ctl, 70+_Male	
Metabolite Code	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
M01	0.122	0.017	0.119	0.008	0.113	0.006	0.132	0.007	0.130	0.006
M02	0.056	0.008	0.058	0.006	0.058	0.004	0.059	0.007	0.056	0.005
M03	0.102	0.014	0.085	0.006	0.095	0.005	0.103	0.008	0.110	0.010
M04	0.026	0.004	0.027	0.003	0.025	0.002	0.027	0.003	0.027	0.003
M05	0.014	0.002	0.012	0.001	0.011	0.001	0.012	0.001	0.011	0.001
M06	0.032	0.005	0.026	0.002	0.026	0.001	0.025	0.002	0.027	0.002
M07	0.078	0.015	0.053	0.007	0.063	0.005	0.061	0.007	0.060	0.006
M08	0.010	0.002	0.007	0.001	0.007	0.001	0.007	0.001	0.006	0.001
M09	0.019	0.004	0.013	0.002	0.019	0.002	0.019	0.002	0.022	0.003
M10	0.058	0.009	0.052	0.004	0.049	0.003	0.055	0.004	0.053	0.003
M11	0.131	0.021	0.099	0.007	0.098	0.005	0.099	0.007	0.104	0.007
M12	0.244	0.037	0.186	0.015	0.210	0.012	0.213	0.017	0.202	0.016
M13	0.015	0.002	0.013	0.001	0.013	0.001	0.013	0.001	0.012	0.001
M14	0.034	0.005	0.026	0.003	0.036	0.002	0.040	0.004	0.047	0.006
M15	0.085	0.012	0.075	0.005	0.074	0.004	0.074	0.006	0.076	0.005
M16	0.291	0.043	0.220	0.016	0.244	0.013	0.223	0.018	0.246	0.018
M17	0.489	0.102	0.332	0.035	0.429	0.029	0.412	0.048	0.410	0.044
M18	0.032	0.005	0.025	0.003	0.027	0.002	0.026	0.004	0.023	0.002
M19	0.086	0.014	0.063	0.008	0.094	0.008	0.098	0.012	0.114	0.017
M20	0.086	0.013	0.070	0.006	0.068	0.004	0.069	0.006	0.071	0.006
M21	0.294	0.044	0.236	0.017	0.247	0.014	0.222	0.018	0.236	0.018
M22	1.054	0.220	0.788	0.079	0.930	0.067	0.933	0.102	0.906	0.104
M23	0.022	0.003	0.019	0.001	0.019	0.001	0.020	0.003	0.017	0.001
M24	0.077	0.014	0.063	0.008	0.086	0.007	0.088	0.010	0.103	0.016
M25	0.205	0.014	0.195	0.017	0.274	0.018	0.310	0.025	0.374	0.031
M26	0.091	0.011	0.082	0.005	0.096	0.003	0.109	0.009	0.114	0.009

Table 21. Ratio and T-test values between males of different ages

	50-59 vs. 40-49, Male		60-69 vs. 40-49, Male		70+ vs. 40-49, Male	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest
M01	0.955	6.0E-01	1.110	2.2E-01	1.097	2.4E-01

(continued)

	50-59 vs. 40-49, Male		60-69 vs. 40-49, Male		70+ vs. 40-49, Male	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest
M02	0.998	9.9E-01	1.024	8.8E-01	0.965	8.1E-01
M03	1.125	2.3E-01	1.213	9.4E-02	1.296	5.0E-02
M04	0.954	7.0E-01	1.019	9.1E-01	1.015	9.3E-01
M05	0.953	6.3E-01	1.011	9.3E-01	0.979	8.5E-01
M06	1.031	7.5E-01	0.976	8.3E-01	1.054	6.2E-01
M07	1.198	2.4E-01	1.164	4.1E-01	1.133	4.8E-01
M08	1.031	8.2E-01	1.014	9.4E-01	0.907	5.4E-01
M09	1.443	2.7E-02	1.473	4.5E-02	1.701	2.1E-02
M10	0.953	5.9E-01	1.061	5.9E-01	1.013	8.9E-01
M11	0.992	9.3E-01	1.004	9.7E-01	1.058	5.6E-01
M12	1.128	2.5E-01	1.147	2.5E-01	1.085	4.8E-01
M13	1.007	9.4E-01	1.032	8.0E-01	0.921	4.4E-01
M14	1.383	1.5E-02	1.536	7.0E-03	1.802	2.8E-03
M15	0.987	8.9E-01	0.985	8.9E-01	1.020	8.5E-01
M16	1.109	2.7E-01	1.013	9.1E-01	1.118	2.9E-01
M17	1.291	5.4E-02	1.241	2.1E-01	1.235	1.9E-01
M18	1.055	6.6E-01	1.032	8.7E-01	0.904	4.9E-01
M19	1.484	1.9E-02	1.540	2.6E-02	1.789	1.9E-02
M20	0.971	7.8E-01	0.976	8.4E-01	1.014	9.0E-01
M21	1.048	6.3E-01	0.941	5.8E-01	1.000	1.0E+00
M22	1.179	2.1E-01	1.183	2.9E-01	1.149	3.9E-01
M23	1.008	9.3E-01	1.066	7.5E-01	0.900	3.6E-01
M24	1.365	5.2E-02	1.403	6.0E-02	1.642	4.7E-02
M25	1.405	9.0E-03	1.589	6.7E-04	1.912	1.7E-05
M26	1.175	1.8E-02	1.324	1.7E-02	1.389	6.3E-03

Table 22. Effect of Age on Serum Ethanolamine Phospholipid Levels in Females

	Age Ctl, 30-39, Female		Age Ctl, 40-49, Female		Age Ctl, 50-59, Female		Age Ctl, 60-69, Female		Age Ctl, 70+_Female	
Metabolite Code	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
M01	0.103	0.012	0.114	0.006	0.105	0.006	0.127	0.007	0.126	0.009
M02	0.047	0.006	0.069	0.006	0.058	0.004	0.058	0.004	0.056	0.004
M03	0.095	0.015	0.101	0.007	0.093	0.005	0.091	0.006	0.100	0.005
M04	0.028	0.005	0.033	0.003	0.025	0.002	0.023	0.002	0.026	0.002
M05	0.011	0.002	0.013	0.001	0.010	0.000	0.010	0.001	0.011	0.001
M06	0.031	0.005	0.031	0.002	0.025	0.001	0.023	0.001	0.025	0.002
M07	0.061	0.010	0.071	0.007	0.057	0.003	0.051	0.005	0.052	0.005
M08	0.008	0.001	0.010	0.001	0.007	0.000	0.006	0.001	0.006	0.001
M09	0.021	0.004	0.021	0.002	0.020	0.001	0.017	0.002	0.019	0.002
M10	0.050	0.007	0.059	0.003	0.049	0.002	0.052	0.003	0.051	0.003
M11	0.120	0.018	0.119	0.008	0.100	0.004	0.099	0.006	0.100	0.008
M12	0.196	0.022	0.222	0.015	0.191	0.009	0.181	0.011	0.188	0.013
M13	0.013	0.001	0.015	0.001	0.012	0.001	0.011	0.001	0.012	0.001

(continued)

	Age Ctl, 30-39, Female		Age Ctl, 40-49, Female		Age Ctl, 50-59, Female		Age Ctl, 60-69, Female		Age Ctl, 70+_Female	
Metabolite Code	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
M14	0.040	0.007	0.043	0.004	0.042	0.003	0.041	0.003	0.049	0.004
M15	0.071	0.009	0.079	0.005	0.068	0.003	0.066	0.004	0.069	0.004
M16	0.274	0.044	0.268	0.021	0.226	0.011	0.210	0.013	0.232	0.017
M17	0.419	0.076	0.458	0.053	0.392	0.024	0.354	0.036	0.360	0.033
M18	0.028	0.004	0.032	0.003	0.025	0.002	0.019	0.002	0.023	0.003
M19	0.107	0.024	0.100	0.012	0.099	0.007	0.087	0.009	0.103	0.008
M20	0.074	0.013	0.075	0.006	0.063	0.003	0.063	0.004	0.068	0.005
M21	0.294	0.057	0.275	0.024	0.228	0.012	0.210	0.014	0.229	0.020
M22	0.938	0.170	1.025	0.108	0.853	0.055	0.759	0.068	0.837	0.096
M23	0.021	0.003	0.022	0.002	0.017	0.001	0.015	0.001	0.017	0.002
M24	0.102	0.025	0.093	0.011	0.089	0.006	0.081	0.008	0.096	0.008
M25	0.239	0.023	0.236	0.014	0.277	0.012	0.326	0.022	0.373	0.020
M26	0.091	0.012	0.093	0.006	0.093	0.003	0.094	0.004	0.107	0.007

Table 23. Ratio and T-test values between females of different ages

	50-59 vs. 40-49, Female		60-69 vs. 40-49, Female		70+ vs. 40-49, Female	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest
M01	0.925	3.7E-01	1.118	1.8E-01	1.110	2.6E-01
M02	0.838	1.3E-01	0.835	9.5E-02	0.812	1.1E-01
M03	0.927	4.0E-01	0.906	2.9E-01	0.989	9.0E-01
M04	0.772	2.1E-02	0.709	5.1E-03	0.811	1.2E-01
M05	0.811	1.1E-02	0.798	2.0E-02	0.832	8.7E-02
M06	0.815	1.1E-02	0.731	1.5E-03	0.805	5.7E-02
M07	0.798	3.4E-02	0.718	1.9E-02	0.726	4.9E-02
M08	0.721	4.2E-03	0.569	1.3E-04	0.640	1.9E-02
M09	0.934	5.8E-01	0.784	9.4E-02	0.912	5.6E-01
M10	0.841	3.1E-02	0.882	1.3E-01	0.863	1.1E-01
M11	0.843	2.3E-02	0.832	3.5E-02	0.843	1.1E-01
M12	0.862	6.2E-02	0.815	2.5E-02	0.848	1.2E-01
M13	0.806	8.8E-03	0.737	2.0E-03	0.839	1.3E-01
M14	0.981	8.6E-01	0.953	6.9E-01	1.149	2.6E-01
M15	0.864	5.6E-02	0.841	3.7E-02	0.871	1.5E-01
M16	0.846	5.3E-02	0.786	1.5E-02	0.867	2.3E-01
M17	0.856	2.0E-01	0.773	1.0E-01	0.786	1.9E-01
M18	0.778	2.4E-02	0.594	1.8E-04	0.733	7.4E-02
M19	0.986	9.2E-01	0.872	3.8E-01	1.030	8.5E-01
M20	0.843	5.6E-02	0.842	9.5E-02	0.905	4.0E-01
M21	0.829	5.0E-02	0.763	1.8E-02	0.832	1.9E-01
M22	0.832	1.2E-01	0.741	3.3E-02	0.817	2.3E-01
M23	0.797	1.5E-02	0.663	3.3E-04	0.776	7.4E-02
M24	0.957	7.4E-01	0.871	3.6E-01	1.040	8.1E-01
M25	1.176	4.8E-02	1.381	1.7E-03	1.581	2.4E-07

(continued)

	50-59 vs. 40-49, Female		60-69 vs. 40-49, Female		70+ vs. 40-49, Female	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest
M26	1.003	9.6E-01	1.021	7.9E-01	1.159	1.2E-01

Table 24. Effect of Dementia State on Serum Ethanolamine Phospholipid Levels in Females

	Cognitive Normal, Female		SDAT all, Female		SDAT, ADAS 5-19, Female		SDAT, ADAS 20-39, Female		SDAT, ADAS 40-70, Female	
Metabolite Code	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
M01	0.118	0.005	0.113	0.003	0.109	0.004	0.112	0.005	0.118	0.006
M02	0.062	0.005	0.053	0.002	0.050	0.003	0.057	0.004	0.052	0.004
M03	0.099	0.005	0.076	0.002	0.080	0.004	0.076	0.004	0.073	0.004
M04	0.026	0.002	0.025	0.001	0.024	0.002	0.027	0.002	0.024	0.003
M05	0.011	0.001	0.009	0.000	0.010	0.001	0.009	0.001	0.009	0.001
M06	0.027	0.001	0.022	0.001	0.024	0.001	0.023	0.001	0.020	0.001
M07	0.056	0.005	0.041	0.002	0.044	0.004	0.042	0.004	0.036	0.003
M08	0.006	0.001	0.005	0.000	0.005	0.000	0.006	0.001	0.005	0.000
M09	0.019	0.002	0.013	0.001	0.015	0.001	0.014	0.001	0.012	0.001
M10	0.054	0.003	0.048	0.001	0.049	0.002	0.047	0.002	0.048	0.003
M11	0.105	0.004	0.088	0.003	0.094	0.004	0.090	0.005	0.080	0.004
M12	0.196	0.012	0.153	0.005	0.166	0.009	0.152	0.010	0.142	0.010
M13	0.013	0.001	0.010	0.000	0.011	0.000	0.010	0.001	0.010	0.001
M14	0.046	0.003	0.035	0.002	0.040	0.003	0.034	0.002	0.033	0.003
M15	0.073	0.004	0.059	0.002	0.061	0.003	0.061	0.003	0.056	0.003
M16	0.250	0.013	0.192	0.007	0.214	0.013	0.201	0.012	0.164	0.008
M17	0.408	0.033	0.288	0.015	0.317	0.026	0.304	0.026	0.247	0.021
M18	0.024	0.002	0.018	0.001	0.019	0.001	0.019	0.002	0.016	0.001
M19	0.103	0.008	0.071	0.004	0.079	0.007	0.072	0.006	0.063	0.006
M20	0.077	0.004	0.059	0.002	0.064	0.004	0.060	0.004	0.054	0.003
M21	0.265	0.015	0.195	0.008	0.219	0.015	0.205	0.015	0.165	0.011
M22	0.933	0.077	0.702	0.036	0.753	0.061	0.738	0.066	0.620	0.057
M23	0.018	0.001	0.014	0.001	0.015	0.001	0.014	0.001	0.013	0.001
M24	0.103	0.009	0.073	0.004	0.079	0.008	0.073	0.007	0.067	0.008
M25	0.241	0.013	0.211	0.007	0.218	0.013	0.212	0.014	0.204	0.011
M26	0.069	0.003	0.073	0.002	0.076	0.003	0.072	0.004	0.072	0.003

Table 25. Ratio and T-test values between females of various levels of dementia

	AD, All to CN, Female		ADAS 5-19 to CN, Female		ADAS 20-39 to CN, Female		ADAS 40-70 to CN, Female	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest	Ratio	ttest
M01	0.963	5.2E-01	0.929	2.1E-01	0.951	4.4E-01	1.004	9.6E-01
M02	0.856	9.0E-02	0.806	4.5E-02	0.912	3.9E-01	0.833	1.2E-01
M03	0.772	5.2E-05	0.814	6.0E-03	0.775	8.0E-04	0.737	1.8E-04
M04	0.963	7.5E-01	0.912	3.8E-01	1.027	8.3E-01	0.932	6.2E-01

(continued)

	AD, All to CN, Female		ADAS 5-19 to CN, Female		ADAS 20-39 to CN, Female		ADAS 40-70 to CN, Female	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest	Ratio	ttest
M05	0.893	1.1E-01	0.925	3.4E-01	0.895	2.1E-01	0.867	8.4E-02
M06	0.843	1.4E-02	0.910	2.2E-01	0.869	9.8E-02	0.761	5.1E-04
M07	0.732	1.8E-03	0.798	5.9E-02	0.753	2.0E-02	0.656	1.1E-03
M08	0.821	5.0E-02	0.849	1.4E-01	0.889	3.7E-01	0.722	4.7E-03
M09	0.696	2.6E-04	0.777	3.9E-02	0.702	2.9E-03	0.624	4.3E-04
M10	0.877	3.1E-02	0.895	8.6E-02	0.860	4.1E-02	0.883	9.8E-02
M11	0.832	2.5E-03	0.894	7.5E-02	0.850	2.7E-02	0.762	1.4E-04
M12	0.778	5.3E-04	0.847	4.2E-02	0.776	4.7E-03	0.726	5.8E-04
M13	0.800	8.5E-04	0.834	2.5E-02	0.794	8.6E-03	0.780	3.2E-03
M14	0.772	4.8E-03	0.869	1.9E-01	0.746	3.0E-03	0.724	5.6E-03
M15	0.811	8.5E-04	0.835	1.5E-02	0.831	2.3E-02	0.770	4.4E-04
M16	0.765	7.5E-05	0.853	4.3E-02	0.801	6.9E-03	0.656	6.4E-08
M17	0.705	3.5E-04	0.776	3.2E-02	0.745	1.4E-02	0.605	4.3E-05
M18	0.754	3.4E-03	0.804	5.9E-02	0.792	6.8E-02	0.673	7.9E-04
M19	0.688	1.8E-04	0.768	2.5E-02	0.699	2.9E-03	0.612	7.0E-05
M20	0.768	4.9E-04	0.828	3.0E-02	0.782	1.1E-02	0.703	4.8E-05
M21	0.737	1.9E-04	0.826	3.7E-02	0.776	1.1E-02	0.624	6.8E-07
M22	0.752	5.2E-03	0.807	7.0E-02	0.790	6.1E-02	0.665	1.3E-03
M23	0.764	2.5E-03	0.809	3.2E-02	0.789	4.1E-02	0.699	7.8E-04
M24	0.708	2.5E-03	0.768	4.5E-02	0.713	9.3E-03	0.654	4.2E-03
M25	0.876	6.6E-02	0.907	2.3E-01	0.880	1.5E-01	0.847	3.5E-02
M26	1.056	3.8E-01	1.092	1.8E-01	1.043	5.8E-01	1.041	5.5E-01

Table 26. Ratio and T-test values between females of various levels of dementia

	ADAS 20-39 to 5-19, Female		ADAS 40-70 to 5-19, Female		ADAS 40-70 to 20-39, Female	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest
M01	1.023	7.2E-01	1.080	2.8E-01	1.056	4.4E-01
M02	1.132	2.3E-01	1.034	7.6E-01	0.914	4.1E-01
M03	0.951	5.1E-01	0.906	2.2E-01	0.952	5.3E-01
M04	1.126	3.6E-01	1.022	8.8E-01	0.907	5.0E-01
M05	0.967	7.0E-01	0.936	4.2E-01	0.968	7.1E-01
M06	0.955	5.9E-01	0.837	2.5E-02	0.876	1.2E-01
M07	0.944	6.4E-01	0.822	1.2E-01	0.871	2.BE-01
M08	1.046	7.2E-01	0.850	1.1E-01	0.812	1.1E-01
M09	0.903	3.9E-01	0.802	9.5E-02	0.889	3.5E-01
M10	0.961	5.8E-01	0.987	8.6E-01	1.027	7.2E-01
M11	0.951	5.1E-01	0.853	2.8E-02	0.896	1.6E-01
M12	0.917	3.1E-01	0.858	7.7E-02	0.935	4.7E-01
M13	0.953	5.4E-01	0.936	3.6E-01	0.982	8.2E-01
M14	0.858	1.6E-01	0.833	1.5E-01	0.971	8.0E-01
M15	0.996	9.6E-01	0.922	2.3E-01	0.926	3.1 E-01
M16	0.940	4.7E-01	0.769	9.7E-04	0.819	1.6E-02
M17	0.960	7.4E-01	0.779	4.0E-02	0.812	9.8E-02

(continued)

	ADAS 20-39 to 5-19, Female		ADAS 40-70 to 5-19, Female		ADAS 40-70 to 20-39, Female	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest
M18	0.985	9.0E-01	0.837	7.6E-02	0.850	1.8E-01
M19	0.911	4.7E-01	0.798	8.5E-02	0.875	3.1E-01
M20	0.945	5.7E-01	0.849	5.8E-02	0.898	2.7E-01
M21	0.939	5.5E-01	0.755	4.6E-03	0.804	4.1E-02
M22	0.979	8.7E-01	0.824	1.2E-01	0.841	1.9E-01
M23	0.975	8.3E-01	0.864	1.4E-01	0.886	3.0E-01
M24	0.928	6.0E-01	0.852	3.2E-01	0.918	5.8E-01
M25	0.971	7.5E-01	0.934	4.0E-01	0.962	6.6E-01
M26	0.955	5.2E-01	0.954	4.5E-01	0.998	9.8E-01

Table 27. Average Serum Ethanolamine Phospholipid Levels in Males of Different Levels of Dementia Severity

	Cognitive Normal, Male		SDAT all, Male		SDAT, ADAS 5-19, Male		SDAT, ADAS 20-39, Male		SDAT, ADAS 40-70, Male	
Metabolite Code	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
M01	0.116	0.006	0.119	0.004	0.117	0.006	0.117	0.006	0.117	0.011
M02	0.066	0.006	0.056	0.004	0.060	0.009	0.054	0.004	0.046	0.006
M03	0.109	0.007	0.084	0.004	0.091	0.006	0.080	0.005	0.072	0.007
M04	0.030	0.002	0.026	0.002	0.025	0.004	0.027	0.002	0.022	0.003
M05	0.012	0.001	0.010	0.000	0.011	0.001	0.010	0.001	0.010	0.001
M06	0.028	0.002	0.025	0.001	0.024	0.002	0.025	0.002	0.024	0.002
M07	0.062	0.005	0.044	0.002	0.047	0.004	0.044	0.003	0.036	0.004
M08	0.007	0.001	0.005	0.000	0.006	0.001	0.005	0.000	0.004	0.001
M09	0.022	0.002	0.015	0.001	0.016	0.002	0.015	0.001	0.011	0.001
M10	0.054	0.002	0.052	0.002	0.053	0.003	0.051	0.002	0.047	0.005
M11	0.110	0.005	0.095	0.004	0.095	0.007	0.095	0.006	0.088	0.009
M12	0.205	0.011	0.162	0.006	0.170	0.011	0.160	0.008	0.141	0.013
M13	0.013	0.001	0.011	0.000	0.011	0.001	0.010	0.001	0.010	0.001
M14	0.051	0.004	0.036	0.002	0.041	0.004	0.034	0.002	0.028	0.003
M15	0.076	0.004	0.064	0.002	0.067	0.005	0.062	0.003	0.060	0.006
M16	0.266	0.015	0.207	0.009	0.213	0.015	0.202	0.012	0.191	0.018
M17	0.470	0.038	0.302	0.015	0.338	0.031	0.292	0.020	0.242	0.026
M18	0.026	0.003	0.019	0.001	0.020	0.002	0.018	0.001	0.016	0.002
M19	0.127	0.013	0.078	0.004	0.088	0.009	0.076	0.006	0.056	0.006
M20	0.078	0.005	0.064	0.003	0.069	0.005	0.061	0.003	0.059	0.007
M21	0.265	0.017	0.217	0.010	0.226	0.019	0.211	0.014	0.201	0.023
M22	1.040	0.087	0.736	0.037	0.789	0.071	0.723	0.052	0.624	0.067
M23	0.018	0.001	0.015	0.001	0.016	0.001	0.014	0.001	0.013	0.001
M24	0.116	0.012	0.079	0.005	0.090	0.010	0.075	0.006	0.061	0.008
M25	0.240	0.017	0.218	0.009	0.249	0.018	0.208	0.010	0.183	0.017
M26	0.072	0.003	0.070	0.002	0.074	0.004	0.070	0.003	0.065	0.006

Table 28. Ratio and T-test Values Between Males of Various Levels of Dementia

	AD, All to CN, Male		ADAS 5-19 to CN, Male		ADAS 20-39 to CN, Male		ADAS 40-70 to CN, Male	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest	Ratio	ttest
M01	1.028	7.1E-01	1.011	8.9E-01	1.016	8.3E-01	1.014	8.9E-01
M02	0.845	2.1E-01	0.898	5.5E-01	0.816	7.5E-02	0.690	2.4E-02
M03	0.769	1.6E-03	0.836	6.9E-02	0.735	6.4E-04	0.655	1.4E-03
M04	0.882	3.9E-01	0.836	2.9E-01	0.896	4.1E-01	0.726	2.7E-02
M05	0.882	1.3E-01	0.896	2.7E-01	0.865	9.1E-02	0.836	1.5E-01
M06	0.877	1.3E-01	0.855	9.1E-02	0.876	1.6E-01	0.856	1.4E-01
M07	0.709	3.9E-04	0.753	1.8E-02	0.704	1.6E-03	0.589	1.1E-03
M08	0.759	1.9E-02	0.806	1.8E-01	0.755	2.1E-02	0.629	1.5E-02
M09	0.658	2.7E-04	0.731	2.7E-02	0.654	1.4E-03	0.472	2.2E-04
M10	0.960	6.0E-01	0.978	7.9E-01	0.942	4.0E-01	0.877	1.7E-01
M11	0.866	9.3E-02	0.861	1.1E-01	0.861	8.1E-02	0.798	2.6E-02
M12	0.793	1.8E-03	0.831	3.9E-02	0.783	2.2E-03	0.686	8.3E-04
M13	0.850	2.7E-02	0.890	1.8E-01	0.827	1.3E-02	0.786	1.8E-02
M14	0.704	3.7E-04	0.800	6.9E-02	0.666	1.1E-04	0.553	2.3E-04
M15	0.842	2.2E-02	0.883	1.8E-01	0.810	3.0E-03	0.784	1.9E-02
M16	0.778	1.6E-03	0.802	1.7E-02	0.759	1.2E-03	0.718	3.2E-03
M17	0.644	4.5E-06	0.718	7.5E-03	0.621	1.3E-05	0.515	1.0E-04
M18	0.708	1.6E-03	0.758	6.0E-02	0.689	2.0E-03	0.613	7.7E-03
M19	0.611	1.0E-05	0.688	1.1E-02	0.596	6.1E-05	0.442	2.0E-04
M20	0.826	2.3E-02	0.892	2.7E-01	0.786	6.1E-03	0.762	3.9E-02
M21	0.818	2.7E-02	0.852	1.3E-01	0.796	2.0E-02	0.757	2.9E-02
M22	0.708	4.4E-04	0.758	2.7E-02	0.695	1.3E-03	0.600	1.9E-03
M23	0.801	1.1E-02	0.857	1.6E-01	0.776	4.0E-03	0.723	8.6E-03
M24	0.680	1.1E-03	0.777	9.8E-02	0.647	1.3E-03	0.524	2.8E-03
M25	0.909	2.4E-01	1.035	7.4E-01	0.865	8.0E-02	0.760	3.0E-02
M26	0.978	7.4E-01	1.023	7.5E-01	0.968	6.5E-01	0.907	2.9E-01

Table 29. Ratio and T-test Values Between Males of Various Levels of Dementia

	ADAS 20-39 to 5-19, Male		ADAS 40-70 to 5-19, Male		ADAS 40-70 to 20-39, Male	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest
M01	1.005	9.4E-01	1.003	9.8E-01	0.998	9.8E-01
M02	0.908	5.3E-01	0.768	3.2E-01	0.846	2.8E-01
M03	0.880	1.5E-01	0.784	7.0E-02	0.891	3.4E-01
M04	1.072	6.8E-01	0.868	5.8E-01	0.810	2.8E-01
M05	0.966	7.0E-01	0.933	6.1E-01	0.966	7.7E-01
M06	1.024	8.1E-01	1.001	9.9E-01	0.978	8.6E-01
M07	0.935	5.5E-01	0.783	1.3E-01	0.837	2.5E-01
M08	0.936	6.3E-01	0.780	2.7E-01	0.833	2.4E-01
M09	0.895	4.2E-01	0.646	3.3E-02	0.721	1.0E-01
M10	0.963	6.3E-01	0.897	3.7E-01	0.932	5.0E-01
M11	1.000	1.0E+00	0.927	5.7E-01	0.927	5.4E-01
M12	0.942	4.8E-01	0.826	1.3E-01	0.877	2.4E-01
M13	0.930	3.8E-01	0.883	3.2E-01	0.950	6.3E-01

(continued)

	ADAS 20-39 to 5-19, Male		ADAS 40-70 to 5-19, Male		ADAS 40-70 to 20-39, Male	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest
M14	0.832	1.1E-01	0.691	4.5E-02	0.830	2.0E-01
M15	0.917	3.0E-01	0.888	3.7E-01	0.968	7.4E-01
M16	0.947	5.4E-01	0.895	3.9E-01	0.946	6.4E-01
M17	0.865	1.9E-01	0.716	5.6E-02	0.828	1.9E-01
M18	0.909	4.5E-01	0.809	2.8E-01	0.890	4.4E-01
M19	0.866	2.5E-01	0.642	3.1E-02	0.741	7.4E-02
M20	0.880	1.6E-01	0.854	2.7E-01	0.970	8.0E-01
M21	0.934	5.2E-01	0.889	4.4E-01	0.952	7.2E-01
M22	0.917	4.5E-01	0.791	1.6E-01	0.863	3.3E-01
M23	0.906	3.3E-01	0.844	2.8E-01	0.931	5.6E-01
M24	0.833	1.7E-01	0.674	5.9E-02	0.810	2.3E-01
M25	0.836	3.7E-02	0.735	2.8E-02	0.879	2.1E-01
M26	0.946	4.3E-01	0.887	2.3E-01	0.937	5.2E-01

Table 30. Effect of Pathology State on Serum EthanolaminePhospholipid Levels in Males

	Post Mortem Ctl, Male		Post Mortem SDAT Male		SDAT vs Control	
Metabolite Code	Mean	SEM	Mean	SEM	Ratio	ttest
M01	0.127	0.017	0.089	0.013	0.702	0.091
M02	0.046	0.006	0.026	0.005	0.568	0.022
M03	0.059	0.006	0.036	0.006	0.610	0.014
M04	0.017	0.004	0.007	0.002	0.420	0.024
M05	0.006	0.001	0.004	0.000	0.479	0.019
M06	0.009	0.001	0.006	0.001	0.475	0.005
M07	0.012	0.003	0.009	0.001	0.451	0.033
M08	0.003	0.001	0.002	0.000	0.410	0.015
M09	0.006	0.002	0.003	0.001	0.269	0.048
M10	0.041	0.005	0.036	0.006	0.608	0.019
M11	0.052	0.006	0.041	0.006	0.474	0.001
M12	0.094	0.013	0.084	0.012	0.587	0.024
M13	0.009	0.001	0.008	0.001	0.576	0.008
M14	0.025	0.005	0.021	0.007	0.429	0.009
M15	0.045	0.005	0.029	0.004	0.648	0.026
M16	0.092	0.012	0.053	0.007	0.570	0.012
M17	0.097	0.021	0.047	0.007	0.489	0.036
M18	0.010	0.001	0.005	0.001	0.521	0.004
M19	0.032	0.006	0.014	0.002	0.452	0.011
M20	0.031	0.004	0.017	0.002	0.542	0.006
M21	0.072	0.011	0.033	0.006	0.464	0.006
M22	0.217	0.040	0.106	0.017	0.486	0.020
M23	0.009	0.001	0.005	0.001	0.565	0.005
M24	0.029	0.004	0.013	0.003	0.448	0.007
M25	0.238	0.023	0.180	0.026	0.757	0.114
M26	0.073	0.008	0.050	0.006	0.684	0.034

Table 31. Effect of Pathology State on Serum Ethanolamine Phospholipid Levels in Females

	Post Mortem Ctl, Female		Post Mortem SDAT Female		Autopsy AD vs. Control, Female	
Metabolite Code	Mean	SEM	Mean	SEM	Ratio	ttest
M01	0.179	0.050	0.124	0.016	0.697	0.300
M02	0.062	0.022	0.048	0.011	0.773	0.557
M03	0.070	0.019	0.043	0.005	0.619	0.178
M04	0.016	0.005	0.012	0.004	0.775	0.563
M05	0.007	0.002	0.003	0.001	0.508	0.095
M06	0.011	0.003	0.004	0.001	0.531	0.060
M07	0.016	0.003	0.005	0.001	0.530	0.037
M08	0.003	0.001	0.001	0.000	0.684	0.258
M09	0.005	0.001	0.002	0.000	0.566	0.047
M10	0.053	0.015	0.025	0.004	0.672	0.293
M11	0.064	0.013	0.025	0.004	0.650	0.132
M12	0.114	0.021	0.055	0.008	0.742	0.241
M13	0.010	0.002	0.005	0.001	0.865	0.537
M14	0.023	0.004	0.011	0.002	0.904	0.792
M15	0.060	0.017	0.034	0.004	0.577	0.151
M16	0.107	0.021	0.064	0.008	0.594	0.061
M17	0.113	0.024	0.067	0.009	0.592	0.079
M18	0.014	0.004	0.008	0.001	0.579	0.186
M19	0.035	0.007	0.022	0.004	0.635	0.132
M20	0.050	0.014	0.021	0.002	0.410	0.042
M21	0.100	0.020	0.041	0.007	0.414	0.010
M22	0.283	0.058	0.168	0.024	0.593	0.071
M23	0.012	0.003	0.007	0.001	0.560	0.112
M24	0.035	0.007	0.018	0.002	0.496	0.025
M25	0.189	0.015	0.198	0.022	1.051	0.727
M26	0.054	0.008	0.061	0.006	1.123	0.496

Table 32. Effect of Age on Ethanolamine Phospholipid Ratios to M01 in Males

	Age Ctl, 30-39, Male		Age Ctl, 40-49, Male		Age Ctl, 50-59, Male		Age Ctl, 60-69, Male		Age Ctl, 70+ Male	
Metabolite Code	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
M01	1.000	0.000	1.000	0.000	1.000	0.000	1.000	0.000	1.000	0.000
M02	0.476	0.042	0.477	0.034	0.517	0.027	0.431	0.031	0.420	0.028
M03	0.863	0.063	0.751	0.049	0.864	0.030	0.792	0.051	0.848	0.071
M04	0.224	0.025	0.229	0.026	0.236	0.013	0.203	0.019	0.204	0.017
M05	0.113	0.008	0.102	0.007	0.101	0.004	0.091	0.005	0.088	0.005
M06	0.263	0.029	0.234	0.021	0.243	0.012	0.199	0.016	0.210	0.012
M07	0.683	0.136	0.493	0.070	0.581	0.041	0.479	0.052	0.457	0.039
M08	0.079	0.010	0.064	0.007	0.067	0.004	0.054	0.005	0.049	0.004
M09	0.161	0.025	0.124	0.017	0.173	0.013	0.154	0.018	0.172	0.024
M10	0.464	0.025	0.454	0.022	0.445	0.012	0.419	0.018	0.407	0.016
M11	1.063	0.111	0.899	0.069	0.908	0.037	0.789	0.052	0.811	0.038

(continued)

	Age Ctl, 30-39, Male		Age Ctl, 40-49, Male		Age Ctl, 50-59, Male		Age Ctl, 60-69, Male		Age Ctl, 70+ Male	
Metabolite Code	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
M12	2.068	0.251	1.728	0.168	1.942	0.099	1.664	0.111	1.552	0.087
M13	0.126	0.009	0.117	0.009	0.121	0.005	0.102	0.006	0.092	0.005
M14	0.294	0.033	0.242	0.029	0.332	0.020	0.316	0.029	0.363	0.041
M15	0.699	0.034	0.658	0.041	0.675	0.023	0.567	0.031	0.590	0.029
M16	2.429	0.285	2.020	0.175	2.284	0.118	1.778	0.145	1.922	0.112
M17	4.127	0.757	3.164	0.418	3.980	0.257	3.167	0.320	3.178	0.294
M18	0.258	0.025	0.229	0.025	0.244	0.014	0.195	0.021	0.174	0.014
M19	0.725	0.101	0.607	0.094	0.865	0.063	0.769	0.085	0.881	0.131
M20	0.691	0.049	0.616	0.043	0.619	0.030	0.529	0.034	0.553	0.034
M21	2.395	0.215	2.163	0.189	2.287	0.122	1.773	0.148	1.840	0.108
M22	8.811	1.529	7.346	0.883	8.537	0.549	7.124	0.644	6.920	0.635
M23	0.189	0.019	0.175	0.016	0.178	0.009	0.150	0.016	0.133	0.008
M24	0.649	0.086	0.606	0.098	0.787	0.057	0.700	0.072	0.799	0.122
M25	2.182	0.444	1.975	0.265	2.747	0.211	2.608	0.251	3.066	0.284

Table 33. Ratio and T-test values of Ethanolamine Phospholipid Ratios to M01 between males of different ages

	50-59 vs. 40-49, Male		60-69 vs. 40-49, Male		70+ vs. 40-49, Male	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest
M01	1.000	#DIV/0!	1.000	#DIV/0!	1.000	#DIV/0!
M02	1.082	3.9E-01	0.903	3.2E-01	0.879	1.9E-01
M03	1.149	4.5E-02	1.054	5.8E-01	1.128	3.0E-01
M04	1.023	8.4E-01	0.883	4.0E-01	0.889	3.9E-01
M05	0.984	8.3E-01	0.884	1.6E-01	0.863	8.5E-02
M06	1.041	6.8E-01	0.851	1.9E-01	0.898	3.1E-01
M07	1.177	2.6E-01	0.970	8.6E-01	0.927	6.4E-01
M08	1.053	6.7E-01	0.847	2.6E-01	0.765	5.4E-02
M09	1.404	2.5E-02	1.243	2.4E-01	1.391	1.3E-01
M10	0.981	7.1E-01	0.924	2.3E-01	0.896	7.6E-02
M11	1.010	9.0E-01	0.878	2.0E-01	0.903	2.5E-01
M12	1.124	2.5E-01	0.963	7.4E-01	0.898	3.3E-01
M13	1.035	6.7E-01	0.873	1.7E-01	0.787	1.3E-02
M14	1.372	1.2E-02	1.306	7.7E-02	1.500	2.7E-02
M15	1.026	7.0E-01	0.862	7.8E-02	0.896	1.7E-01
M16	1.131	2.1E-01	0.880	2.9E-01	0.951	6.2E-01
M17	1.258	8.8E-02	1.001	1.0E+00	1.004	9.8E-01
M18	1.067	5.6E-01	0.851	3.0E-01	0.761	4.9E-02
M19	1.426	2.4E-02	1.266	2.1E-01	1.451	1.1E-01
M20	1.004	9.6E-01	0.858	1.1E-01	0.898	2.5E-01
M21	1.057	5.8E-01	0.820	1.0E-01	0.851	1.2E-01
M22	1.162	2.4E-01	0.970	8.4E-01	0.942	6.9E-01
M23	1.016	8.7E-01	0.858	2.8E-01	0.759	1.5E-02
M24	1.300	9.4E-02	1.156	4.3E-01	1.319	2.4E-01

(continued)

	50-59 vs. 40-49, Male		60-69 vs. 40-49, Male		70+ vs. 40-49, Male	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest
M25	1.391	3.5E-02	1.321	9.0E-02	1.553	8.2E-03

Table 34. Effect of Age on Ethanolamine Phospholipid Ratios to M01 in Females

	Age Ctl, 30-39, Female		Age Ctl, 40-49, Female		Aqe Ctl, 50-59, Female		Age Ctl, 60-69, Female		Age Ctl, 70+ Female	
Metabolite Code	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
M01	1.000	0.000	1.000	0.000	1.000	0.000	1.000	0.000	1.000	0.000
M02	0.474	0.037	0.597	0.028	0.551	0.020	0.460	0.018	0.455	0.023
M03	0.931	0.089	0.911	0.043	0.926	0.030	0.750	0.034	0.838	0.048
M04	0.279	0.036	0.283	0.017	0.241	0.011	0.184	0.010	0.221	0.020
M05	0.112	0.009	0.118	0.006	0.105	0.003	0.085	0.005	0.089	0.006
M06	0.311	0.044	0.291	0.019	0.261	0.010	0.193	0.012	0.213	0.017
M07	0.618	0.090	0.667	0.056	0.582	0.030	0.435	0.039	0.430	0.041
M08	0.079	0.008	0.089	0.007	0.070	0.003	0.047	0.004	0.052	0.007
M09	0.204	0.036	0.194	0.017	0.197	0.011	0.139	0.012	0.163	0.015
M10	0.491	0.027	0.535	0.024	0.490	0.010	0.424	0.015	0.422	0.022
M11	1.220	0.159	1.092	0.060	1.021	0.031	0.823	0.037	0.840	0.058
M12	1.979	0.150	2.044	0.117	1.952	0.063	1.534	0.086	1.564	0.100
M13	0.129	0.008	0.136	0.007	0.122	0.004	0.092	0.005	0.104	0.010
M14	0.379	0.047	0.381	0.024	0.414	0.018	0.333	0.021	0.412	0.033
M15	0.706	0.044	0.720	0.034	0.699	0.019	0.560	0.024	0.578	0.033
M16	2.739	0.333	2.483	0.161	2.345	0.091	1.783	0.096	1.964	0.136
M17	4.055	0.499	4.149	0.401	3.987	0.209	2.963	0.275	3.010	0.268
M18	0.282	0.022	0.289	0.022	0.245	0.010	0.160	0.012	0.191	0.024
M19	1.009	0.175	0.902	0.085	0.974	0.056	0.716	0.061	0.877	0.077
M20	0.708	0.059	0.682	0.045	0.637	0.021	0.524	0.029	0.565	0.039
M21	2.885	0.411	2.537	0.187	2.331	0.092	1.757	0.105	1.935	0.158
M22	8.971	0.932	9.244	0.790	8.625	0.450	6.263	0.484	6.923	0.683
M23	0.198	0.011	0.202	0.014	0.177	0.006	0.124	0.008	0.140	0.014
M24	0.955	0.174	0.834	0.078	0.882	0.049	0.661	0.054	0.814	0.071
M25	2.505	0.217	2.286	0.164	3.219	0.181	2.995	0.239	3.280	0.248

Table 35. Ratio and T-test values of Ethanolamine Phospholipid Ratios to M01 between females of different ages

	50-59 vs. 40-49, Female		60-69 vs. 40-49, Female		70+ vs. 40-49, Female	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest
M01	1.000	#DIV/0!	1.000	#DIV/0!	1.000	#DIV/0!
M02	0.923	2.1E-01	0.771	5.7E-05	0.763	8.4E-04
M03	1.017	7.8E-01	0.823	3.7E-03	0.920	2.8E-01
M04	0.850	3.5E-02	0.652	1.1E-06	0.782	2.3E-02
M05	0.892	4.7E-02	0.721	5.0E-05	0.758	3.7E-03
M06	0.896	1.3E-01	0.662	1.3E-05	0.733	6.5E-03

(continued)

	50-59 vs. 40-49, Female		60-69 vs. 40-49, Female		70+ vs. 40-49, Female	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest
M07	0.873	1.5E-01	0.652	7.2E-04	0.644	3.5E-03
M08	0.783	4.7E-03	0.533	6.9E-07	0.583	9.9E-04
M09	1.016	8.8E-01	0.717	7.8E-03	0.841	2.2E-01
M10	0.917	4.8E-02	0.792	7.9E-05	0.789	2.0E-03
M11	0.935	2.5E-01	0.754	1.3E-04	0.770	5.9E-03
M12	0.955	4.6E-01	0.751	5.1E-04	0.765	5.8E-03
M13	0.900	7.0E-02	0.680	4.8E-06	0.764	9.1E-03
M14	1.088	3.1E-01	0.876	1.4E-01	1.083	4.3E-01
M15	0.970	5.6E-01	0.778	1.8E-04	0.802	6.7E-03
M16	0.944	4.3E-01	0.718	1.8E-04	0.791	2.8E-02
M17	0.961	7.0E-01	0.714	1.4E-02	0.726	4.4E-02
M18	0.847	4.1E-02	0.552	6.0E-07	0.660	5.6E-03
M19	1.079	4.9E-01	0.794	7.2E-02	0.972	8.4E-01
M20	0.935	3.1E-01	0.769	2.9E-03	0.828	7.5E-02
M21	0.919	2.7E-01	0.693	2.4E-04	0.763	2.9E-02
M22	0.933	4.8E-01	0.678	1.2E-03	0.749	4.6E-02
M23	0.876	5.5E-02	0.614	1.3E-06	0.696	3.9E-03
M24	1.058	6.0E-01	0.793	6.5E-02	0.976	8.6E-01
M25	1.408	2.4E-03	1.310	2.2E-02	1.435	8.6E-04

Table 36. Average Serum Ethanolamine Phospholipid Ratios to M01 in Males of Different Levels of Dementia Severity

	Cognitive Normal, Male		SDAT all, Male		SDAT, ADAS 5-19, Male		SDAT, ADAS 20-39, Male		SDAT, ADAS 40-70, Male	
Metabolite Code	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
M01	1.000	0.000	1.000	0.000	1.000	0.000	1.000	0.000	1.000	0.000
M02	0.564	0.031	0.453	0.015	0.475	0.032	0.455	0.017	0.383	0.022
M03	0.960	0.050	0.712	0.018	0.779	0.037	0.694	0.024	0.617	0.027
M04	0.262	0.015	0.210	0.009	0.203	0.017	0.219	0.013	0.183	0.014
M05	0.106	0.006	0.089	0.002	0.091	0.004	0.089	0.003	0.085	0.004
M06	0.255	0.014	0.213	0.007	0.211	0.012	0.214	0.010	0.211	0.012
M07	0.554	0.041	0.373	0.014	0.396	0.025	0.375	0.020	0.321	0.028
M08	0.062	0.005	0.044	0.002	0.047	0.004	0.045	0.003	0.038	0.003
M09	0.195	0.015	0.126	0.006	0.139	0.012	0.127	0.009	0.093	0.008
M10	0.483	0.021	0.440	0.009	0.450	0.016	0.441	0.013	0.408	0.016
M11	0.985	0.043	0.817	0.025	0.828	0.051	0.824	0.035	0.761	0.036
M12	1.843	0.088	1.399	0.036	1.460	0.059	1.406	0.053	1.252	0.090
M13	0.114	0.006	0.092	0.002	0.096	0.004	0.091	0.003	0.088	0.006
M14	0.442	0.023	0.310	0.013	0.348	0.028	0.301	0.015	0.255	0.025
M15	0.682	0.031	0.548	0.012	0.571	0.022	0.541	0.016	0.520	0.024
M16	2.398	0.128	1.790	0.057	1.856	0.105	1.777	0.082	1.687	0.115
M17	4.203	0.304	2.569	0.105	2.853	0.205	2.501	0.135	2.187	0.243
M18	0.232	0.017	0.156	0.006	0.166	0.012	0.155	0.009	0.140	0.010
M19	1.103	0.092	0.663	0.032	0.740	0.066	0.660	0.041	0.503	0.045

(continued)

	Cognitive Normal, Male		SDAT all, Male		SDAT, ADAS 5-19, Male		SDAT, ADAS 20-39, Male		SDAT, ADAS 40-70, Male	
Metabolite Code	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
M20	0.692	0.037	0.548	0.016	0.593	0.030	0.532	0.021	0.509	0.034
M21	2.377	0.126	1.857	0.066	1.951	0.128	1.829	0.090	1.754	0.143
M22	9.309	0.674	6.230	0.231	6.651	0.434	6.157	0.305	5.616	0.592
M23	0.164	0.009	0.125	0.004	0.133	0.008	0.124	0.006	0.114	0.008
M24	1.010	0.088	0.672	0.034	0.770	0.076	0.647	0.039	0.539	0.053
M25	2.160	0.133	2.085	0.115	2.215	0.145	2.102	0.197	1.811	0.222

Table 37. Ratio and T-test Values of Ethanolamine Phospholipid Ratios to M01 between Males of Various Levels of Dementia

	AD, All to CN, Male		ADAS 5-19 to CN, Male		ADAS 20-39 to CN, Male		ADAS 40-70 to CN, Male	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest	Ratio	ttest
M01	1.000	#DIV/0!	1.000	#DIV/0!	1.000	#DIV/0!	1.000	#DIV/0!
M02	0.803	7.2E-04	0.842	5.2E-02	0.807	1.2E-03	0.680	1.8E-04
M03	0.742	6.4E-08	0.812	3.8E-03	0.724	4.5E-07	0.643	9.8E-06
M04	0.802	8.4E-03	0.774	1.6E-02	0.836	4.1E-02	0.700	1.3E-03
M05	0.840	9.2E-04	0.858	2.9E-02	0.841	5.5E-03	0.798	1.2E-02
M06	0.833	5.0E-03	0.827	2.0E-02	0.840	2.2E-02	0.828	4.7E-02
M07	0.673	4.7E-07	0.715	1.1E-03	0.676	3.1E-05	0.580	2.4E-04
M08	0.713	1.1E-04	0.747	1.3E-02	0.727	1.5E-03	0.602	8.4E-04
M09	0.645	2.8E-06	0.713	4.4E-03	0.654	7.5E-05	0.476	1.6E-05
M10	0.910	3.4E-02	0.932	2.1E-01	0.913	8.0E-02	0.843	1.8E-02
M11	0.830	1.9E-03	0.841	2.5E-02	0.837	5.8E-03	0.773	9.3E-04
M12	0.759	3.4E-07	0.792	3.9E-04	0.763	1.9E-05	0.679	7.0E-05
M13	0.811	1.0E-04	0.846	1.2E-02	0.802	4.0E-04	0.772	4.7E-03
M14	0.701	4.1E-06	0.787	1.4E-02	0.680	1.1E-06	0.576	4.9E-06
M15	0.803	2.7E-06	0.837	3.8E-03	0.792	2.4E-05	0.762	8.6E-04
M16	0.747	4.3E-06	0.774	1.5E-03	0.741	4.8E-05	0.704	5.4E-04
M17	0.611	2.1E-09	0.679	3.1E-04	0.595	7.2E-08	0.520	4.0E-05
M18	0.672	9.8E-07	0.714	1.7E-03	0.666	2.3E-05	0.603	3.3E-04
M19	0.601	6.5E-08	0.672	1.7E-03	0.599	2.1E-06	0.456	2.2E-05
M20	0.793	9.1E-05	0.858	3.8E-02	0.769	1.0E-04	0.736	1.8E-03
M21	0.782	3.7E-04	0.821	2.2E-02	0.770	5.6E-04	0.738	3.0E-03
M22	0.669	2.0E-07	0.714	9.9E-04	0.661	4.8E-06	0.603	6.0E-04
M23	0.763	1.2E-04	0.810	1.5E-02	0.754	4.8E-04	0.696	6.5E-04
M24	0.665	3.5E-05	0.763	4.2E-02	0.641	3.5E-05	0.533	4.0E-04
M25	0.965	7.5E-01	1.025	7.9E-01	0.973	8.4E-01	0.838	1.6E-01

Table 38. Ratio and T-test Values of Ethanolamine Phospholipid Ratios to M01 Between Males of Various Levels of Dementia

	ADAS 20-39 to 5-19, Male		ADAS 40-70 to 5-19, Male		ADAS 40-70 to 20-39, Male	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest
M01	1.000	#DIV/0!	1.000	#DIV/0!	1.000	#DIV/0!
M02	0.958	5.5E-01	0.807	7.1E-02	0.843	3.5E-02
M03	0.891	4.6E-02	0.792	6.9E-03	0.888	9.3E-02
M04	1.080	4.5E-01	0.903	4.8E-01	0.837	1.4E-01
M05	0.980	7.2E-01	0.930	3.2E-01	0.948	4.4E-01
M06	1.016	8.4E-01	1.002	9.8E-01	0.987	8.9E-01
M07	0.946	5.1E-01	0.811	8.4E-02	0.857	1.8E-01
M08	0.973	7.8E-01	0.806	1.3E-01	0.828	1.3E-01
M09	0.917	4.2E-01	0.668	1.5E-02	0.728	3.5E-02
M10	0.980	6.6E-01	0.905	1.1E-01	0.923	1.9E-01
M11	0.995	9.4E-01	0.919	4.0E-01	0.924	3.5E-01
M12	0.964	5.1E-01	0.858	5.8E-02	0.890	1.6E-01
M13	0.948	3.5E-01	0.913	2.6E-01	0.963	6.3E-01
M14	0.864	1.1E-01	0.732	4.1E-02	0.847	1.4E-01
M15	0.947	2.6E-01	0.911	1.7E-01	0.962	5.2E-01
M16	0.957	5.5E-01	0.909	3.4E-01	0.950	5.8E-01
M17	0.877	1.4E-01	0.767	6.0E-02	0.875	2.6E-01
M18	0.932	4.5E-01	0.844	1.9E-01	0.905	3.9E-01
M19	0.891	2.8E-01	0.679	2.6E-02	0.762	4.5E-02
M20	0.896	8.6E-02	0.858	9.6E-02	0.957	5.9E-01
M21	0.937	4.2E-01	0.899	3.6E-01	0.959	6.8E-01
M22	0.926	3.4E-01	0.844	1.8E-01	0.912	4.0E-01
M23	0.931	3.9E-01	0.860	1.8E-01	0.923	4.5E-01
M24	0.840	1.2E-01	0.699	5.7E-02	0.832	1.5E-01
M25	0.949	6.7E-01	0.818	1.3E-01	0.862	4.4E-01

Table 39. Effect of Dementia State on Ethanolamine Phospholipid Ratios to M01 in Females

	Cognitive Normal, Female		SDAT all, Female		SDAT, ADAS 5-19, Female		SDAT, ADAS 20-39, Female		SDAT, ADAS 40-70, Female	
Metabolite Code	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
M01	1.000	0.000	1.000	0.000	1.000	0.000	1.000	0.000	1.000	0.000
M02	0.520	0.029	0.463	0.012	0.454	0.021	0.499	0.023	0.431	0.018
M03	0.852	0.034	0.687	0.017	0.742	0.030	0.704	0.031	0.624	0.022
M04	0.222	0.013	0.219	0.010	0.215	0.013	0.241	0.021	0.197	0.015
M05	0.092	0.004	0.086	0.003	0.091	0.004	0.088	0.005	0.081	0.004
M06	0.234	0.012	0.207	0.007	0.226	0.011	0.217	0.013	0.180	0.009
M07	0.474	0.034	0.368	0.018	0.422	0.039	0.377	0.028	0.314	0.025
M08	0.054	0.004	0.047	0.002	0.050	0.003	0.051	0.004	0.039	0.002
M09	0.167	0.013	0.121	0.005	0.140	0.010	0.123	0.009	0.103	0.008
M10	0.469	0.016	0.431	0.010	0.451	0.016	0.428	0.018	0.418	0.016
M11	0.929	0.039	0.807	0.023	0.886	0.041	0.839	0.044	0.708	0.030
M12	1.682	0.078	1.384	0.042	1.568	0.090	1.384	0.067	1.239	0.062

(continued)

	Cognitive Normal, Female		SDAT all, Female		SDAT, ADAS 5-19, Female		SDAT, ADAS 20-39, Female		SDAT, ADAS 40-70, Female	
Metabolite Code	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
M13	0.111	0.005	0.095	0.003	0.101	0.005	0.095	0.005	0.089	0.004
M14	0.392	0.023	0.315	0.013	0.367	0.029	0.309	0.019	0.279	0.019
M15	0.627	0.024	0.539	0.014	0.564	0.021	0.563	0.030	0.493	0.016
M16	2.214	0.114	1.780	0.064	1.994	0.107	1.906	0.127	1.470	0.069
M17	3.497	0.247	2.593	0.127	2.976	0.266	2.750	0.226	2.115	0.146
M18	0.202	0.014	0.161	0.007	0.178	0.011	0.170	0.014	0.138	0.008
M19	0.895	0.061	0.634	0.030	0.728	0.057	0.656	0.055	0.537	0.041
M20	0.669	0.036	0.535	0.018	0.587	0.032	0.553	0.036	0.474	0.022
M21	2.318	0.118	1.798	0.076	2.039	0.132	1.922	0.147	1.467	0.086
M22	8.068	0.596	6.310	0.304	7.041	0.600	6.681	0.568	5.313	0.360
M23	0.158	0.009	0.127	0.005	0.139	0.009	0.131	0.010	0.112	0.006
M24	0.893	0.068	0.651	0.034	0.724	0.063	0.669	0.059	0.573	0.053
M25	2.145	0.127	2.031	0.086	2.072	0.129	2.109	0.162	1.910	0.139

Table 40. Ratio and T-test values of Ethanolamine Phospholipid Ratios to M01 between females of various levels of dementia

	AD, All to CN, Female		ADAS 5-19 to CN, Female		ADAS 20-39 to CN, Female		ADAS 40-70 to CN, Female	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest	Ratio	ttest
M01	1.000	#DIV/0!	1.000	#DIV/0!	1.000	#DIV/0!	1.000	#DIV/0!
M02	0.891	4.7E-02	0.872	6.4E-02	0.960	5.7E-01	0.828	7.0E-03
M03	0.806	1.3E-05	0.871	1.6E-02	0.826	2.1E-03	0.732	6.8E-08
M04	0.986	8.8E-01	0.968	7.0E-01	1.086	4.9E-01	0.887	2.3E-01
M05	0.941	3.5E-01	0.989	8.7E-01	0.962	6.4E-01	0.879	5.5E-02
M06	0.885	6.6E-02	0.966	6.3E-01	0.928	3.7E-01	0.771	2.8E-04
M07	0.776	6.7E-03	0.890	3.2E-01	0.796	3.2E-02	0.663	2.3E-04
M08	0.869	1.3E-01	0.934	4.9E-01	0.943	6.2E-01	0.735	1.5E-03
M09	0.724	3.1E-04	0.837	1.0E-01	0.740	5.4E-03	0.618	4.2E-05
M10	0.919	7.3E-02	0.963	4.4E-01	0.913	1.1E-01	0.892	3.1E-02
M11	0.868	1.6E-02	0.953	4.4E-01	0.902	1.5E-01	0.762	2.0E-05
M12	0.823	1.5E-03	0.932	3.4E-01	0.823	5.0E-03	0.736	2.0E-05
M13	0.854	6.6E-03	0.914	1.8E-01	0.854	3.1E-02	0.806	9.4E-04
M14	0.802	5.5E-03	0.935	4.9E-01	0.789	6.6E-03	0.711	2.4E-04
M15	0.860	4.8E-03	0.900	5.1E-02	0.897	1.3E-01	0.786	9.1E-06
M16	0.804	2.1E-03	0.901	1.6E-01	0.861	9.3E-02	0.664	8.8E-08
M17	0.742	1.5E-03	0.851	1.6E-01	0.786	3.2E-02	0.605	2.3E-06
M18	0.798	9.5E-03	0.879	1.8E-01	0.844	1.4E-01	0.683	6.3E-05
M19	0.709	1.6E-04	0.813	5.1E-02	0.733	5.3E-03	0.600	3.2E-06
M20	0.800	1.0E-03	0.878	8.7E-02	0.826	2.8E-02	0.709	3.4E-06
M21	0.776	1.4E-03	0.879	1.2E-01	0.829	5.6E-02	0.633	5.4E-08
M22	0.782	9.6E-03	0.873	2.3E-01	0.828	1.1E-01	0.659	7.8E-05
M23	0.801	5.3E-03	0.877	1.3E-01	0.831	6.8E-02	0.707	4.5E-05

(continued)

	AD, All to CN, Female		ADAS 5-19 to CN, Female		ADAS 20-39 to CN, Female		ADAS 40-70 to CN, Female	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest	Ratio	ttest
M24	0.729	1.6E-03	0.811	7.2E-02	0.750	1.7E-02	0.642	3.3E-04
M25	0.947	5.3E-01	0.966	6.9E-01	0.983	8.7E-01	0.890	2.3E-01

Table 41. Ratio and T-test values of Ethanolamine Phospholipid Ratios to M01 between females of various levels of dementia

	ADAS 20-39 to 5-19, Female		ADAS 40-70 to 5-19, Female		ADAS 40-70 to 20-39, Female	
Metabolite Code	Ratio	ttest	Ratio	ttest	Ratio	ttest
M01	1.000	#DIV/0!	1.000	#DIV/0!	1.000	#DIV/0!
M02	1.101	1.6E-01	0.949	4.1E-01	0.862	2.2E-02
M03	0.949	4.0E-01	0.841	1.5E-03	0.887	4.2E-02
M04	1.122	3.3E-01	0.917	3.8E-01	0.817	9.2E-02
M05	0.972	7.3E-01	0.889	7.6E-02	0.914	2.6E-01
M06	0.961	6.3E-01	0.797	1.3E-03	0.830	2.4E-02
M07	0.895	3.4E-01	0.745	1.7E-02	0.833	9.8E-02
M08	1.010	9.4E-01	0.787	1.1E-02	0.780	3.5E-02
M09	0.884	2.4E-01	0.738	6.7E-03	0.835	1.0E-01
M10	0.948	3.5E-01	0.926	1.5E-01	0.977	6.8E-01
M11	0.947	4.6E-01	0.799	6.4E-04	0.844	1.9E-02
M12	0.883	9.7E-02	0.790	2.5E-03	0.895	1.2E-01
M13	0.934	3.6E-01	0.882	5.3E-02	0.944	4.1E-01
M14	0.844	8.6E-02	0.761	9.9E-03	0.902	2.6E-01
M15	0.998	9.7E-01	0.874	7.7E-03	0.876	5.3E-02
M16	0.956	6.2E-01	0.737	5.0E-05	0.771	4.2E-03
M17	0.924	5.2E-01	0.711	3.6E-03	0.769	2.4E-02
M18	0.960	7.2E-01	0.777	4.1E-03	0.809	5.7E-02
M19	0.901	3.8E-01	0.738	7.1E-03	0.819	9.2E-02
M20	0.941	4.9E-01	0.808	3.7E-03	0.858	7.3E-02
M21	0.943	5.8E-01	0.720	3.1E-04	0.763	1.1E-02
M22	0.949	6.7E-01	0.755	1.2E-02	0.795	5.1E-02
M23	0.948	6.1E-01	0.806	1.4E-02	0.851	1.1E-01
M24	0.925	5.4E-01	0.791	6.9E-02	0.856	2.3E-01
M25	1.018	8.7E-01	0.922	4.0E-01	0.906	3.6E-01

Table 42. Effect of Pathology State on Ethanolamine Phospholipid Ratios to M01 in Males

	Post Mortem Ctl, Male		Post Mortem SDAT Male		SDAT vs Control	
Metabolite Code	Mean	SEM	Mean	SEM	Ratio	ttest
M01	1.000	0.000	1.000	0.000	1.000	#DIV/0!
M02	0.367	0.029	0.290	0.029	0.791	0.076
M03	0.482	0.042	0.391	0.013	0.811	0.054
M04	0.143	0.031	0.076	0.009	0.529	0.052
M05	0.048	0.009	0.029	0.002	0.607	0.052

(continued)

	Post Mortem Ctl, Male		Post Mortem SDAT Male		SDAT vs Control	
Metabolite Code	Mean	SEM	Mean	SEM	Ratio	ttest
M06	0.080	0.014	0.046	0.003	0.581	0.033
M07	0.107	0.025	0.059	0.005	0.549	0.074
M08	0.024	0.005	0.012	0.001	0.511	0.037
M09	0.052	0.018	0.018	0.002	0.341	0.074
M10	0.337	0.038	0.269	0.013	0.798	0.107
M11	0.452	0.066	0.272	0.017	0.602	0.016
M12	0.819	0.130	0.616	0.024	0.753	0.143
M13	0.079	0.009	0.060	0.005	0.759	0.085
M14	0.212	0.039	0.115	0.010	0.542	0.026
M15	0.375	0.035	0.344	0.025	0.918	0.483
M16	0.792	0.128	0.627	0.047	0.791	0.240
M17	0.849	0.191	0.561	0.040	0.660	0.156
M18	0.085	0.011	0.056	0.004	0.656	0.018
M19	0.273	0.051	0.164	0.015	0.601	0.056
M20	0.254	0.027	0.187	0.009	0.737	0.028
M21	0.613	0.109	0.371	0.021	0.605	0.042
M22	1.890	0.379	1.199	0.083	0.634	0.092
M23	0.074	0.008	0.055	0.004	0.750	0.061
M24	0.241	0.039	0.142	0.011	0.588	0.025
M25	2.066	0.225	2.384	0.388	1.154	0.487

Table 43. Effect of Pathology State on Ethanolamine Phospholipid Ratios to M01 in Females

	Post Mortem Ctl, Female		Post Mortem SDAT Female		Autopsy AD vs. Control, Female	
Metabolite Code	Mean	SEM	Mean	SEM	Ratio	ttest
M01	1.000	0.000	1.000	0.000	1.000	#DIV/0!
M02	0.322	0.028	0.367	0.047	1.140	0.440
M03	0.400	0.022	0.361	0.023	0.902	0.237
M04	0.086	0.012	0.092	0.019	1.069	0.798
M05	0.040	0.003	0.032	0.005	0.809	0.225
M06	0.069	0.008	0.059	0.017	0.855	0.605
M07	0.102	0.016	0.077	0.013	0.752	0.242
M08	0.017	0.002	0.017	0.002	0.981	0.922
M09	0.033	0.005	0.024	0.003	0.725	0.133
M10	0.290	0.025	0.291	0.027	1.003	0.981
M11	0.384	0.044	0.364	0.057	0.950	0.797
M12	0.731	0.096	0.699	0.059	0.957	0.777
M13	0.061	0.008	0.069	0.007	1.122	0.489
M14	0.144	0.015	0.155	0.033	1.071	0.791
M15	0.339	0.021	0.301	0.027	0.889	0.297
M16	0.670	0.066	0.599	0.112	0.895	0.605
M17	0.697	0.063	0.591	0.082	0.848	0.329
M18	0.081	0.014	0.069	0.008	0.854	0.462
M19	0.211	0.017	0.180	0.018	0.853	0.230

(continued)

	Post Mortem Ctl, Female		Post Mortem SDAT Female		Autopsy AD vs. Control, Female	
Metabolite Code	Mean	SEM	Mean	SEM	Ratio	ttest
M20	0.283	0.025	0.193	0.032	0.680	0.042
M21	0.624	0.079	0.421	0.127	0.674	0.203
M22	1.782	0.251	1.480	0.225	0.831	0.382
M23	0.073	0.011	0.060	0.006	0.816	0.275
M24	0.214	0.018	0.149	0.016	0.697	0.016
M25	1.382	0.214	1.767	0.221	1.279	0.229

Table 44. Effect of Dementia State on White and Gray Matter Scores in Males

	White Matter Score		Gray Matter Score	
Cohort	Mean	SEM	Mean	SEM
Cognitive Normal, Male	-0.25	0.08	-0.44	0.11
SDAT_all, Male	-0.63	0.06	-1.11	0.08
SDAT, ADAS 5-19, Male	-0.56	0.09	-1.00	0.13
SDAT, ADAS 20-39, Male	-0.67	0.08	-1.11	0.10
SDAT, ADAS 40-70, Male	-0.71	0.14	-1.45	0.16
Post Mortem Ctl, Male	-0.44	0.13	-0.41	0.21
Post Mortem SDAT Male	-1.62	0.19	-1.28	0.23
Comparison	White Matter Score		Gray Matter Score	
AD, All to CN, Male	Delta ttest	-0.37 1.9E-03	Delta ttest	-0.67 2.4E-05
ADAS 5-19 to CN, Male	Delta ttest	-0.31 1.8E-02	Delta ttest	-0.56 2.5E-03
ADAS 20-39 to CN, Male	Delta ttest	-0.41 1.5E-03	Delta ttest	-0.67 7.8E-05
ADAS 40-70 to CN, Male	Delta ttest	-0.46 3.7E-03	Delta ttest	-1.01 1.8E-06
ADAS 20-39 to 5-19, Male	Delta ttest	-0.10 4.2E-01	Delta ttest	-0.11 5.0E-01
ADAS 40-70 to 5-19, Male	Delta ttest	-0.15 3.9E-01	Delta ttest	-0.45 5.2E-02
ADAS 40-70 to 20-39, Male	Delta ttest	-0.04 8.0E-01	Delta ttest	-0.34 1.1E-01
Autopsy AD vs. Control, Mal	Delta ttest	-0.89 8.9E-03	Delta ttest	-1.13 2.8E-03

Table 45. Effect of Dementia State on White and Gray Matter Scores in Females

	White Matter Score		Gray Matter Score	
Cohort	Mean	SEM	Mean	SEM
Cognitive Normal, Female	-0.27	0.09	-0.42	0.13
SDAT_all, Female	-0.73	0.05	-1.01	0.07
SDAT, ADAS 5-19, Female	-0.55	0.08	-0.85	0.11
SDAT, ADAS 20-39, Female	-0.69	0.09	-0.94	0.11
SDAT, ADAS 40-70, Female	-0.91	0.08	-1.21	0.12
Post Mortem Ctl, Female	-0.50	0.29	-0.53	0.26
Post Mortem SDAT Female	-1.34	0.27	-1.54	0.25

(continued)

Comparison	White Matter Score		Gray Matter Score	
AD, All to CN, Female	Delta ttest	-0.46 4.6E-05	Delta ttest	-0.59 1.1E-04
ADAS 5-19 to CN, Female	Delta ttest	-0.29 1.7E-02	Delta ttest	-0.43 1.3E-02
ADAS 20-39 to CN, Female	Delta ttest	-0.43 1.9E-03	Delta ttest	-0.52 3.6E-03
ADAS 40-70 to CN, Female	Delta ttest	-0.64 9.5E-07	Delta ttest	-0.79 2.2E-05
ADAS 20-39 to 5-19, Female	Delta ttest	-0.14 2.7E-01	Delta ttest	-0.09 5.8E-01
ADAS 40-70 to 5-19, Female	Delta ttest	-0.36 2.9E-03	Delta ttest	-0.37 3.1E-02
ADAS 40-70 to 20-39, Female	Delta ttest	-0.21 9.4E-02	Delta ttest	-0.27 1.0E-01
Autopsy AD vs. Control, Female	Delta ttest	-1.17 2.0E-03	Delta ttest	-0.81 2.5E-02

Table 46. Distribution of White and Gray Matter Scores in Males (Mean Normalized to CN Male)

White Matter Distribution

	MMSE ≥ 28	ADAS-cog 8-19	ADAS-cog 20-39	ADAS-cog 40-70	Autopsy Control	Autopsy AD
Bin	*Frequency*	*Frequency*	*Frequency*	*Frequency*	*Frequency*	*Frequency*
-2	0	1	1	0	0	2
-1.75	0	0	0	0	0	0
-1.5	0	0	3	1	0	0
-1.25	0	2	4	0	0	1
-1	1	2	3	1	0	2
-0.75	1	3	3	4	0	2
-0.5	3	2	6	4	2	0
-0.25	3	8	13	4	3	1
0	7	13	12	0	2	1
0.25	9	6	5	1	2	1
0.5	5	1	5	2	0	0
0.75	1	0	1	0	1	0
1	2	0	2	1	0	0
More	0	2	0	0	0	0

Gray Matter distribution

	MMSE ≥ 28	ADAS-cog 8-19	ADAS-cog 20-39	ADAS-cog 40-70	Autopsy Control	Autopsy AD
Bin	*Frequency*	*Frequency*	*Frequency*	*Frequency*	*Frequency*	*Frequency*
-2	0	1	4	2	0	2
-1.75	0	2	2	1	0	0
-1.5	0	1	3	0	0	0
-1.25	1	4	2	2	0	1
-1	0	6	7	4	0	2
-0.75	1	4	9	2	1	3
-0.5	7	3	5	4	1	1
-0.25	3	5	9	1	2	0
0	3	2	7	1	1	0
0.25	5	4	2	1	3	0
0.5	7	3	4	0	1	1
0.75	3	1	2	0	0	0
1	0	3	2	0	0	0

(continued)

Gray Matter distribution

	MMSE ≥ 28	ADAS-cog 8-19	ADAS-cog 20-39	ADAS-cog 40-70	Autopsy Control	Autopsy AD
Bin	*Frequency*	*Frequency*	*Frequency*	*Frequency*	*Frequency*	*Frequency*
More	2	1	0	0	1	0

Table 47. Distribution of White and Gray Matter Scores in Females (Mean Normalized to CN Female)

White Matter Distribution

	MSE ≥ 28	ADAS-cog 8-19	ADAS-cog 20-39	ADAS-cog 40-70	Autopsy Control	Autopsy AD
Bin	*Frequency*	*Frequency*	*Frequency*	*Frequency*	*Frequency*	*Frequency*
-2	0	0	0	1	0	1
-1.75	0	0	0	0	0	1
-1.5	0	0	3	4	1	3
-1.25	1	0	2	1	0	0
-1	1	2	8	4	0	3
-0.75	1	5	6	11	1	0
-0.5	2	6	6	10	1	1
-0.25	4	8	6	3	2	1
0	9	5	8	9	1	0
0.25	8	6	5	3	2	0
0.5	3	3	6	1	0	0
0.75	4	3	1	1	0	0
1	3	0	2	0	0	0
More	0	0	1	0	1	0

Gray Matter distribution

	MMSE ≥ 28	ADAS-cog 8-19	ADAS-cog 20-39	ADAS-cog 40-70	Autopsy Control	Autopsy AD
Bin	*Frequency*	*Frequency*	*Frequency*	*Frequency*	*Frequency*	*Frequency*
-2	0	0	1	4	0	1
-1.75	0	1	2	1	0	1
-1.5	1	1	3	6	0	0
-1.25	2	2	4	6	0	0
-1	2	3	8	4	1	2
-0.75	1	5	6	5	0	1
-0.5	1	6	4	6	1	2
-0.25	5	6	7	3	2	0
0	4	5	4	3	2	2
0.25	6	3	6	6	2	1
0.5	5	2	2	1	0	0
0.75	3	1	2	2	0	0
1	3	2	2	0	0	0
More	3	1	3	1	1	0

Table 48. Effect of Age on White and Gray Matter Scores in Males

	White Matter Score		Gray Matter Score	
Cohort	Mean	SEM	Mean	SEM
Age Ctl, 30-39, Male	-0.25	0.29	-0.92	0.28

(continued)

	White Matter Score		Gray Matter Score	
Cohort	Mean	SEM	Mean	SEM
Age Ctl, 40-49, Male	-0.48	0.10	-1.28	0.14
Age Ctl, 50-59, Male	-0.47	0.08	-0.90	0.11
Age Ctl, 60-69, Male	-0.53	0.10	-0.84	0.14
Age Ctl, 70+_Male	-0.43	0.09	-0.78	0.14
Comparison	White Matter Score		Gray Matter Score	
50-59 vs. 40-49, Male	Delta ttest	0.01 9.4E-01	Delta ttest	0.38 4.2E-02
60-69 vs. 40-49, Male	Delta ttest	-0.05 7.4E-01	Delta ttest	0.45 3.2E-02
70+ vs. 40-49, Male	Delta ttest	0.05 7.2E-01	Delta ttest	0.50 1.4E-02

Table 49. Effect of Age on White and Gray Matter Scores in Females

	White Matter Score		Gray Matter Score	
Cohort	Mean	SEM	Mean	SEM
Age Ctl, 30-39, Female	-0.36	0.18	-0.56	0.27
Age Ctl, 40-49, Female	-0.33	0.10	-0.61	0.13
Age Ctl, 50-59, Female	-0.55	0.06	-0.71	0.09
Age Ctl, 60-69, Female	-0.62	0.09	-0.90	0.12
Age Ctl, 70+_Female	-0.47	0.11	-0.58	0.14
Comparison	White Matter Score		Gray Matter Score	
50-59 vs. 40-49, Female	Delta ttest	-0.22 6.9E-02	Delta ttest	-0.10 5.4E-01
60-69 vs. 40-49, Female	Delta ttest	-0.29 3.6E-02	Delta ttest	-0.30 1.1E-01
70+ vs. 40-49, Female	Delta ttest	-0.14 3.7E-01	Delta ttest	0.03 8.8E-01

Table 50. Risk prediction in Males

Stats	CN White Matter Score Control Normalized	Low White Matter Score Control Normalized	Moderate White Matter Score Control Normalized	Severe White Matter Score Control Normalized	PM Ctl White Matter Score Control Normalized	PM SDAT White Matter Score Control Normalized
Total N	32	40	58	18	10	10
Total L	27	30	38	8	8	3
Total H	5	10	20	10	2	7
L%	84.4	75.0	65.5	44.4	80.0	30.0

(continued)

		Gray Matter Score Control Normalized	Gray Matter Score Control Normalized	Gray Matter Score Control Normalized	Gray Matter Score Control Normalized	Gray Matter Score Control Normalized	Gray Matter Score Control Normalized
Total N		32	40	58	18	10	10
Total L		23	19	26	3	8	1
Total H		9	21	32	15	2	9
L%		71.9	47.5	44.8	16.7	80.0	10.0
Low risk	LL	22	19	25	3	7	1
%	LL	68.8	47.5	43.1	16.7	70.0	10.0
Intermediate risk	IM	6	11	14	5	2	2
%	IM	18.8	27.5	24.1	27.8	20.0	20.0
High risk	HH	4	10	19	10	1	7
%	HH	12.5	25.0	32.8	55.6	10.0	70.0

Table 51. Risk Prediction in Females

Stats		CN White Matter Score Control Normalized	Low White Matter Score Control Normalized	Moderate White Matter Score Control Normalized	Severe White Matter Score Control Normalized	PM Ctl White Matter Score Control Normalized	PM SDAT White Matter Score Control Normalized
Total N		36	38	54	48	9	10
Total L		31	25	29	17	6	1
Total H		5	13	25	31	3	9
L%		86.1	65.8	53.7	35.4	66.7	10.0

		Gray Matter Score Control Normalized	Gray Matter Score Control Normalized	Gray Matter Score Control Normalized	Gray Matter Score Control Normalized	Gray Matter Score Control Normalized	Gray Matter Score Control Normalized
Total N		36	38	54	48	9	10
Total L		29	20	26	16	7	3
Total H		7	18	28	32	2	7
L%		80.6	52.6	48.1	33.3	77.8	30.0
Low risk	LL	29	17	24	11	5	0
%	LL	80.6	44.7	44.4	22.9	55.6	0.0

(continued)

		Gray Matter Score Control Normalized	Gray Matter Score Control Normalized	Gray Matter Score Control Normalized	Gray Matter Score Control Normalized	Gray Matter Score Control Normalized	Gray Matter Score Control Normalized
Intermediate risk	IM	2	11	7	11	3	4
%	IM	5.6	28.9	13.0	22.9	33.3	40.0
High risk	HH	5	10	23	26	1	6
%	HH	13.9	26.3	42.6	54.2	11.1	60.0

Table 52. Summary ofkey ratio and p-value statistics for EtnPls 16:0/22:6 (M19) to PtdEt 16:0/18:0 (M01) serum ratio for males and females combined.

Comparison	Ratio	T-test
60-69 to 50-59	0.75	1.2E-02
70-95 to 50-59	0.95	6.4E-01
CN to 50-59	1.07	4.8E-01
SDAT to 50-59	0.70	4.7E-07
70-95 to 60-69	1.26	6.9E-02
CN to 60-69	1.42	3.8E-04
SDAT to 70-95	0.74	1.3E-04
SDAT to CN	0.65	7.6E-11
ADAS 5-19 to CN	0.74	3.0E-04
ADAS 20-39 to CN	0.66	1.3E-07
ADAS 40-70 to CN	0.53	3.9E-11
ADAS 20-39 to ADAS 5-19	0.90	1.6E-01
ADAS 40-70 to ADAS 5-19	0.72	3.4E-04
ADAS 40-70 to ADAS 20-39	0.80	1.0E-02
Post-Mortem SDAT to Control*	0.55	4.7E-03
*ratio and p-value of EtnPls 16:0/22:6 alone.		

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[0203] In a further aspect, the present invention provides a method of identifying one or more than one metabolite marker for differentially diagnosing AD dementia, non-AD dementia, cognitive impairment, or a combination thereof, comprising the steps of: introducing one or more than one sample from one or more than one patient with clinically diagnosed AD dementia, clinically diagnosed non-AD dementia, significant cognitive impairment, or any combination thereof, said sample containing a plurality of metabolites into a high resolution mass spectrometer; obtaining quantifying data for the metabolites; creating a database of said quantifying data; comparing the identifying and quantifying data from the sample with corresponding data from a sample from a reference sample; identifying one or more than one metabolite marker that differs between same sample and said reference sample, wherein the metabolite markers are selected from the metabolites listed in Tables 1-7, 10-13, and 18, or any combination thereof.

[0204] This method may further comprise selecting a minimal number of metabolite markers needed for optimal diagnosis.

[0205] The high resolution mass spectrometer may be a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (FTMS).

[0206] The present disclosure will now be explained with reference to the following numbered paragraphs:

1. A method for diagnosing dementia or the risk of dementia in a patient, the method comprising the steps of:

a) analyzing a blood sample from said patient by high resolution mass spectrometry to obtain accurate mass intensity data;

b) comparing the accurate mass intensity data to corresponding data obtained for one or more than one reference sample to identify an increase or decrease in accurate mass intensity; and

c) using said increase or decrease in accurate mass intensity to diagnose said patient's Alzheimer's disease health state or change in health state, or for diagnosing Alzheimer's disease, dementia, cognitive impairment, the risk of Alzheimer's disease, the risk of cognitive impairment, or the risk of dementia in said patient,
wherein the accurate mass intensity is measured, in Daltons, at or substantially equivalent to a hydrogen and electron adjusted accurate mass, or neutral accurate mass, selected from the group consisting of: 161.1053, 174.1409, 183.0661, 183.0662, 186.1408, 188.1566, 190.0330, 195.8577, 197.8549, 200.1564, 202.0453, 202.1720, 203.1157, 204.1876, 205.8865, 206.0789, 207.0822, 214.1720, 215.9153, 216.1877, 218.0192, 220.0798, 228.1877, 231.8893, 232.2188, 242.2030, 243.0718, 244.0559, 244.2187, 246.1465, 246.1472, 250.0366, 252.2095, 253.8163, 253.8164, 255.8135, 257.8105, 260.2135, 262.0221, 262.0777, 262.2293, 264.2452, 265.8423, 270.2343, 275.8712, 276.2095, 278.2254, 278.2255, 282.2573, 283.2602, 283.9028, 287.2824, 294.1443, 294.2207, 295.2239, 295.2287, 302.2255, 303.1079, 304.2402, 304.2410, 305.2438,

306.2569, 310.2883, 311.7750, 312.2312, 312.2663, 313.1153, 313.2690, 313.7721, 313.7722, 315.7693, 320.2356, 320.2357, 321.8039, 328.2402, 336.2662, 338.2821, 339.2850, 340.2976, 341.8614, 350.2423, 351.8903, 365.3159, 369.7338, 371.3542, 371.7311, 373.7280, 380.3096, 382.1082, 382.1083, 383.3283, 383.3284, 392.2938, 399.8196, 401.8166, 409.0208, 409.8484, 411.3211, 411.3212, 419.8773, 429.3749, 429.6888, 429.6890, 430.3818, 431.3860, 431.9570, 432.1532, 432.3254, 440.3532, 444.2717, 446.3403, 458.2404, 458.2405, 467.8070, 469.8042, 474.3706, 478.2540, 478.3664, 481.3172, 482.3215, 484.3041, 484.3794, 485.6503, 487.6482, 488.3873, 489.6451, 490.3641, 492.3816, 493.3850, 494.4342, 494.4343, 495.3320, 496.3355, 501.3212, 504.3814, 505.3229, 506.2851, 506.3213, 506.3214, 507.3316, 507.7055, 508.3356, 509.3493, 509.3494, 512.3356, 512.4082, 513.4122, 514.6879, 517.3136, 517.3140, 517.3722, 518.3174, 518.4345, 518.4346, 519.3321, 520.3353, 520.3354, 520.4499, 520.4500, 521.3474, 521.3477, 521.4522, 522.3511, 522.4634, 522.4635, 523.3634, 523.3635, 523.4678, 523.4679, 523.4680, 529.3166, 529.3167, 530.3213, 530.3471, 530.3820, 530.3821, 535.7944, 536.4794, 538.4224, 541.3139, 541.3430, 541.3432, 541.3433, 541.3435, 541.4425, 542.3173, 542.3461, 543.3296, 544.3970, 544.3971, 544.4479, 544.4481, 545.3453, 545.6062, 546.3485, 546.3486, 547.6031, 548.4815, 549.4844, 549.4845, 549.6005, 550.4956, 550.4957, 551.4985, 551.4986, 552.5021, 552.5022, 555.3098, 555.3101, 555.3102, 558.4667, 559.4690, 559.4700, 562.4600, 564.5134, 565.3393, 565.3394, 565.3396, 565.4104, 566.3434, 566.4130, 567.3545, 567.3547, 568.3573, 568.3574, 569.3685, 569.3687, 569.3690, 569.4784, 570.3724, 570.3725, 572.4468, 572.4816, 573.4852, 574.4597, 574.4637, 575.2728, 575.4632, 575.4990, 576.4770, 576.5097, 576.5098, 577.5136, 577.5137, 578.1574, 578.5277, 579.5325, 580.5350, 580.5351, 580.5352, 581.3344, 581.3345, 582.2473, 582.6334, 584.2646, 585.2664, 585.2673, 588.4731, 589.3403, 589.3404, 590.3430, 590.3431, 591.3542, 592.3571, 593.4743, 594.4878, 595.4932, 596.4791, 597.4840, 598.4965, 598.5124, 599.4936, 600.5127, 601.5164, 602.5282, 603.5317, 604.5432, 604.5433, 605.5456, 605.5457, 606.4869, 607.4919, 610.3686, 613.3405, 614.4914, 615.3539, 615.4798, 615.4938, 616.4673, 616.5052, 617.5089, 618.4829, 622.2539, 624.5131, 625.5075, 625.5076, 625.5161, 626.5104, 626.5108, 626.5277, 626.5278, 627.5201, 627.5302, 627.5304, 628.5237, 628.5421, 629.5449, 630.4861, 630.5586, 630.5587, 631.4902, 631.5619, 631.6280, 632.5032, 632.5035, 632.5762, 633.5078, 638.2465, 638.5149, 640.2637, 640.5294, 641.2661, 646.4837, 651.5221, 653.5360, 653.5361, 656.2587, 661.6233, 662.5175, 663.4870, 663.5216, 664.5322, 664.5323, 665.5010, 665.5354, 666.5455, 666.5456, 667.5474, 667.5475, 670.5689, 670.5690, 671.5722, 671.5723, 671.5726, 675.6357, 675.6377, 678.5477, 680.5623, 684.5489, 684.5491, 685.2600, 685.2601, 685.5538, 686.4877, 686.4880, 691.1957, 691.5960, 694.6161, 699.5198, 699.5199, 699.5200, 699.5203, 700.5520, 701.5359, 702.5677, 703.5516, 703.5709, 705.6093, 709.2594, 709.2595, 711.2577, 715.5167, 715.5169, 717.5308, 719.5465, 719.6231, 719.6233, 720.6258, 720.6438, 721.6390, 722.4789, 722.5334, 722.5335, 722.6424, 723.5194, 723.5195, 723.5197, 723.5203, 724.5256, 724.5257, 724.5258, 724.5493, 725.5359, 725.5385, 725.5527, 726.5459, 726.5461, 726.5462, 727.5516, 727.5567, 727.5568, 727.5569, 728.5626, 728.5627, 728.5629, 729.5672, 730.6493, 731.4914, 731.4916, 731.4917, 731.5463, 731.5464, 731.5829, 731.6530, 732.4937, 732.4938, 732.4939, 732.4940, 733.6426, 738.5445, 738.5448, 739.5141, 739.5142, 739.5143, 739.5164, 741.5305, 741.5307, 741.5319, 742.2972, 743.5464, 743.5466, 743.5467, 743.5468, 743.5469, 743.5470, 743.5471, 744.4954, 744.4956, 744.5500, 744.5535, 744.5536, 745.5621, 745.5656, 745.5658, 746.5119, 746.5570, 746.5714, 746.5717, 746.5719, 746.6210, 747.5201, 747.5203, 747.5244, 747.5245, 747.5778, 748.5286, 748.5287, 748.5721, 748.5735, 749.5359, 749.5365, 749.5367, 749.5406, 749.5407, 749.5408, 749.5760, 749.5761, 749.5777, 750.5402, 750.5403, 750.5438, 750.5440, 751.5516, 751.5529, 751.5553, 751.5555, 751.5556, 752.5564, 752.5581, 752.5583, 753.5672, 753.5672, 755.4860, 755.4861, 755.5467, 755.5468, 757.4989, 757.4991, 757.4993, 757.5014, 757.5016, 757.5625, 757.5626, 758.5092, 758.5094, 758.5655, 758.5656, 759.5162, 759.5163, 759.5164, 759.5165, 759.5779, 760.5215, 760.5216, 760.5217, 760.5811, 761.5843, 761.5846, 763.5157, 765.5313, 765.5334, 765.5335, 767.5469, 767.5470, 767.5494, 767.5495, 768.5503, 768.5504, 768.5538, 768.5539, 769.5654, 769.5655, 769.5656, 771.5813, 771.5814, 771.5815, 772.5278, 772.5280, 772.5860, 772.5862, 772.5863, 773.5347, 773.5368, 773.5370, 774.0313, 774.0316, 775.5516, 775.5527, 775.5528, 775.5530, 775.5533, 775.5535, 777.4426, 777.5287, 777.5288, 777.5530, 777.5531, 777.5672, 779.4393, 779.5441, 779.5442, 779.5444, 779.5829, 780.5474, 780.5475, 781.4354, 781.5607, 781.5616, 781.5617, 781.5620, 781.5985, 782.5084, 782.5085, 782.5086, 782.5647, 782.5649, 782.5650, 782.5653, 783.4315, 783.5147, 783.5148, 783.5671, 783.5672, 783.5778, 784.5235, 784.5237, 784.5239, 784.5810, 784.5811, 785.4288, 785.5933, 786.5415, 786.5416, 786.5967, 787.5464, 787.5465, 787.5728, 787.5729, 789.5892, 789.5893, 793.5386, 793.5387, 793.5679, 793.5681, 794.5421, 794.5422, 795.5181, 795.5182, 795.5183, 795.5550, 795.5551, 795.5837, 795.5838, 795.5839, 796.5290, 796.5292, 796.5874, 796.5876, 798.6742, 801.5550, 802.7056, 803.5445, 803.5677, 803.5678, 803.5680, 803.5681, 804.5475, 804.5476, 804.5713, 804.5718, 804.7227, 804.7230, 805.5604, 805.5605, 805.5831, 805.5832, 805.5839, 806.5637, 806.5638, 806.5639, 806.5873, 807.5757, 807.5758, 807.5768, 807.5899, 807.5900, 808.5792, 808.5803, 809.5936, 809.5937, 810.5399,

810.5400, 810.5401, 810.5969, 810.5971, 811.5732, 811.6096, 812.5761, 812.5762, 813.5885, 814.5917, 814.5919, 817.5375, 817.5376, 817.5377, 817.5378, 817.5838, 817.5840, 819.5551, 819.5552, 819.5553, 819.5641, 819.5642, 820.5677, 820.5679, 820.5680, 821.5711, 821.5712, 821.5713, 824.6892, 825.5544, 825.6926, 825.6927, 826.5581, 826.7048, 826.7069, 826.7070, 827.5448, 827.5699, 827.5700, 827.5701, 827.7083, 827.7086, 828.5736, 828.5737, 828.5742, 828.5743, 828.7202, 828.7207, 829.5604, 829.5856, 829.5859, 829.7239, 829.7242, 829.7244, 829.7246, 830.5894, 830.7352, 830.7355, 830.7362, 830.7363, 831.5759, 831.5760, 831.5995, 831.5997, 831.5998, 831.6000, 831.6001, 831.7387, 831.7408, 832.5791, 832.5792, 832.6024, 832.6026, 832.6027, 832.6036, 832.6037, 832.7492, 832.7495, 832.7521, 832.7522, 832.7523, 833.5931, 833.5932, 833.7551, 833.7558, 833.7570, 833.7571, 835.6998, 835.7001, 835.7006, 836.7076, 837.5027, 837.5881, 837.7180, 838.7226, 838.7232, 839.6031, 840.6063, 842.7387, 847.5316, 847.5953, 847.5954, 851.5698, 852.5738, 852.7250, 853.5854, 853.5855, 853.5862, 853.7296, 854.5902, 855.6015, 855.6016, 855.6023, 855.6025, 855.7417, 856.6061, 856.6063, 856.6720, 856.7481, 857.6186, 857.7531, 858.6211, 858.6212, 858.6860, 858.6861, 858.7632, 858.7663, 859.7694, 859.7695, 859.7696, 859.7706, 860.7752, 860.7753, 860.7756, 861.7801, 861.7806, 863.6876, 863.7336, 864.7380, 864.7596, 865.7486, 865.7487, 866.7532, 866.7533, 867.7579, 867.7581, 870.7307, 871.5527, 871.5528, 871.5529, 871.5934, 871.5935, 874.7645, 878.7400, 879.5999, 879.7454, 880.6035, 880.7516, 880.7566, 881.7558, 881.7616, 882.7660, 882.7723, 883.7705, 883.7765, 884.7801, 884.7877, 885.7854, 885.7922, 886.5582, 886.5584, 886.7916, 886.7917, 886.8012, 887.7352, 887.7999, 887.8001, 887.8005, 888.7394, 889.7492, 890.7535, 894.7810, 908.7832, 909.7882, 910.7968, 911.8032, 913.7513, 914.7583, 915.5191, 915.5192, 915.7681, 916.7743, 921.8142, 921.8145, 921.8153, 928.7505, 931.7695, 942.7879, 1018.9420, 1019.3838, 1019.3840, 1085.3294, 1098.9739, 1098.9740, 1225.0920, 1226.0968, 1226.0970, 1227.1070, 1228.1110, 1228.1111 and combinations thereof.

2. The method of paragraph 1, wherein diagnosing dementia or the risk of dementia in a patient comprises diagnosing a patient's Alzheimer's disease health state or change in health state, Alzheimer's disease, non-Alzheimer's disease dementia, cognitive impairment, the risk of Alzheimer's disease, the risk of cognitive impairment, or the risk of non-Alzheimer's disease dementia in a patient.

3. The method of paragraph 1 or 2, wherein step a) comprises analyzing the blood sample using a Fourier transform ion cyclotron resonance, time of flight, orbitrap, quadrupole or triple quadrupole mass spectrometer.

4. The method any one of paragraphs 1 to 3, wherein the blood sample is a blood serum sample.

5. The method of any one of paragraphs 1 to 4, wherein the accurate mass intensities represent ionized metabolites.

6. The method of any one of paragraphs 1 to 5, wherein a liquid/liquid extraction is performed on the blood sample whereby non-polar metabolites are dissolved in an organic solvent and polar metabolites are dissolved in an aqueous solvent.

7. The method of paragraph 6, wherein the accurate mass intensities are obtained from the ionization of the extracted samples using an ionization method selected from the group consisting of positive electrospray ionization (ESI), negative electrospray ionization, positive atmospheric pressure chemical ionization (APCI), negative atmospheric pressure chemical ionization, and combinations thereof.

8. The method of any one of paragraphs 1 to 7, wherein step a) comprises analyzing the blood sample using a Fourier transform ion cyclotron resonance mass spectrometer.

9. The method of any one of paragraphs 1 to 8, wherein said one or more than one reference sample is:

a) one or more than one reference sample obtained from a non-demented control individual;
b) one or more than one reference sample obtained from a demented subject;
c) one or more than one reference sample obtained from a subject pathologically diagnosed as having Alzheimer's Disease;
d) one or more than one reference sample obtained from a subject clinically diagnosed as having Alzheimer's Disease;
e) one or more than one reference sample obtained from a patient with cognitive impairment as measured by the Alzheimer's Disease Assessment Scale-cognitive subset (ADAS-cog);
f) one or more than one reference sample obtained from a patient with cognitive impairment as measured by

the Folstein's Mini-Mental State Exam (MMSE); or
g) any combination of a) to f) thereof.

10. The method of any of one of paragraphs 1 to 9, wherein the method is for diagnosing:

(a) the presence of or risk of Alzheimer's disease (AD);
(b) the presence of or risk of AD pathology;
(c) the presence of or risk of dementia;
(d) the presence of or risk of cognitive impairment; or
(e) a combination of (a) to (d) above.

11. The method of any one of paragraphs 1 to 10, further comprising:

analyzing a blood sample from said patient to obtain quantifying data for one or more than one internal control metabolite; and
obtaining a ratio for each of the levels of said one or more than one metabolite marker to the level obtained for the one or more than one internal control metabolite;
wherein the comparing step (b) comprises comparing each ratio to one or more corresponding ratios obtained for the one or more than one reference sample.

12. The method of any one of paragraphs 1 to 11, wherein a decrease in accurate mass intensity is identified in the comparing step (b).

13. The method of any one of paragraphs 1 to 12, wherein the hydrogen and electron adjusted accurate mass, or neutral accurate mass, is selected from the group consisting of: 183.0661, 190.033, 195.8577, 202.0453, 205.8865, 215.9153, 218.0192, 231.8893, 244.0559, 246.1465, 252.2095, 265.8423, 278.2254, 282.2573, 283.2602, 287.2824, 302.2255, 303.1079, 304.241, 305.2438, 306.2569, 310.2883, 313.1153, 320.2356, 340.2976, 351.8903, 371.3542, 380.3096, 382.1082, 383.3284, 399.8196, 401.8166, 409.0208, 409.8484, 411.3212, 419.8773, 429.3749, 430.3818, 431.386, 440.3532, 444.2717, 458.2405, 467.807, 469.8042, 478.254, 478.3664, 481.3172, 482.3215, 484.3794, 488.3873, 490.3641, 492.3816, 493.385, 494.4343, 495.332, 495.332, 495.332, 496.3355, 501.3212, 504.3814, 505.3229, 506.2851, 506.3213, 507.3316, 507.7055, 509.3493, 512.4082, 513.4122, 517.314, 518.3174, 518.4345, 519.3321, 520.3354, 520.4499, 521.3477, 521.4522, 522.3511, 522.4635, 523.3634, 523.4679, 529.3167, 530.3821, 535.7944, 536.4794, 541.3139, 541.3432, 541.3435, 541.4425, 542.3173, 542.3461, 543.3296, 544.397, 544.4481, 545.3453, 546.3485, 548.4815, 549.4845, 550.4957, 551.4986, 552.5022, 555.3102, 564.5134, 565.3394, 566.3434, 567.3547, 568.3573, 569.3687, 569.369, 569.4784, 570.3725, 572.4816, 573.4852, 575.2728, 576.5098, 577.5137, 578.5277, 579.5325, 580.5351, 581.3344, 582.2473, 584.2646, 585.2664, 585.2673, 588.4731, 589.3403, 590.343, 591.3542, 592.3571, 598.5124, 599.4936, 600.5127, 601.5164, 604.5433, 605.5457, 610.3686, 614.4914, 615.3539, 615.4798, 615.4938, 616.5052, 617.5089, 618.4829, 625.5161, 626.5104, 626.5278, 628.5237, 630.5587, 631.628, 632.5032, 632.5762, 638.5149, 640.5294, 661.6233, 662.5175, 663.5216, 664.5323, 665.501, 665.5354, 666.5456, 667.5475, 670.569, 671.5723, 675.6377, 678.5477, 684.5489, 685.26, 686.4877, 691.1957, 691.596, 694.6161, 699.5198, 700.552, 703.5709, 705.6093, 709.2594, 711.2577, 715.5167, 719.6231, 720.6258, 720.6438, 721.639, 722.5335, 722.6424, 723.5195, 723.5197, 724.5257, 724.5493, 725.5385, 725.5527, 726.5461, 727.5568, 728.5627, 731.4916, 731.5464, 732.4938, 733.6426, 738.5448, 739.5143, 741.5305, 741.5319, 743.5466, 743.5469, 743.5471, 744.4956, 744.55, 744.5536, 745.565, 746.5119, 746.557, 746.5717, 747.5201, 747.5245, 748.5287, 748.5721, 748.5735, 749.5367, 749.5407, 749.5761, 749.5777, 750.5402, 750.544, 751.5529, 751.5555, 752.5564, 752.5583, 755.486, 755.5467, 755.5468, 757.4991, 757.5014, 757.5625, 757.5626, 758.5092, 758.5655, 758.5656, 759.5163, 759.5779, 760.5216, 760.5811, 761.5843, 761.5846, 765.5313, 765.5334, 767.547, 767.5495, 768.5503, 768.5539, 769.5656, 771.5814, 772.5278, 772.5862, 773.537, 774.0316, 775.5528, 775.5533, 777.5287, 777.553, 779.5441, 779.5444, 780.5474, 781.5617, 781.562, 782.5085, 782.565, 782.5653, 783.5148, 783.5672, 783.5778, 784.5237, 784.5811, 785.5933, 786.5416, 786.5967, 787.5465, 787.5729, 789.5892, 793.5386, 793.5681, 794.5421, 795.5181, 795.555, 795.5838, 796.5292, 796.5876, 801.555, 802.7056, 803.5445, 803.5677, 803.568, 804.5476, 804.5713, 804.5718, 804.7227, 805.5605, 805.5832, 805.5839, 806.5639, 806.5873, 807.5758, 807.5768, 807.59, 808.5792, 808.5803, 809.5936, 809.5937, 810.5399, 810.5969, 810.5971, 811.5732, 811.6096, 812.5762, 813.5885, 814.5917, 817.5377, 819.5551, 819.5642, 820.568, 821.5712, 824.6892, 825.5544, 825.6926, 826.5581, 826.7069, 827.5448, 827.57, 827.5701, 827.7086, 828.5737, 828.5743, 828.7207, 829.5604, 829.5856, 829.5859, 829.7239, 829.7246, 830.5894, 830.7352, 830.7363, 831.5759, 831.5997, 831.6001, 831.7387, 831.7408, 832.5791, 832.6026, 832.6037, 832.7492, 832.7523, 833.5932, 833.7551, 833.7571, 835.7006, 837.5027, 837.5881, 837.718, 838.7226, 839.6031,

840.6063, 847.5316, 847.5954, 853.5854, 853.5862, 854.5902, 855.6016, 855.6023, 856.6061, 856.672, 857.6186, 858.6212, 858.6861, 859.7696, 860.7752, 860.7756, 861.7806, 863.6876, 863.7336, 864.738, 865.7487, 866.7532, 867.7579, 870.7307, 871.5528, 871.5934, 874.7645, 886.5582, 887.7352, 887.7352, 887.8005, 888.7394, 889.7492, 890.7535, 913.7513, 914.7583, 915.5191, 915.7681, 916.7743, 921.8145, 931.7695, 942.7879, 1018.942, 1019.3838, 1019.384, 1098.9739, 1098.974, 1225.092, 1226.097, 1227.107, 1228.111, and combinations thereof.

14. The method of any one of paragraphs 1 to 12, wherein the hydrogen and electron adjusted accurate mass, or neutral accurate mass, is selected from the group consisting of: 699.5198, 723.5195, 723.5197, 751.5555, 541.3432, 569.3687, 803.568, 886.5582, 565.3394, 569.369, 801.555, 857.6186, 207.0822, 275.8712, 371.7311, 373.728, 432.1532, 485.5603, 487.6482, 562.46, 622.2539, 640.2637, 730.6493, 742.2972, 701.53591, 699.52026, 723.52026, 747.52026, 729.56721, 727.55156, 779.58286, 775.55156, and combinations thereof.

15. The method of any one of paragraphs 1 to 14, wherein said diagnosing of the patient's Alzheimer's disease health state or change in health state further comprises evaluating the efficacy of a therapy for treating Alzheimer's disease, dementia or cognitive impairment in said patient.

16. The method of paragraph 15, wherein at least one of said one or more than one reference sample defined in step b) is one or more than one pre-therapy baseline sample obtained from the patient.

17. The method of paragraph 15 or 16, wherein evaluating the efficacy of the therapy includes determining whether the therapy is improving the demented state of the patient.

Claims

1. A method for diagnosing non-AD dementia or the risk of non-AD dementia in a patient, the method comprising the steps of:

a) analyzing a blood sample from said patient to obtain accurate mass intensity data points using a high resolution mass spectrometer capable of measuring accurate mass intensity in Daltons $\pm$ 5 ppm; and
b) comparing the accurate mass intensity data points to corresponding data obtained for one or more than one reference sample to identify the presence of an increase or decrease in accurate mass intensity;
wherein the presence of an increase or decrease in accurate mass intensity indicates that said patient has non-AD dementia or is at risk of non-AD dementia, and
wherein the accurate mass intensity data points are measured at or $\pm$ 5 ppm of a hydrogen and electron adjusted accurate mass, or neutral accurate mass, in Daltons, selected from at least one of the group consisting of:

the following accurate masses are indicators of the presence of or risk of non-AD dementia (table 5): 183.0661, 190.033, 195.8577, 202.0453, 205.8865, 215.9153, 218.0192, 231.8893, 244.0559, 252.2095, 282.2573, 283.2602, 303.1079, 306.2569, 310.2883, 351.8903, 382.1082, 399.8196, 401.8166, 409.8484, 419.8773, 429.3749, 440.3532, 458.2405, 467.807, 469.8042, 481.3172, 482.3215, 484.3794, 494.4343, 495.332, 496.3355, 507.7055, 513.4122, 517.314, 518.3174, 519.3321, 520.3354, 520.4499, 521.3477, 521.4522, 522.3511, 522.4635, 523.3634, 523.4679, 535.7944, 536.4794, 541.3139, 541.3432, 542.3173, 543.3296, 545.3453, 546.3485, 548.4815, 549.4845, 550.4957, 551.4986, 552.5022, 555.3102, 565.3394, 567.3547, 568.3573, 569.3687, 569.4784, 575.2728, 576.5098, 577.5137, 579.5325, 584.2646, 585.2664, 585.2673, 591.3542, 592.3571, 599.4936, 626.5104, 628.5237, 632.5762, 675.6377, 686.4877, 691.1957, 700.552, 703.5709, 720.6438, 721.639, 722.5335, 722.6424, 723.5197, 731.4916, 731.5464, 732.4938, 744.4956, 745.5658, 746.5717, 748.5735, 749.5777, 752.5583, 755.486, 755.5468, 757.4991, 757.5014, 757.5626, 758.5092, 758.5656, 759.5779, 760.5216, 760.5811, 761.5843, 777.5287, 777.553, 779.5441, 779.5444, 780.5474, 780.5474, 781.5617, 782.5085, 782.565, 783.5672, 784.5237, 784.5811, 785.5933, 786.5967, 793.5386, 794.5421, 795.5181, 795.555, 802.7056, 803.5445, 803.568, 804.5476, 804.5713, 804.7227, 805.5605, 805.5832, 805.5839, 806.5639, 806.5873, 807.5758, 807.59, 808.5792, 809.5936, 810.5969, 811.6096, 817.5377, 819.5551, 821.5712, 825.6926, 826.7069, 827.5448, 827.57, 827.7086, 828.5737, 828.7207, 829.5604, 829.5856, 829.7246, 830.7352, 830.7363, 831.5759, 831.5997, 831.7387, 831.7408, 832.5791, 832.6026, 832.7492, 832.7523, 833.5932, 833.7551, 833.7571, 835.7006, 837.5027, 837.718, 838.7226, 839.6031, 840.6063, 847.5316, 853.5854, 855.6016, 856.672, 858.6861, 859.7696, 860.7756, 861.7806, 863.6876, 863.7336, 864.738, 865.7487, 866.7532, 867.7579, 871.5528, 874.7645,

886.5582, 915.5191, 1018.942, 1019.384, 1227.107, and 1228.111.

2. The method of claim 1, wherein the high resolution mass spectrometer is a Fourier transform ion cyclotron resonance, time of flight, orbitrap, quadrupole or triple quadrupole mass spectrometer.

3. The method of any one of claims 1 or 2, wherein the blood sample is a blood serum sample.

4. The method of any one of claims 1 to 3, wherein the accurate mass intensities represent ionized metabolites.

5. The method of any one of claims 1 to 4, wherein a liquid/liquid extraction is performed on the blood sample whereby non-polar metabolites are dissolved in an organic solvent and polar metabolites are dissolved in an aqueous solvent.

6. The method of any one of claims 1 to 5, wherein the high resolution mass spectrometer uses an ionization method selected from the group consisting of positive electrospray ionization (ESI), negative electrospray ionization, positive atmospheric pressure chemical ionization (APCI), negative atmospheric pressure chemical ionization, and combinations thereof.

7. The method of any one of claims 1 to 6, wherein step a) comprises analyzing the blood sample using a Fourier transform ion cyclotron resonance mass spectrometer.

8. The method of any one of claims 1 to 7, wherein said one or more than one reference sample is obtained from a non-demented control individual.

9. The method of any one of claims 1 to 8, further comprising:

analyzing a blood sample from said patient to obtain accurate mass intensity data points for one or more than one internal control metabolite; and
obtaining a ratio for each of the accurate mass intensities of said one or more than one metabolite marker to the accurate mass intensity obtained for the one or more than one internal control metabolite;
wherein the comparing step (b) comprises comparing each ratio to one or more corresponding ratios obtained for the one or more than one reference sample.

10. The method of any one of claims 1 to 9, wherein a decrease in accurate mass intensity is identified in the comparing step (b).

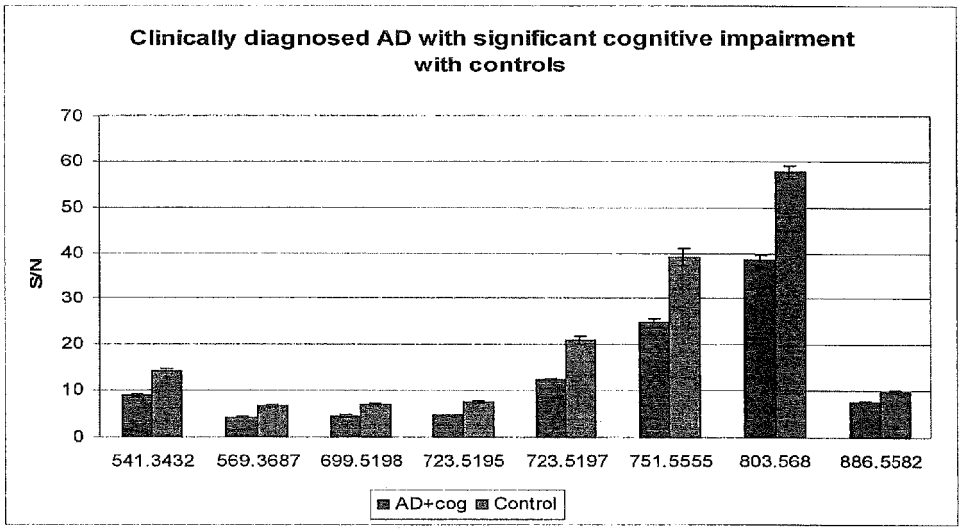
11. The method of any one of claims 1 to 10, wherein the hydrogen and electron adjusted accurate mass, or neutral accurate mass, is selected from the group consisting of: 723.5197, 541.3432, 569.3687, 803.568, 886.5582, 565.3394, and combinations thereof.

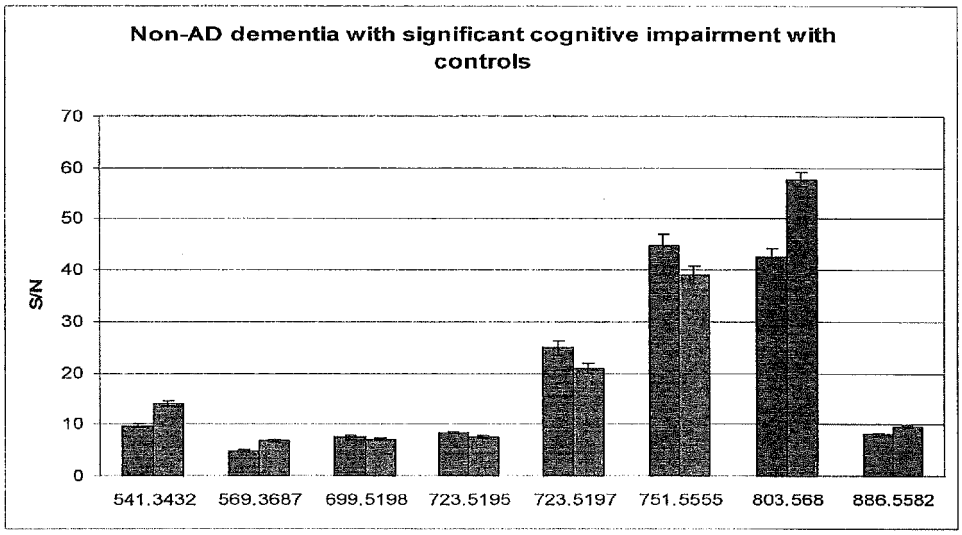
12. The method of any of claims 1 to 11 , wherein at least one of said one or more than one reference sample defined in step b) is one or more than one pre-therapy baseline sample obtained from the patient.

13. The method of claim 12, wherein evaluating the efficacy of the therapy includes determining whether the therapy is improving the demented state of the patient.

14. The method of any one of claims 1 to 13, wherein the method is a high throughput method and step a) comprises analyzing the sample by liquid chromatography and linear ion trap mass spectrometry.

15. The method of any of claims 1 to 8, wherein the accurate mass intensity data points are measured at least at or ± 5 ppm of 541.3432 Da, 569.3687 Da, 723.5197 Da, , 803.568 Da, and 886.5582 Da, and the presence of a decrease in accurate mass intensity at least at said accurate masses indicates that said patient has or is at risk of dementia.


Clinically diagnosed AD with significant cognitive impairment with controls
S/N
70
60
50
40
30
20
10
0
541.3432
569.3687
699.5198
723.5195
723.5197
751.5555
803.568
886.5582
AD+cog
Control


Non-AD dementia with significant cognitive impairment with controls
S/N
70
60
50
40
30
20
10
0
541.3432
569.3687
699.5198
723.5195
723.5197
751.5555
803.568
886.5582

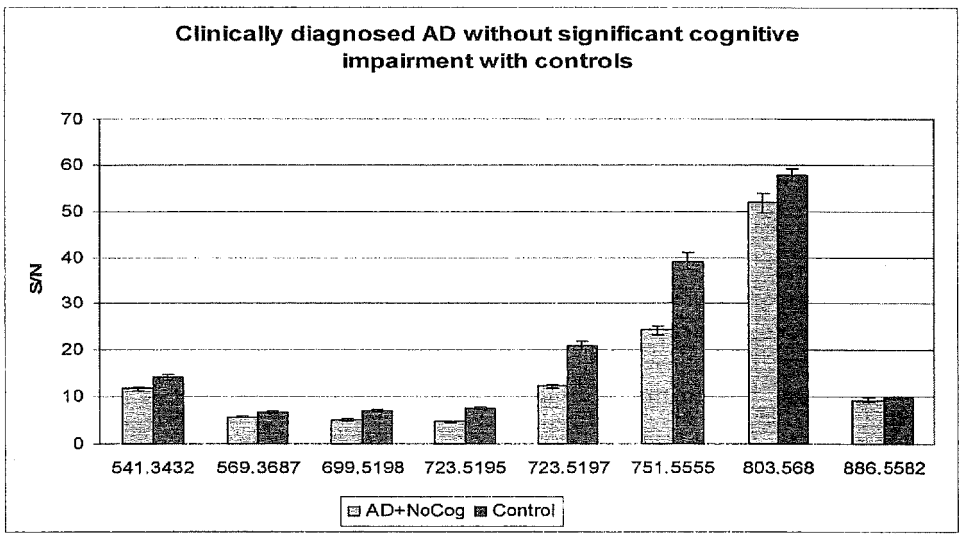

Clinically diagnosed AD without significant cognitive impairment with controls
S/N
70
60
50
40
30
20
10
0
541.3432
569.3687
699.5198
723.5195
723.5197
751.5555
803.568
886.5582
AD+NoCog
Control

Fig. 1

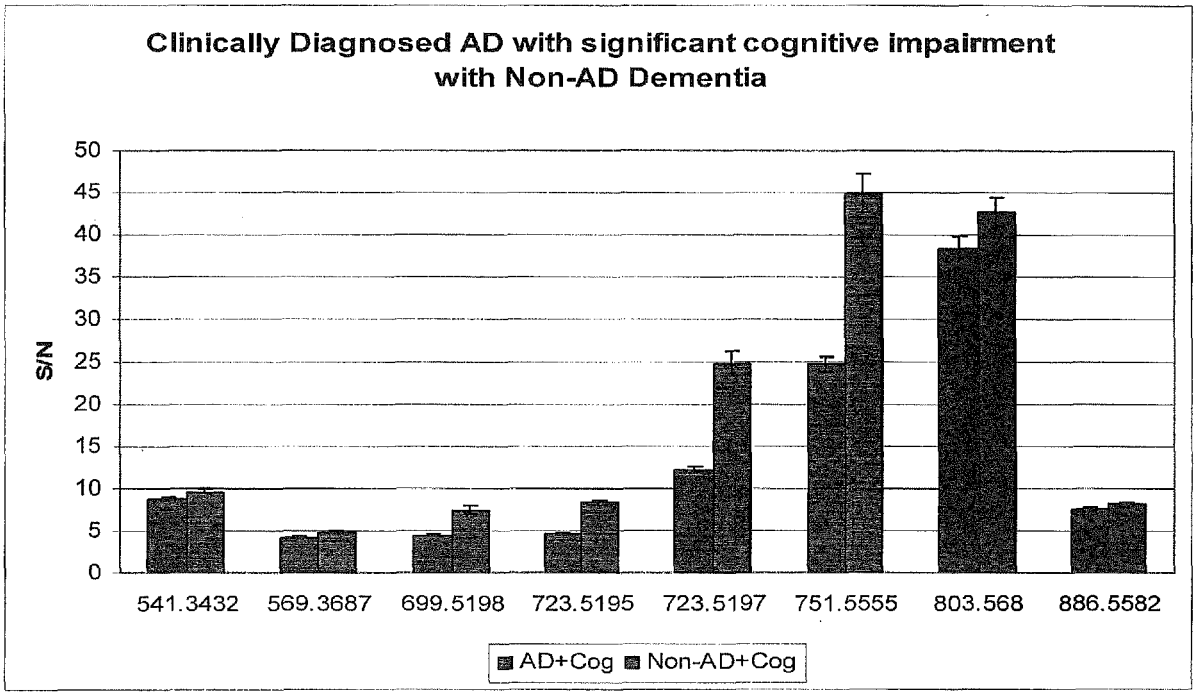

Clinically Diagnosed AD with significant cognitive impairment with Non-AD Dementia
S/N
50
45
40
35
30
25
20
15
10
5
0
541.3432
569.3687
699.5198
723.5195
723.5197
751.5555
803.568
886.5582
AD+Cog
Non-AD+Cog

Fig. 2

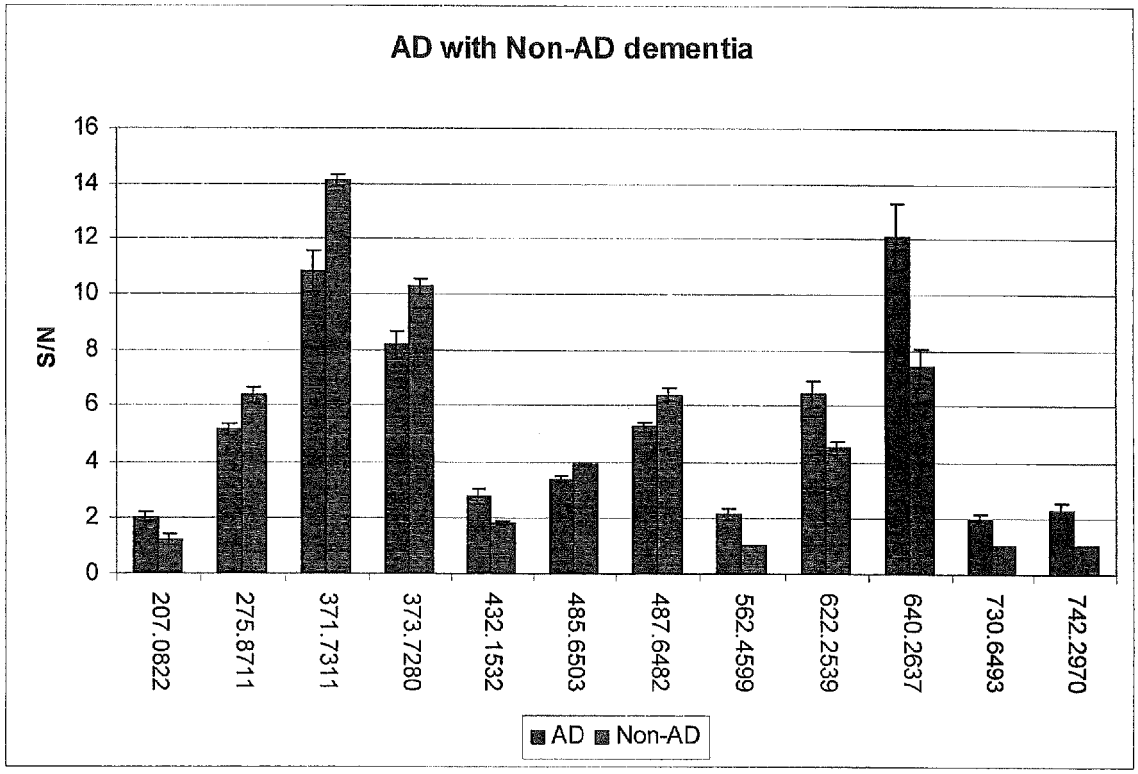

AD with Non-AD dementia
S/N
16
14
12
10
8
6
4
2
0
207.0822
275.8711
371.7311
373.7280
432.1532
485.6503
487.6482
562.4599
622.2539
640.2637
730.6493
742.2970
AD
Non-AD

Fig. 3

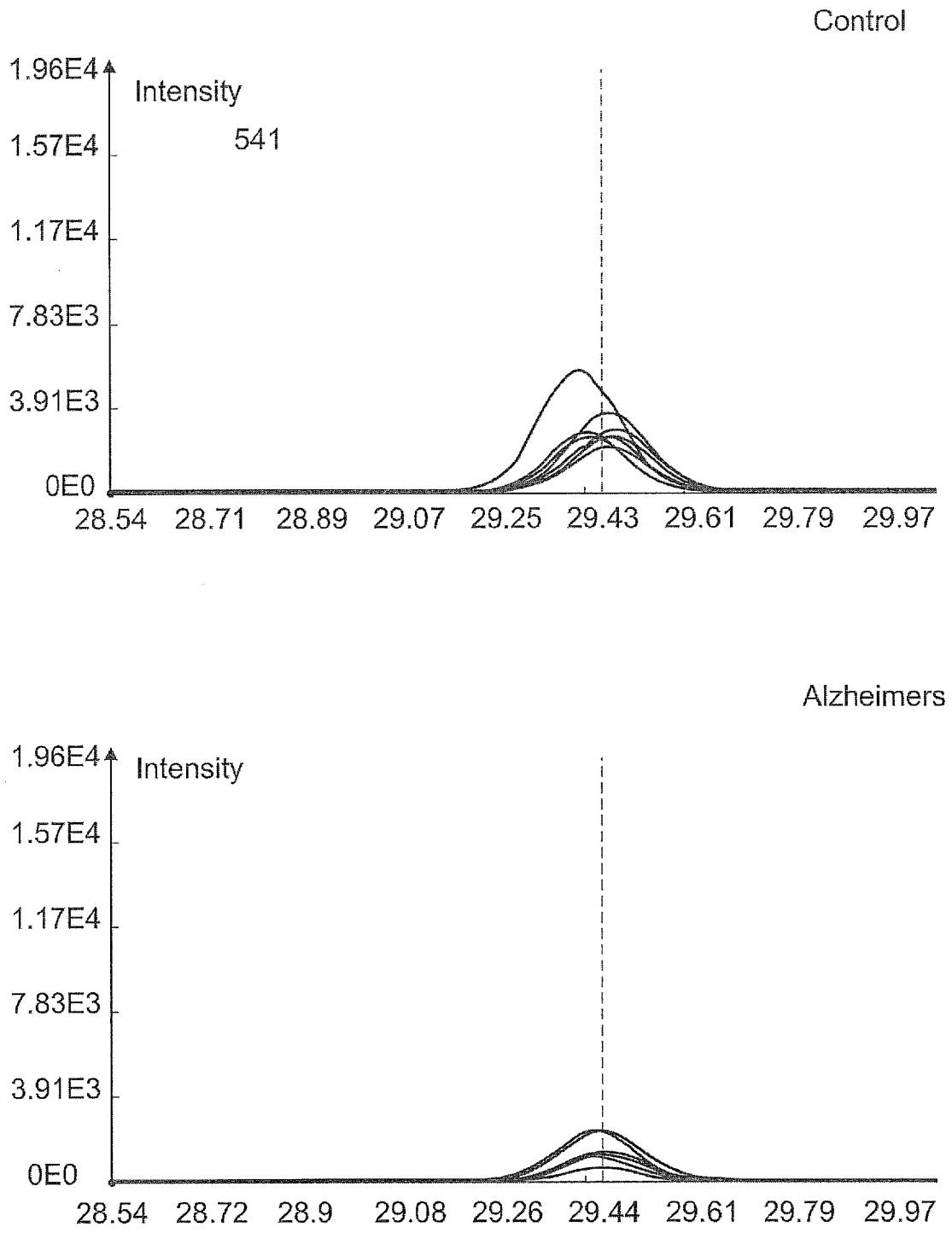

Control
1.96E4
Intensity
541
1.57E4
1.17E4
7.83E3
3.91E3
0E0
28.54
28.71
28.89
29.07
29.25
29.43
29.61
29.79
29.97
Alzheimers
1.96E4
Intensity
1.57E4
1.17E4
7.83E3
3.91E3
0E0
28.54
28.72
28.9
29.08
29.26
29.44
29.61
29.79
29.97

Fig. 4A

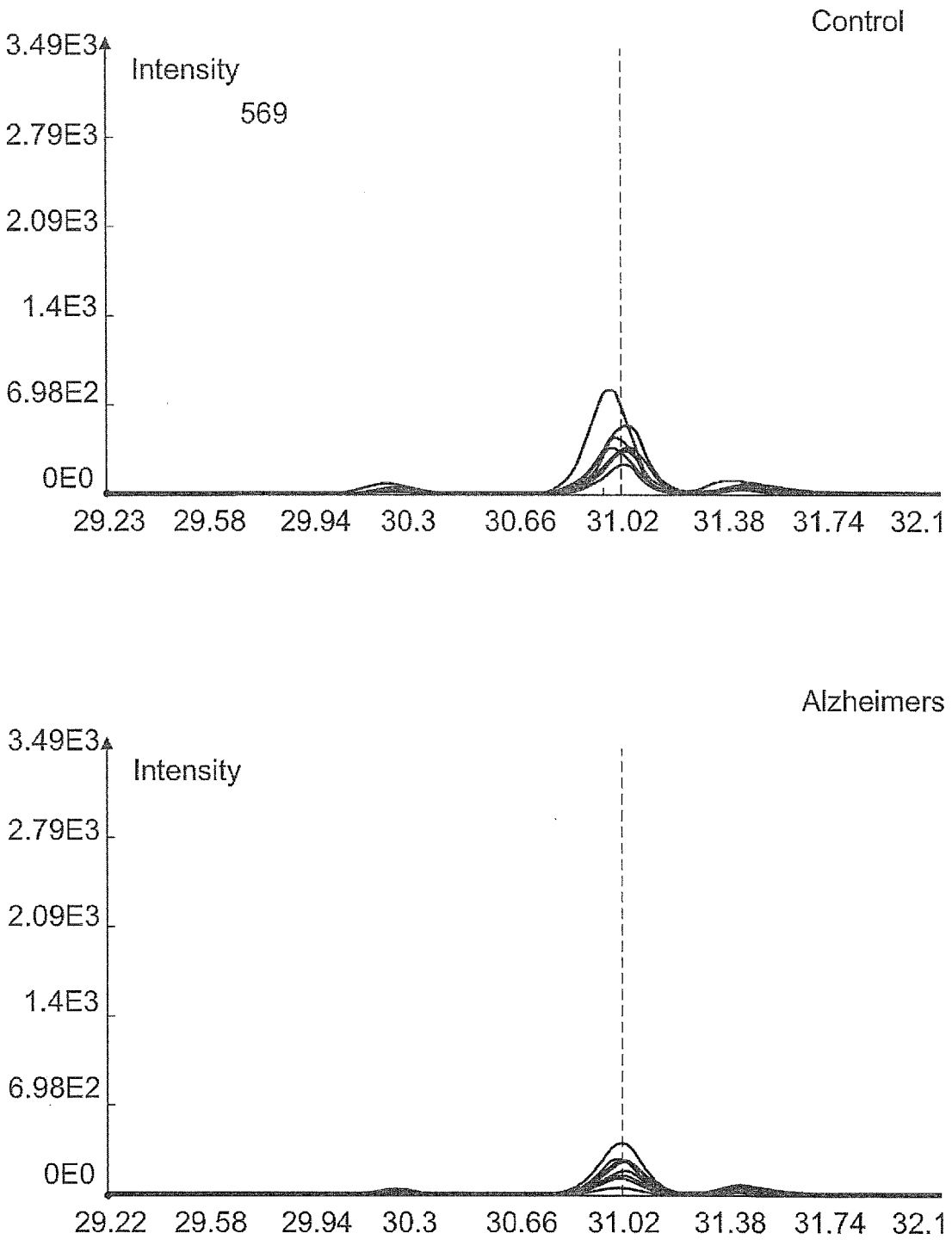

Control
3.49E3
Intensity
569
2.79E3
2.09E3
1.4E3
6.98E2
0E0
29.23
29.58
29.94
30.3
30.66
31.02
31.38
31.74
32.1
Alzheimers
3.49E3
Intensity
2.79E3
2.09E3
1.4E3
6.98E2
0E0
29.22
29.58
29.94
30.3
30.66
31.02
31.38
31.74
32.1

Fig. 4B

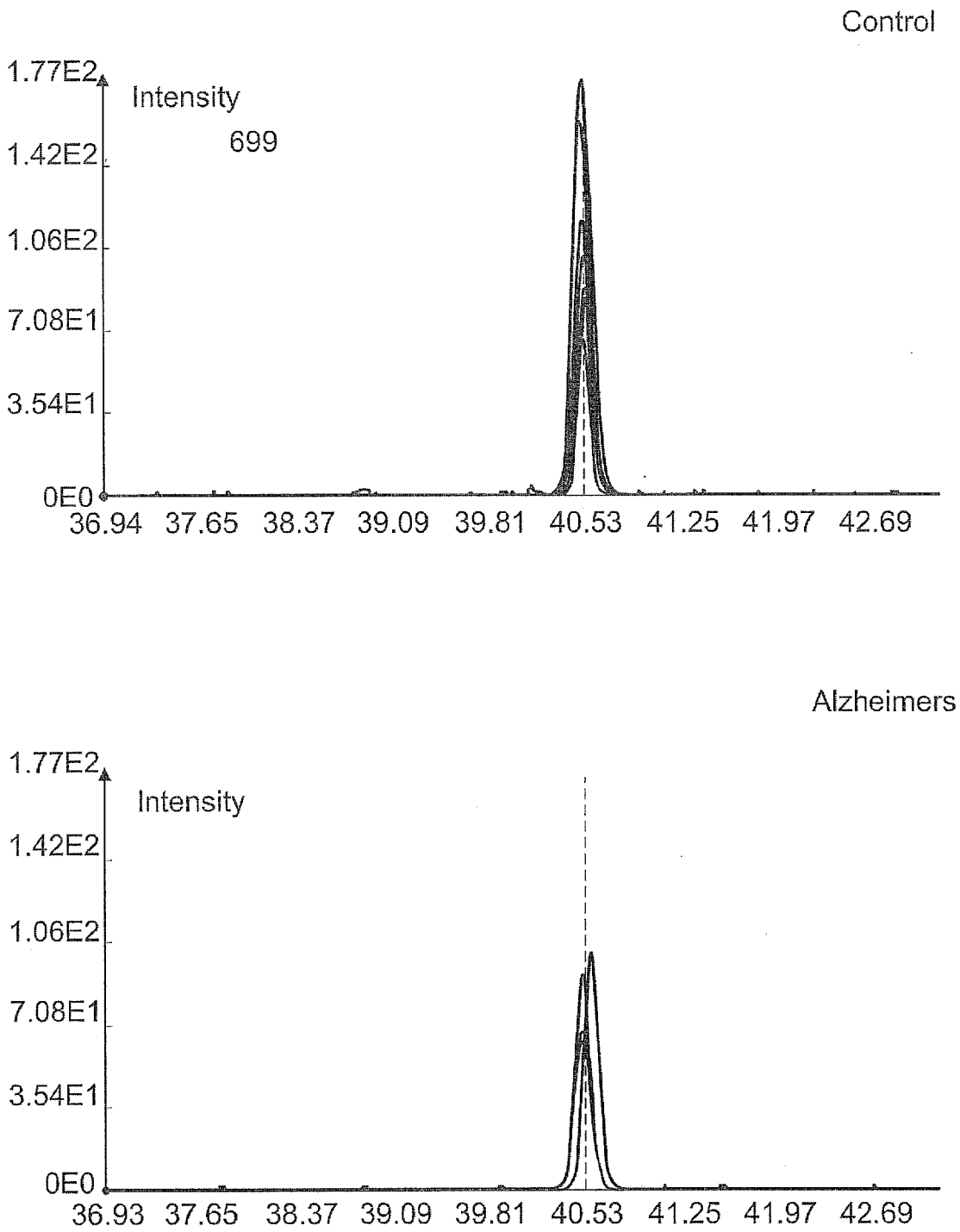

Control
1.77E2
Intensity
699
1.42E2
1.06E2
7.08E1
3.54E1
0E0
36.94 37.65 38.37 39.09 39.81 40.53 41.25 41.97 42.69
Alzheimers
1.77E2
Intensity
1.42E2
1.06E2
7.08E1
3.54E1
0E0
36.93 37.65 38.37 39.09 39.81 40.53 41.25 41.97 42.69

Fig. 4C

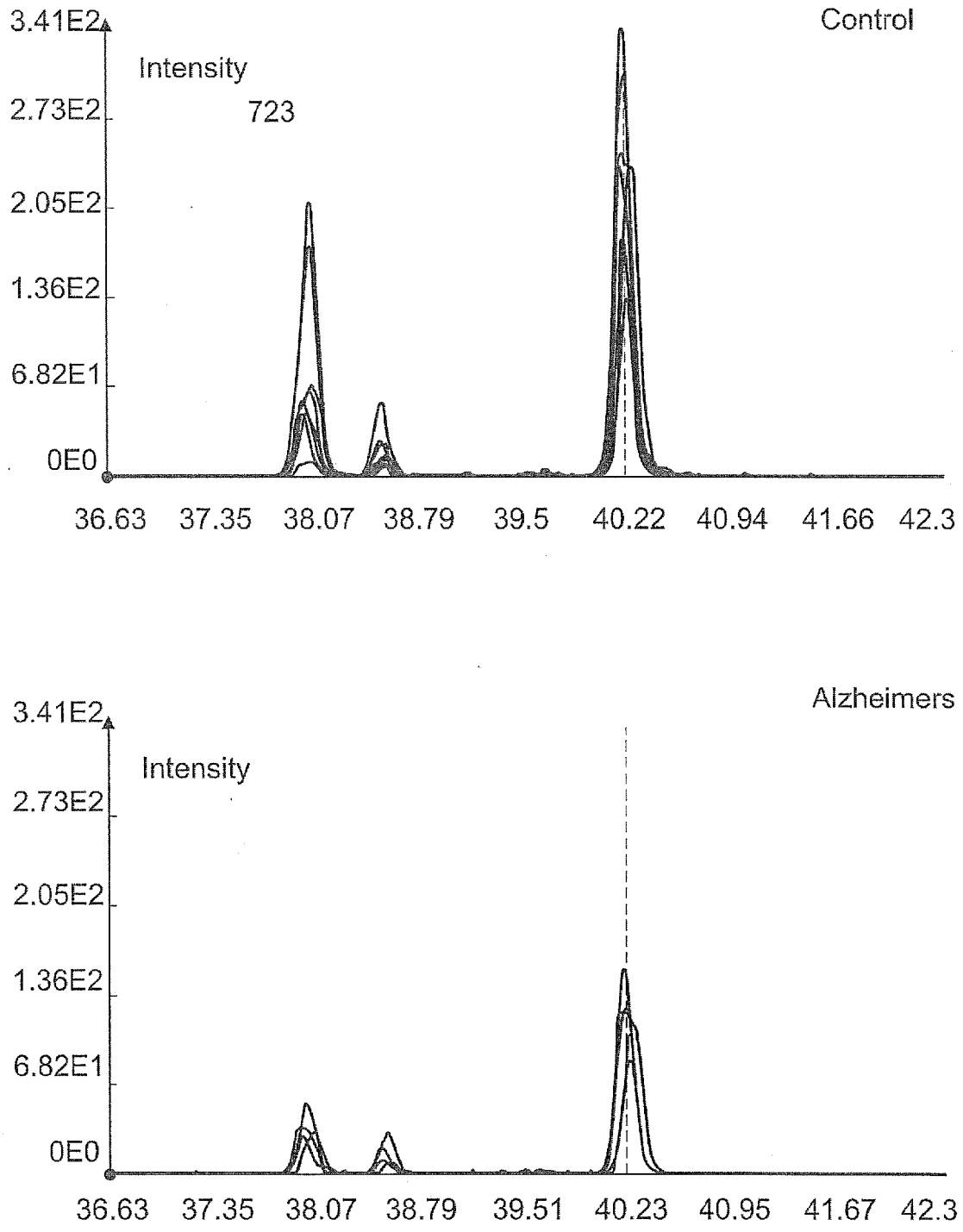

Control
Intensity
723
3.41E2
2.73E2
2.05E2
1.36E2
6.82E1
0E0
36.63
37.35
38.07
38.79
39.5
40.22
40.94
41.66
42.3
Alzheimers
Intensity
3.41E2
2.73E2
2.05E2
1.36E2
6.82E1
0E0
36.63
37.35
38.07
38.79
39.51
40.23
40.95
41.67
42.3

Fig. 4D

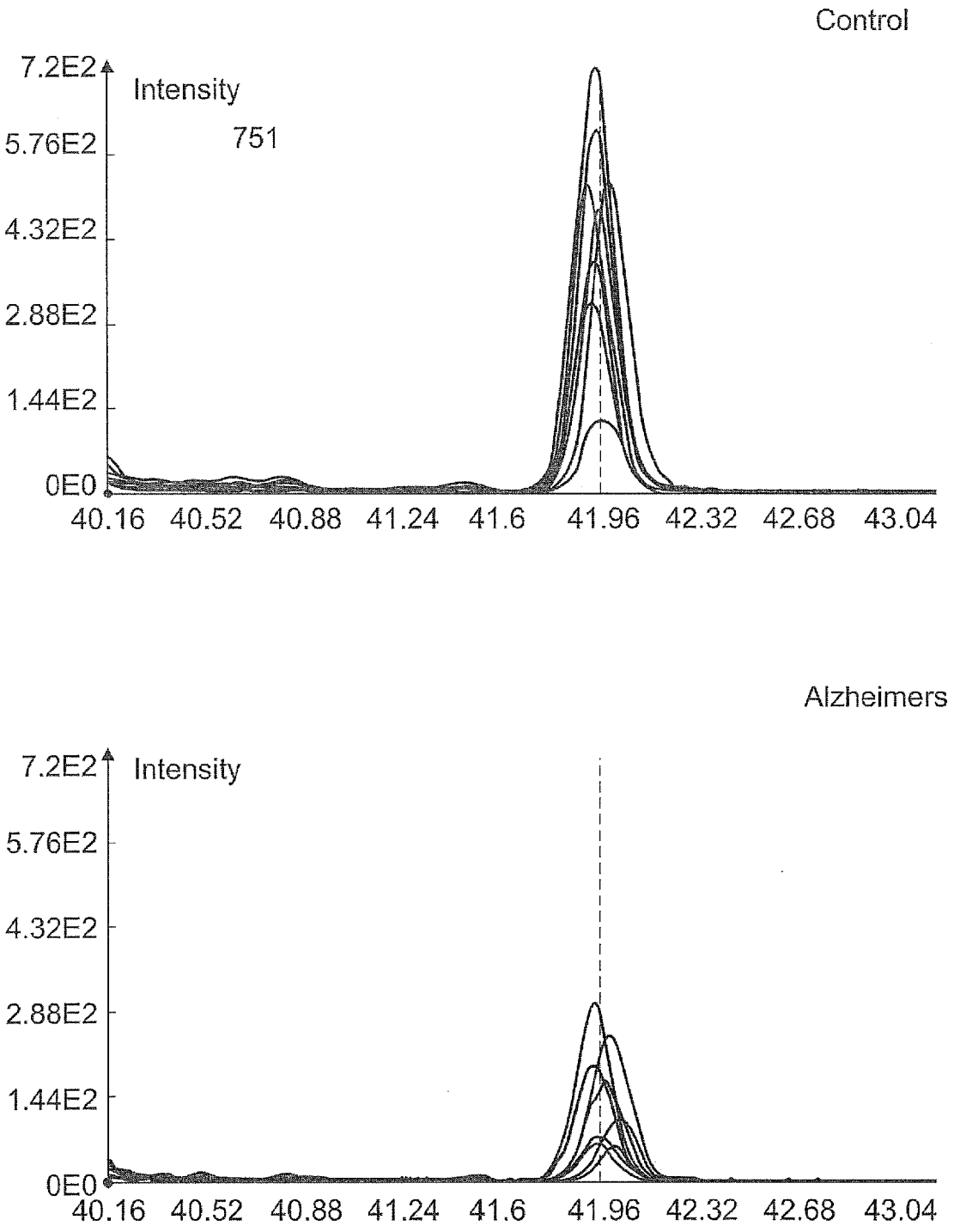

Control
7.2E2
Intensity
751
5.76E2
4.32E2
2.88E2
1.44E2
0E0
40.16
40.52
40.88
41.24
41.6
41.96
42.32
42.68
43.04
Alzheimers
7.2E2
Intensity
5.76E2
4.32E2
2.88E2
1.44E2
0E0
40.16
40.52
40.88
41.24
41.6
41.96
42.32
42.68
43.04

Fig. 4E

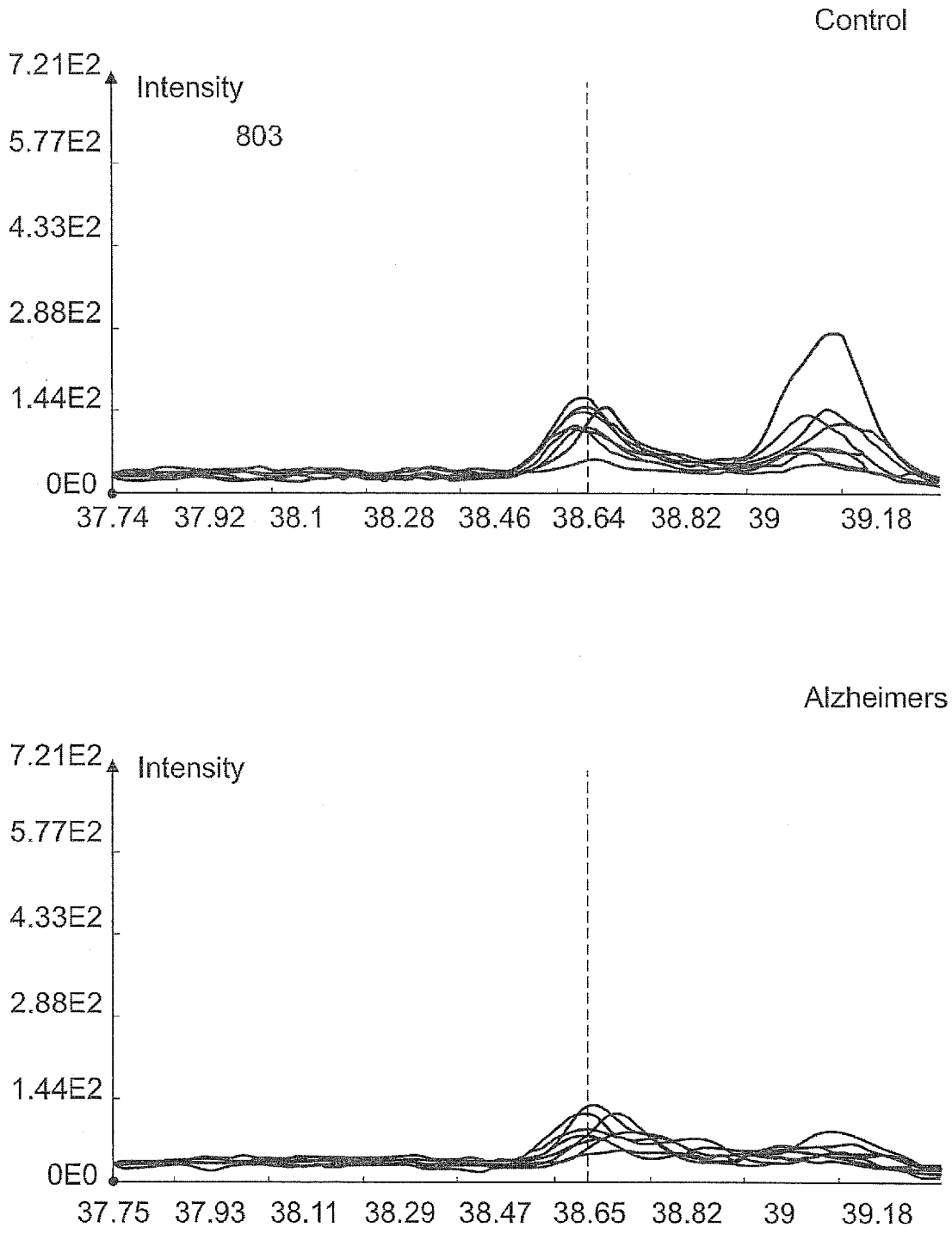

Control
7.21E2
Intensity
803
5.77E2
4.33E2
2.88E2
1.44E2
0E0
37.74
37.92
38.1
38.28
38.46
38.64
38.82
39
39.18
Alzheimers
7.21E2
Intensity
5.77E2
4.33E2
2.88E2
1.44E2
0E0
37.75
37.93
38.11
38.29
38.47
38.65
38.82
39
39.18

Fig. 4F

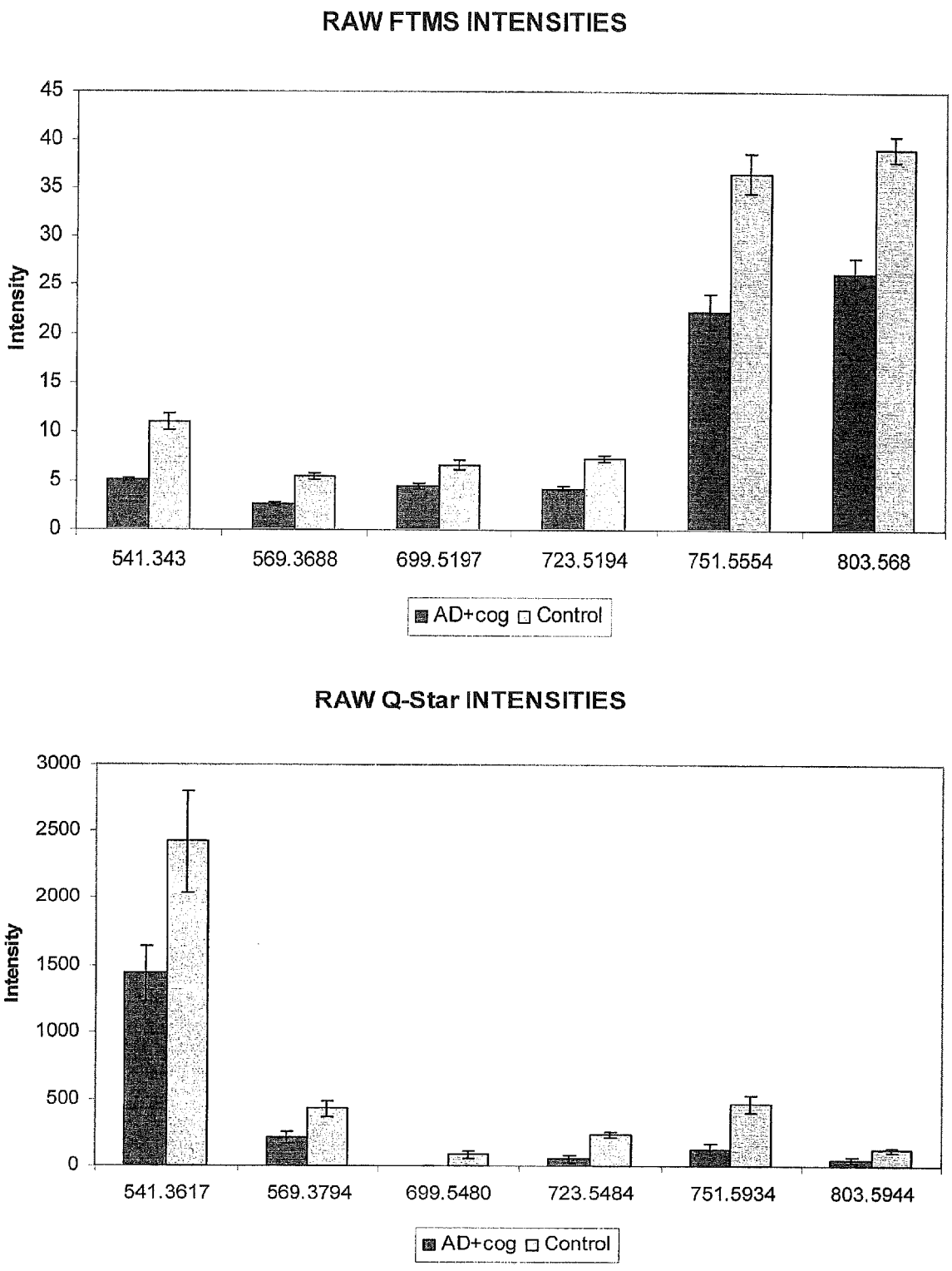

RAW FTMS INTENSITIES
Intensity
45
40
35
30
25
20
15
10
5
0
541.343
569.3688
699.5197
723.5194
751.5554
803.568
AD+cog
Control
RAW Q-Star INTENSITIES
Intensity
3000
2500
2000
1500
1000
500
0
541.3617
569.3794
699.5480
723.5484
751.5934
803.5944
AD+cog
Control

Fig. 5

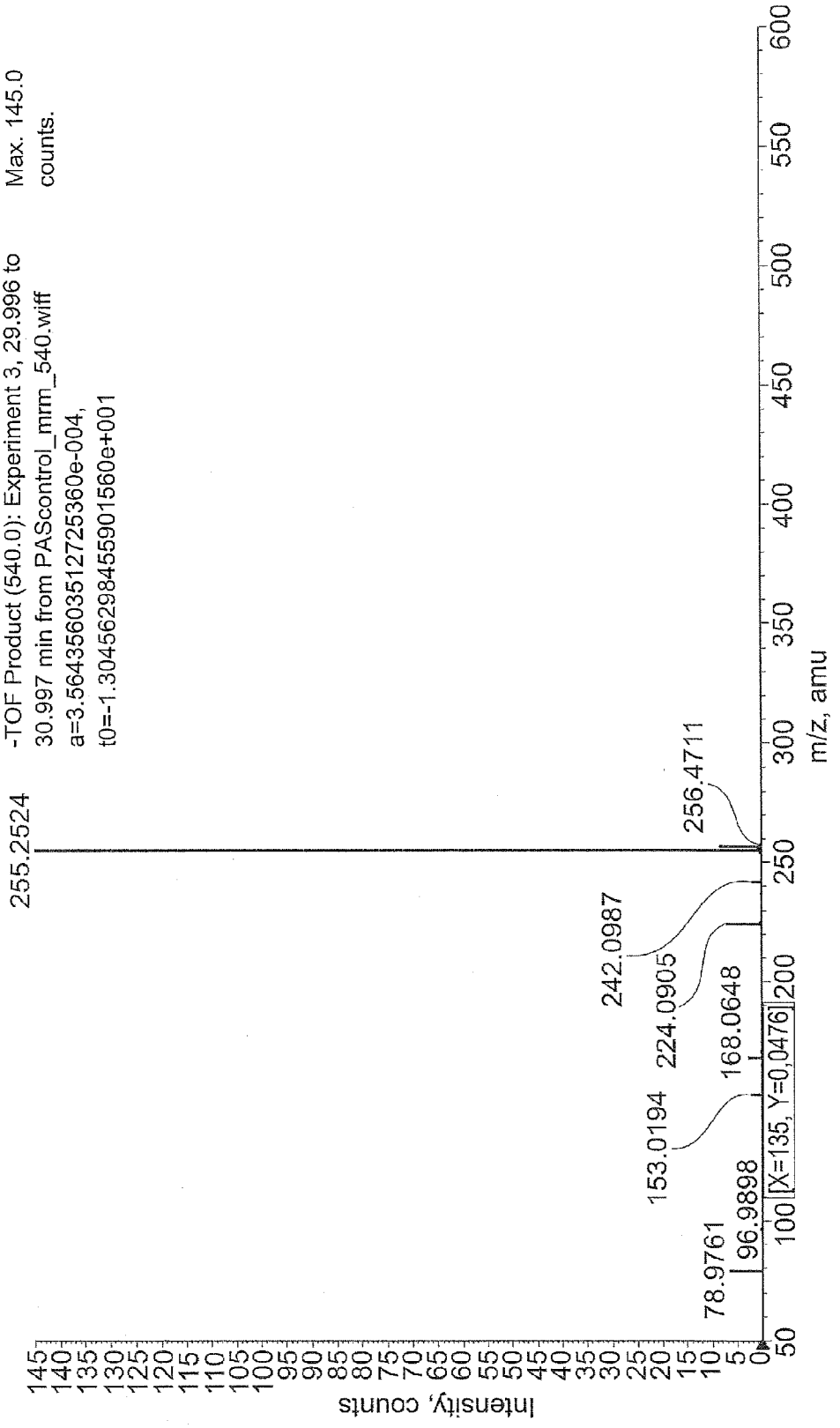

-TOF Product (540.0): Experiment 3, 29.996 to 30.997 min from PAScontrol_mrm_540.wiff
a=3.56435603512725360e-004,
t0=-1.30456298455901560e+001
Max. 145.0 counts.
255.2524
256.4711
242.0987
224.0905
168.0648
153.0194
96.9898
78.9761
X=135, Y=0,0476
Intensity, counts
m/z, amu

Fig. 6

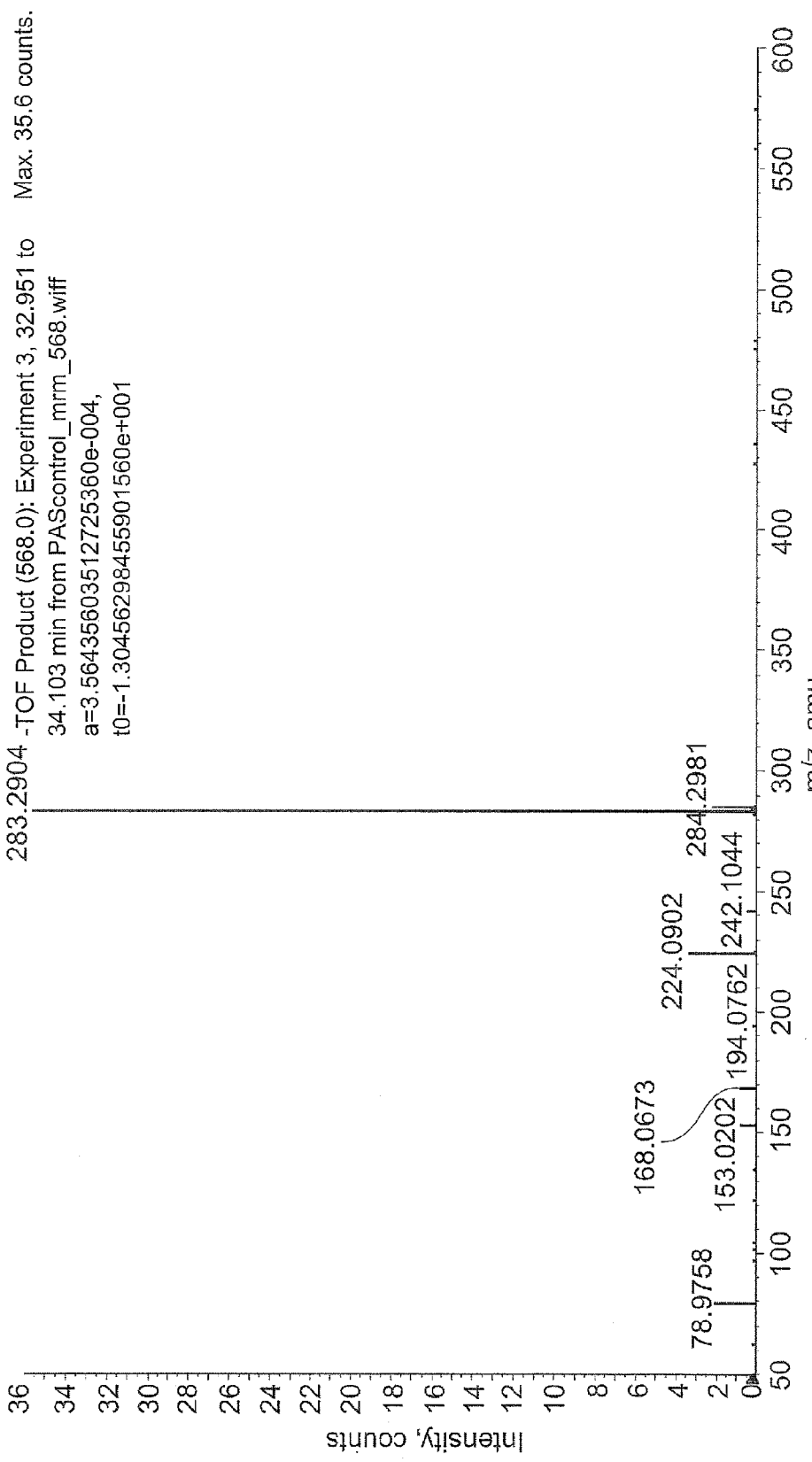

Max. 35.6 counts.
283.2904
-TOF Product (568.0): Experiment 3, 32.951 to 34.103 min from PAScontrol_mrm_568.wiff
a=3.56435603512725360e-004,
t0=-1.30456298455901560e+001
284.2981
242.1044
224.0902
194.0762
168.0673
153.0202
78.9758
Intensity, counts
m/z, amu
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
50
100
150
200
250
300
350
400
450
500
550
600

Fig. 7

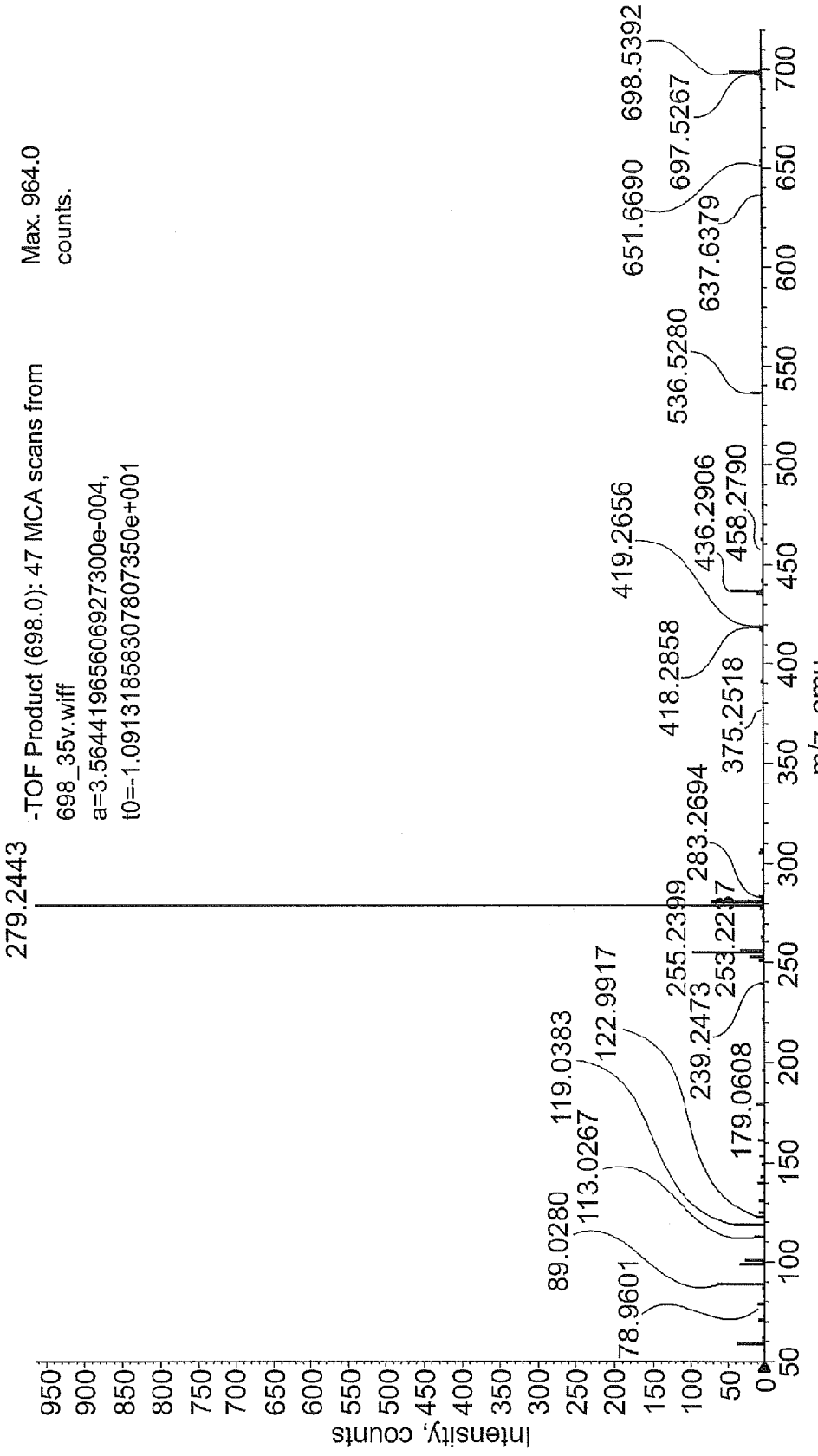

-TOF Product (698.0): 47 MCA scans from
698_35v.wiff
a=3.56441965606927300e-004,
t0=-1.09131858307807350e+001
Max. 964.0
counts.
279.2443
78.9601
89.0280
113.0267
119.0383
122.9917
179.0608
239.2473
253.2237
255.2399
283.2694
375.2518
418.2858
419.2656
436.2906
458.2790
536.5280
637.6379
651.6690
697.5267
698.5392
Intensity, counts
m/z, amu

Fig. 8

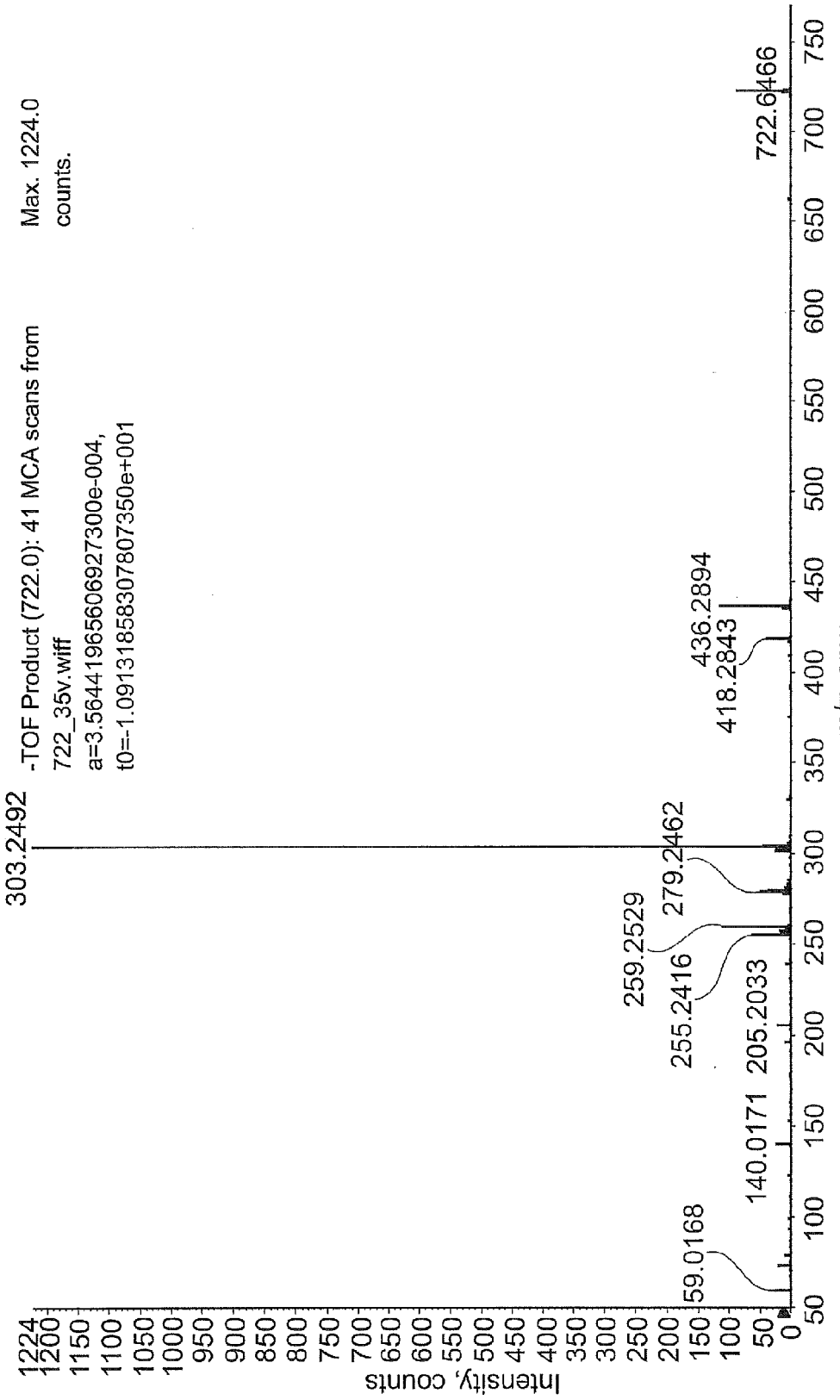

-TOF Product (722.0): 41 MCA scans from
722_35v.wiff
a=3.56441965606927300e-004,
t0=-1.09131858307807350e+001
Max. 1224.0
counts.
303.2492
259.2529
279.2462
255.2416
205.2033
140.0171
59.0168
436.2894
418.2843
722.6466
Intensity, counts
m/z, amu

Fig. 9

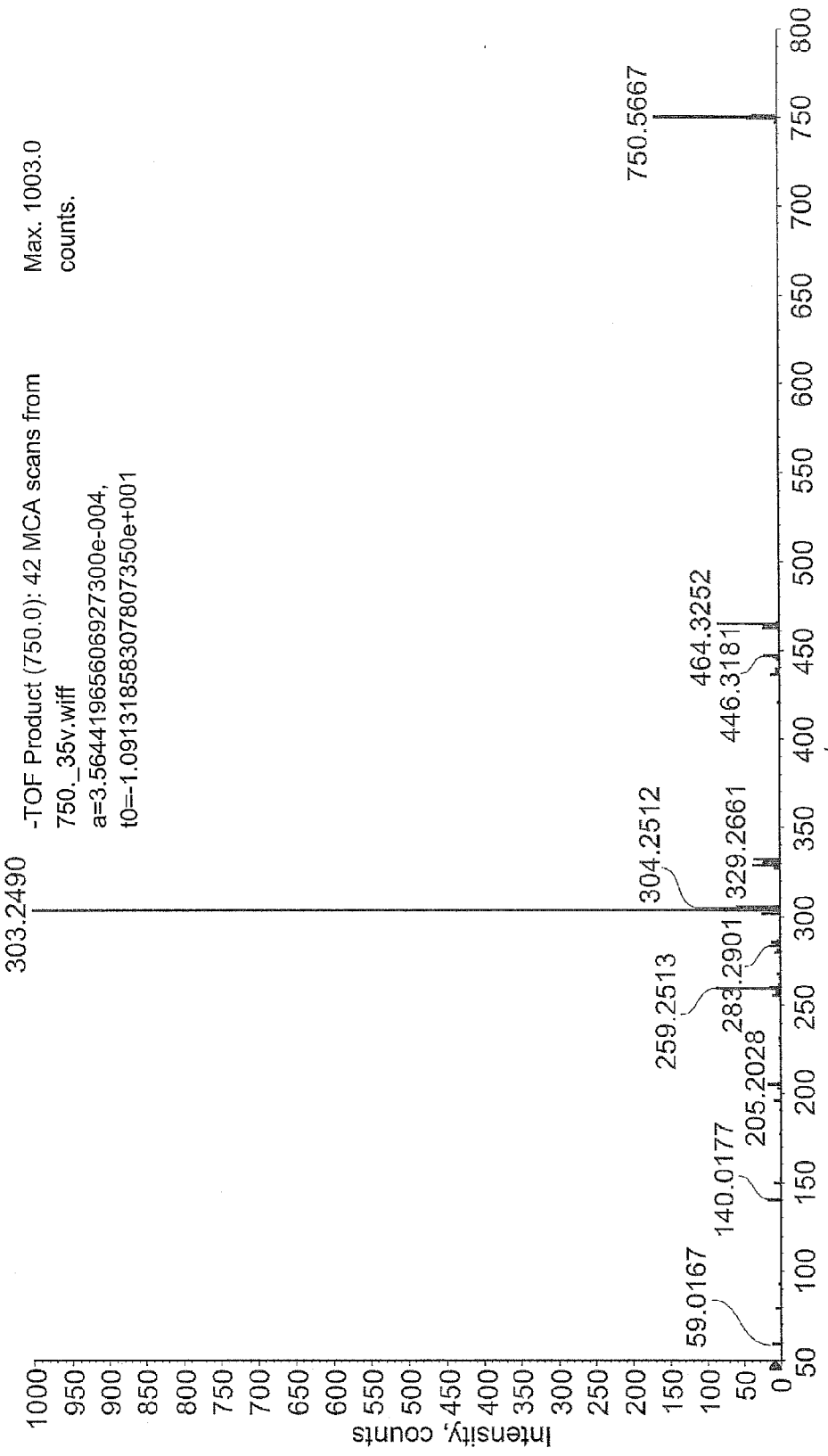

-TOF Product (750.0): 42 MCA scans from
750._35v.wiff
a=3.564419656069273 00e-004,
t0=-1.091318583078073 50e+001
Max. 1003.0
counts.
303.2490
304.2512
329.2661
446.3181
464.3252
750.5667
259.2513
283.2901
205.2028
140.0177
59.0167
Intensity, counts
m/z, amu

Fig. 10

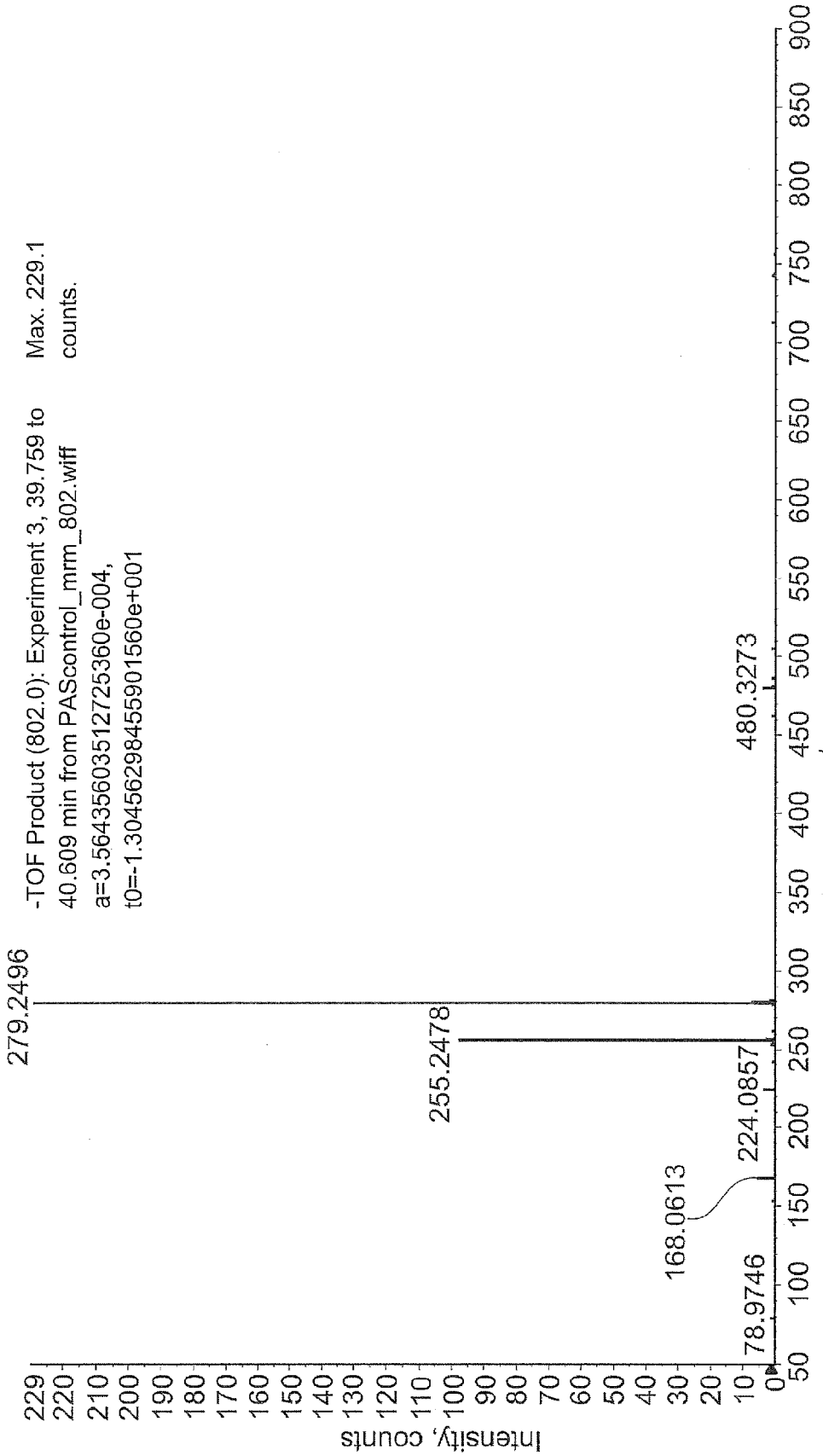

-TOF Product (802.0): Experiment 3, 39.759 to 40.609 min from PAScontrol_mrm_802.wiff
a=3.56435603512725360e-004,
t0=-1.30456298455901560e+001
Max. 229.1 counts.
279.2496
255.2478
480.3273
224.0857
168.0613
78.9746
Intensity, counts
m/z, amu

Fig. 11

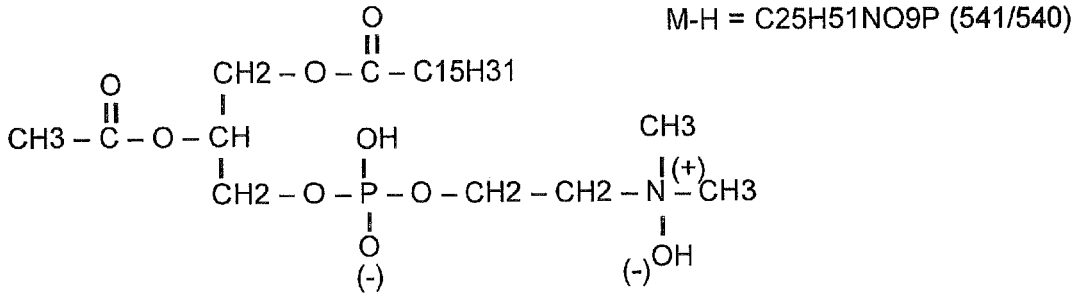


Fig. 12

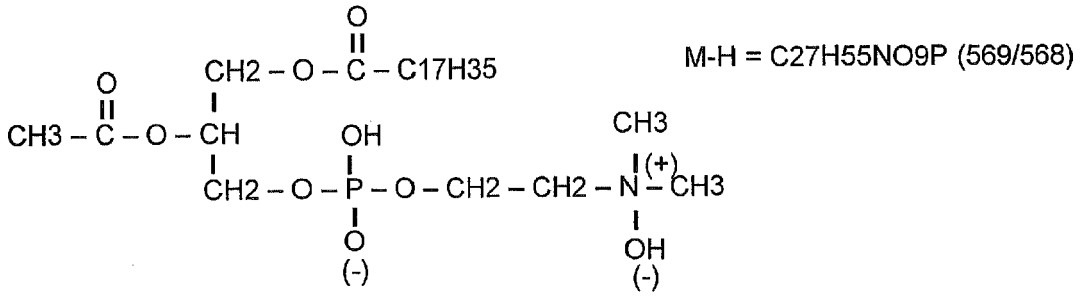


Fig. 13

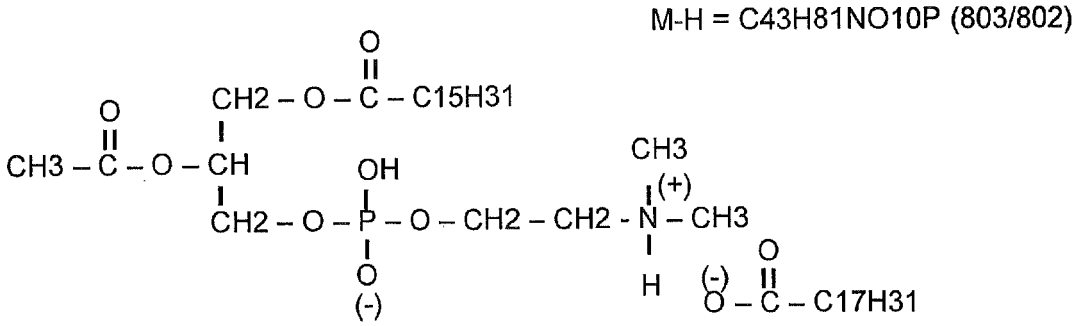
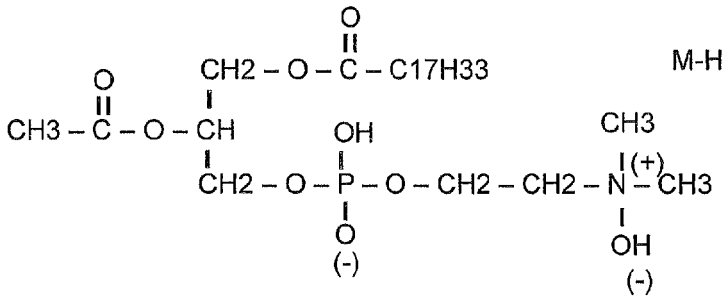


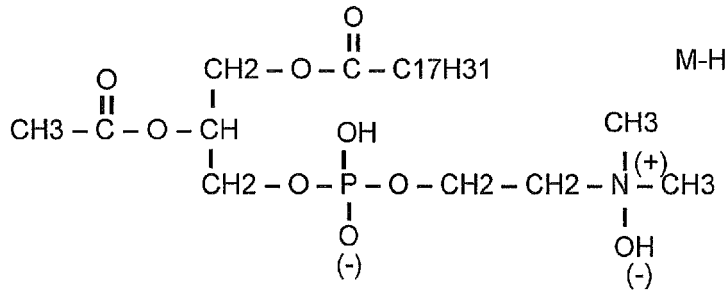
Fig. 14

A



M-H = C27H55NO9P (567/566)

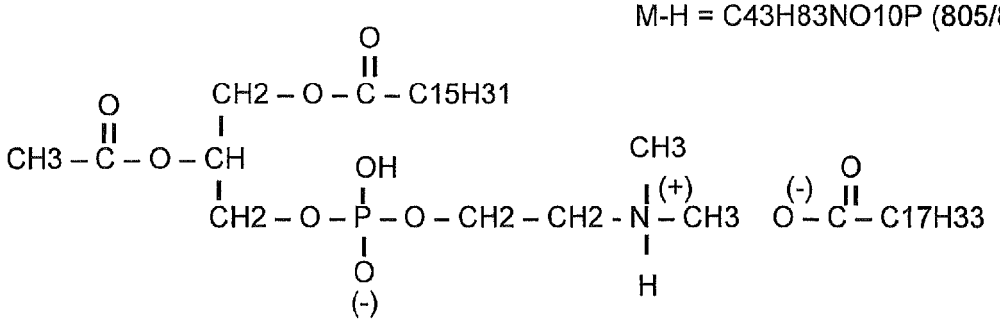
B



M-H = C27H55NO9P (565/564)

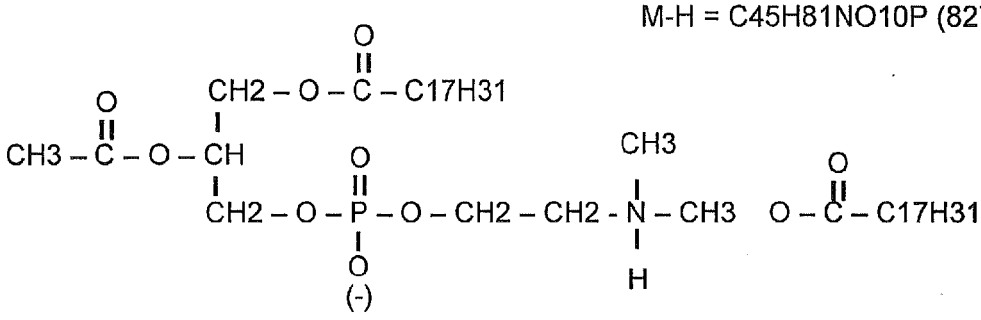
I

C



M-H = C43H83NO10P (805/804)

D

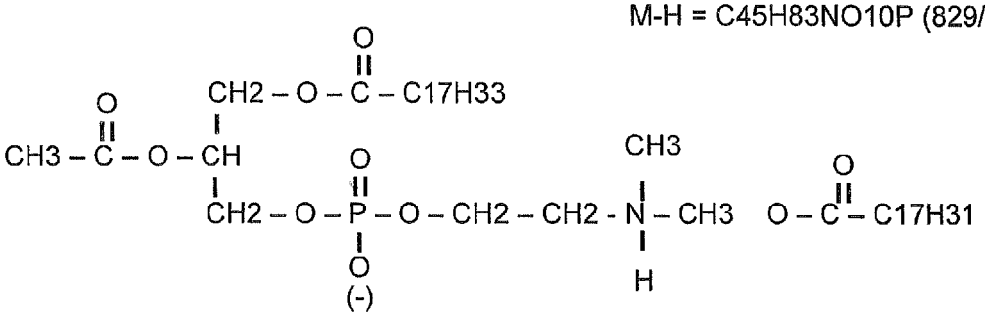


M-H = C45H81NO10P (827/826)

Fig. 15

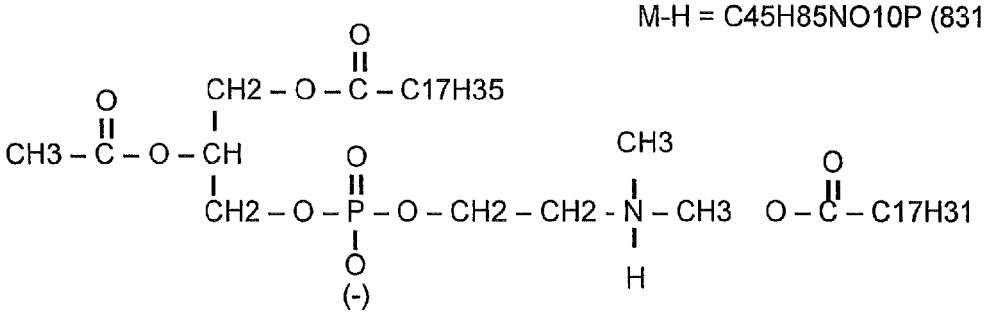
E

M-H = C45H83NO10P (829/828)



F

M-H = C45H85NO10P (831/830)



G

M-H = C47H83NO10P (853/852)

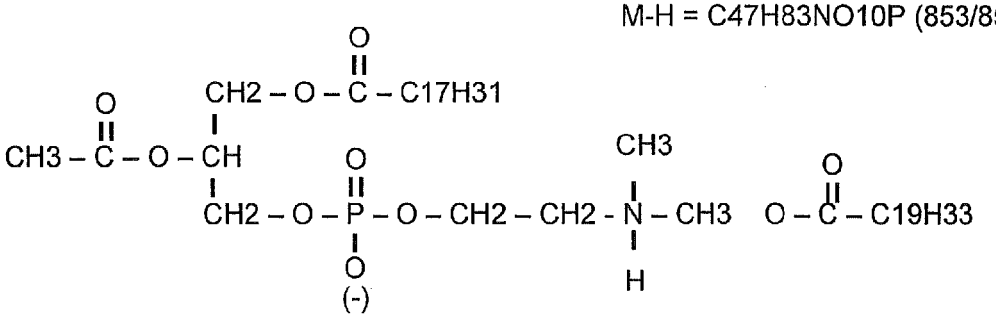
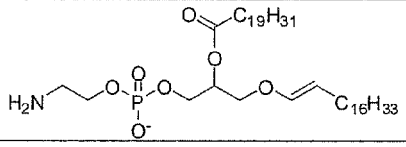
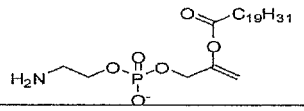
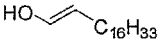
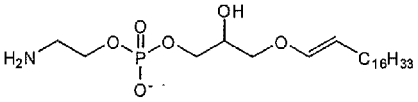
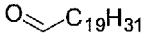
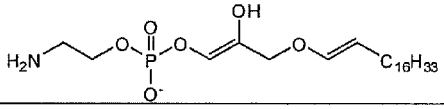
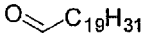
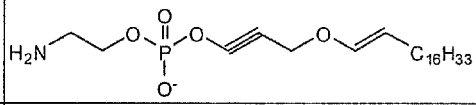
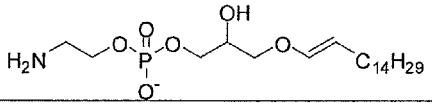
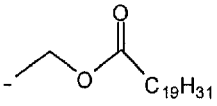
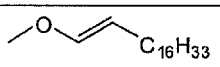
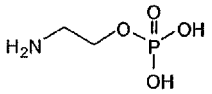
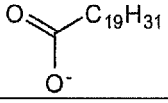
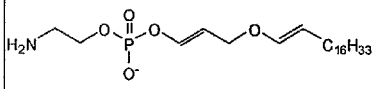
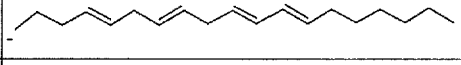
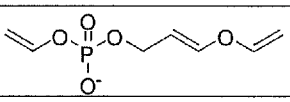


Fig. 15

m/z	Formula	Molecular fragment	Fragment loss
750	$C_{43}H_{77}NO_7P$		H^+
482	$C_{45}H_{41}NO_6P$		
464	$C_{23}H_{47}NO_6P$		
462	$C_{23}H_{45}NO_6P$		
444	$C_{23}H_{43}NO_5P$		$462 - H_2O$
436	$C_{21}H_{43}NO_6P$		$464 - C_2H_8$
331	$C_{22}H_{35}O_2$		i.  ii. 
303	$C_{20}H_{31}O_2$		
259	$C_{19}H_{31}$		$303 - CO_2$
205	$C_7H_{10}O_5P$		$464 - H_2O$, $C_{16}H_{32}$ & NH_3

Metabolite Structure:

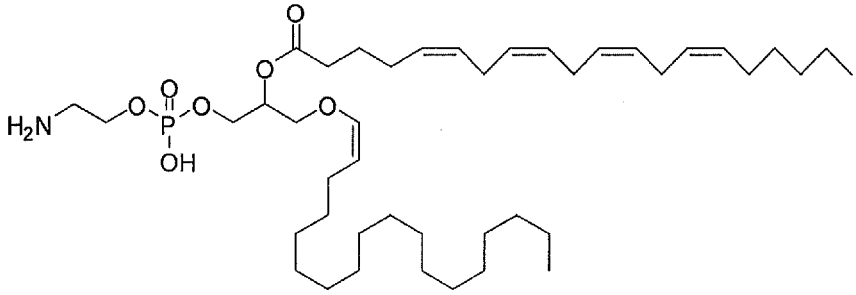
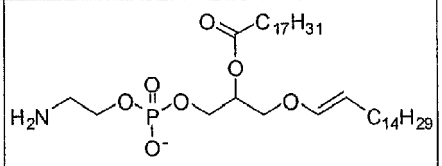
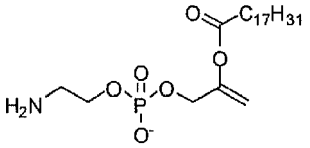
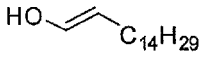
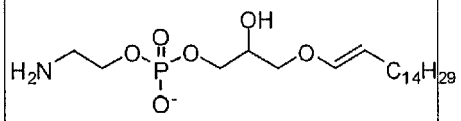
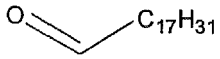
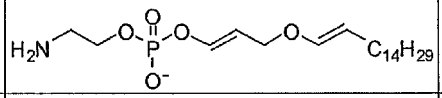
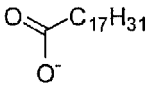
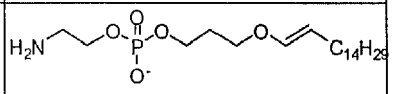
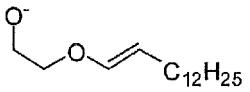
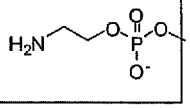


Fig. 16

m/z	Formula	Molecular fragment	Fragment loss
698	$C_{39}H_{73}NO_7P$		H^+
458	$C_{23}H_{41}NO_6P$		
436	$C_{21}H_{43}NO_6P$		
418	$C_{21}H_{41}NO_5P$		$436 - H_2O$
279	$C_{18}H_{31}O_2$		
255	$C_7H_{15}NO_5P^-$		$436 - C_2H_5$ & 

Metabolite Structure:

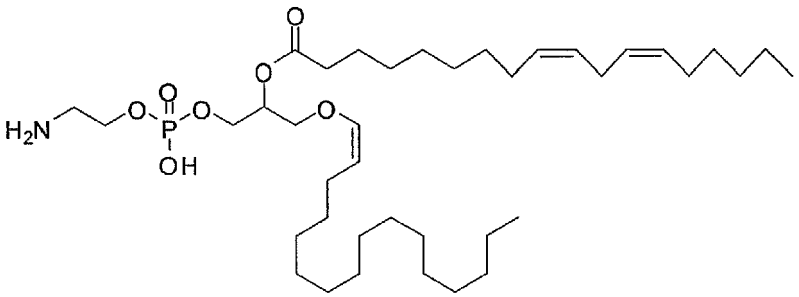
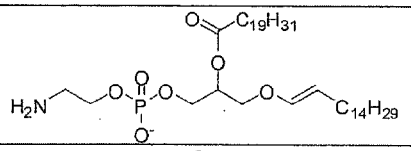
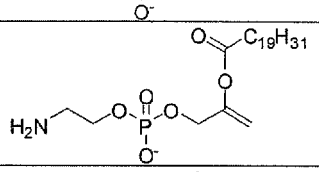
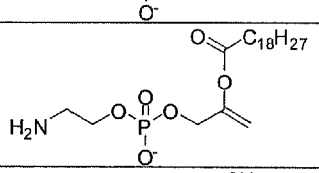
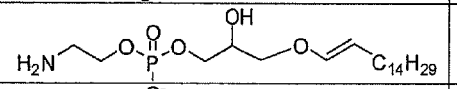
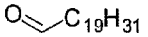
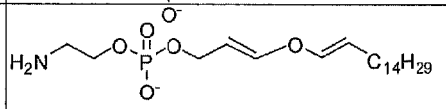
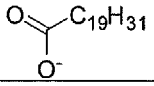
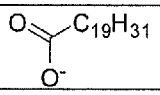
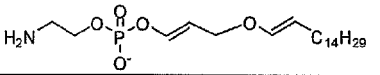
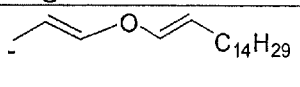
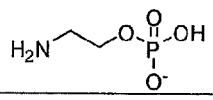
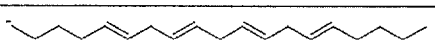
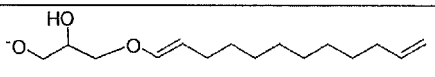
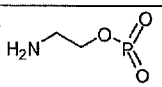
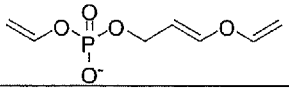
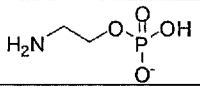


Fig. 17

m/z	Formula	Molecular fragment	Fragment loss
722	$C_{41}H_{72}NO_7P$		H^+
482	$C_{25}H_{41}NO_6P$		
466	$C_{24}H_{37}NO_6P$		482 – CH_4
436	$C_{21}H_{43}NO_6P$		
418	$C_{21}H_{41}NO_5P$		
303	$C_{20}H_{31}O_2$		
279	$C_{19}H_{35}O$		418 – 
259	$C_{19}H_{31}$		303 - CO_2
255	$C_{15}H_{27}O_3$		418 –  & C_4H_{10}
205	$C_7H_{10}O_5P$		418 – $C_{14}H_{30}$ & NH_3
140	$C_2H_7NO_4P$		

Metabolite Structure:

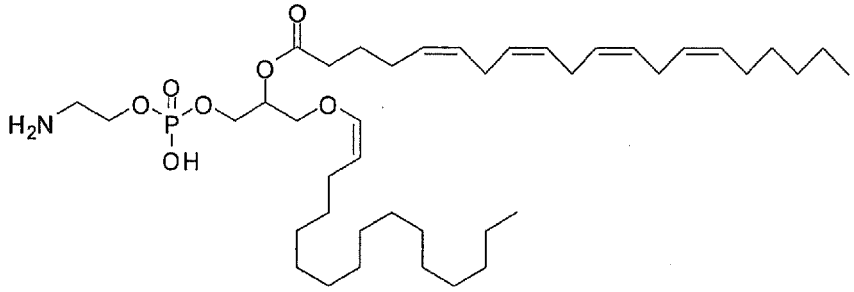


Fig. 18

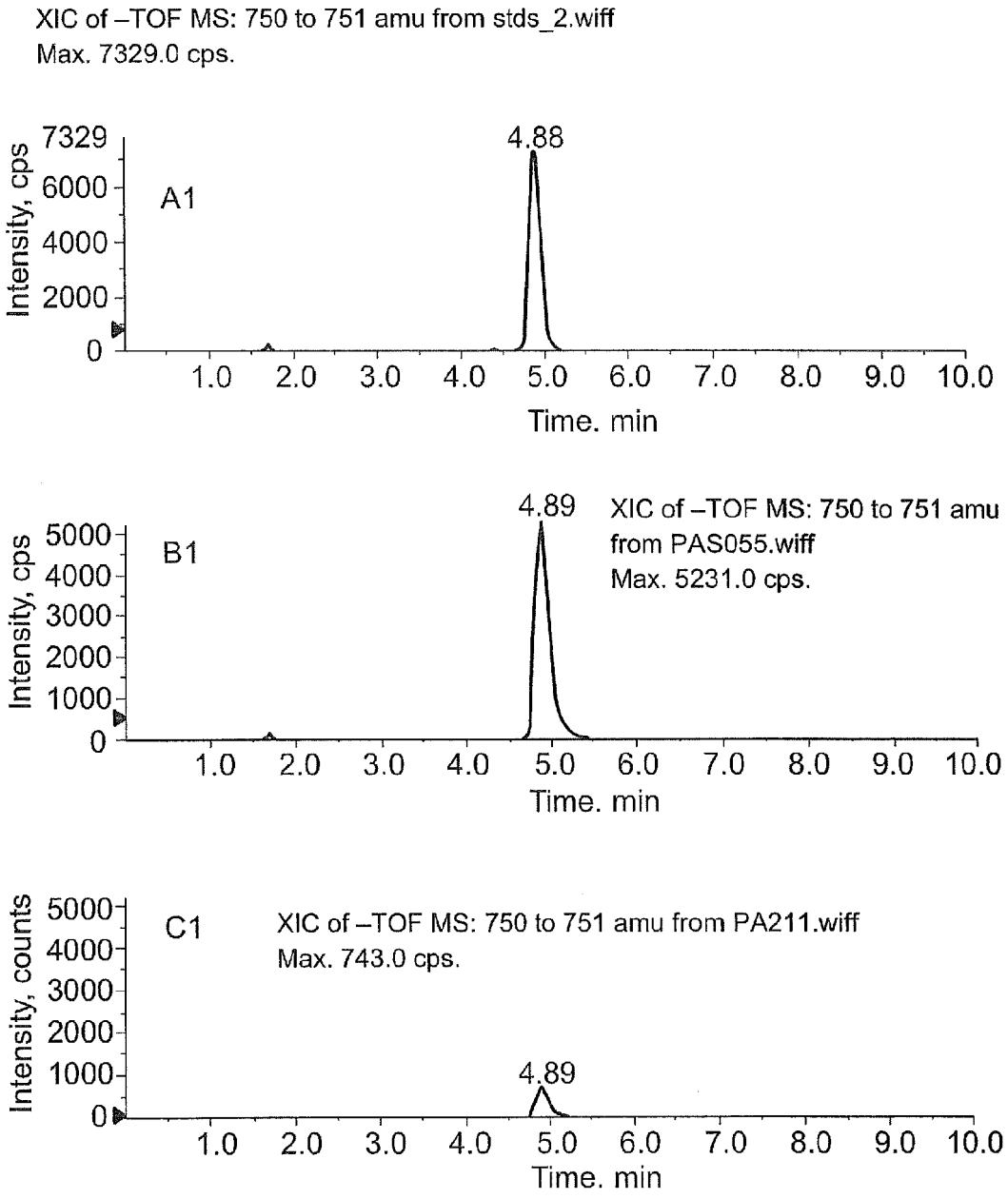
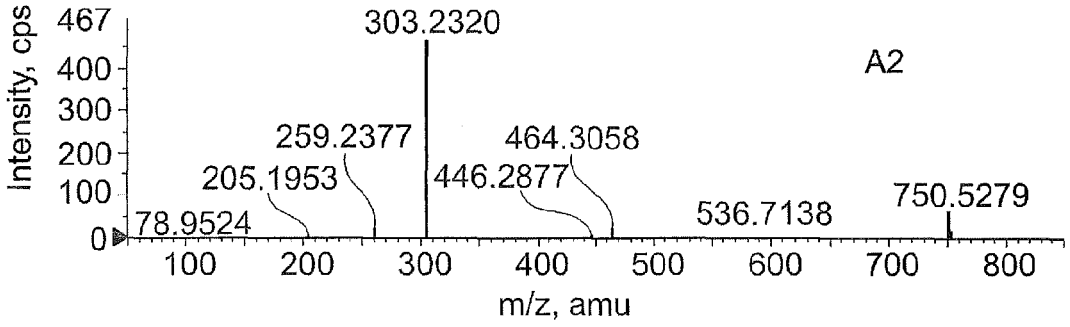
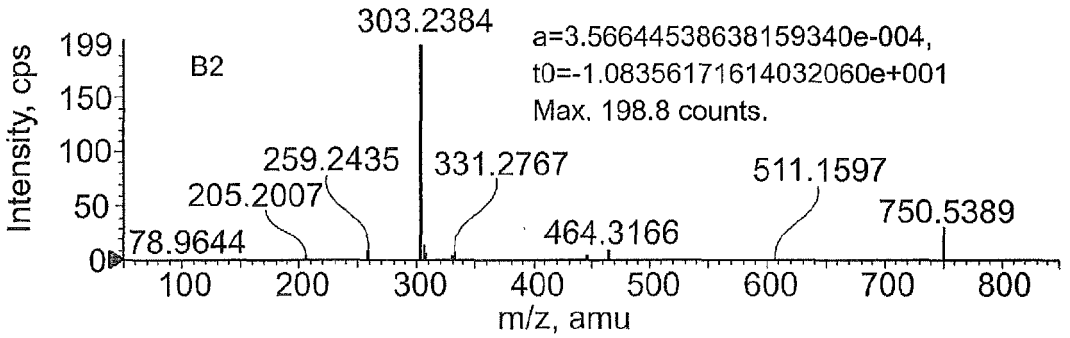

XIC of –TOF MS: 750 to 751 amu from stds_2.wiff
Max. 7329.0 cps.
Intensity, cps
7329
6000
4000
2000
0
A1
4.88
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
Time. min
Intensity, cps
5000
4000
3000
2000
1000
0
B1
4.89
XIC of –TOF MS: 750 to 751 amu
from PAS055.wiff
Max. 5231.0 cps.
Time. min
Intensity, counts
C1
XIC of –TOF MS: 750 to 751 amu from PA211.wiff
Max. 743.0 cps.
4.89
Time. min

Fig. 19a

-TOF Product (750.5): Experiment 1, 4.824 to 4.957 min from stds_MRM_2.wiff
a=3.56644538638159340e-004, t0=-1.08356171614032060e+001
Max. 467.0 counts.



-TOF Product (750.5): Experiment 1, 4.823 to 4.973 min from control_750_722_698.wiff



-TOF Product (750.5): Experiment 1, 4.723 to 4.923 min from AD_750_722_698.wiff

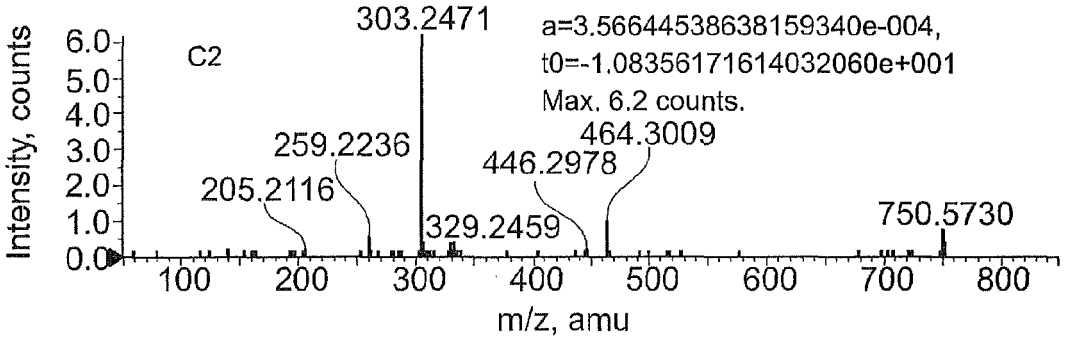


Fig. 19b

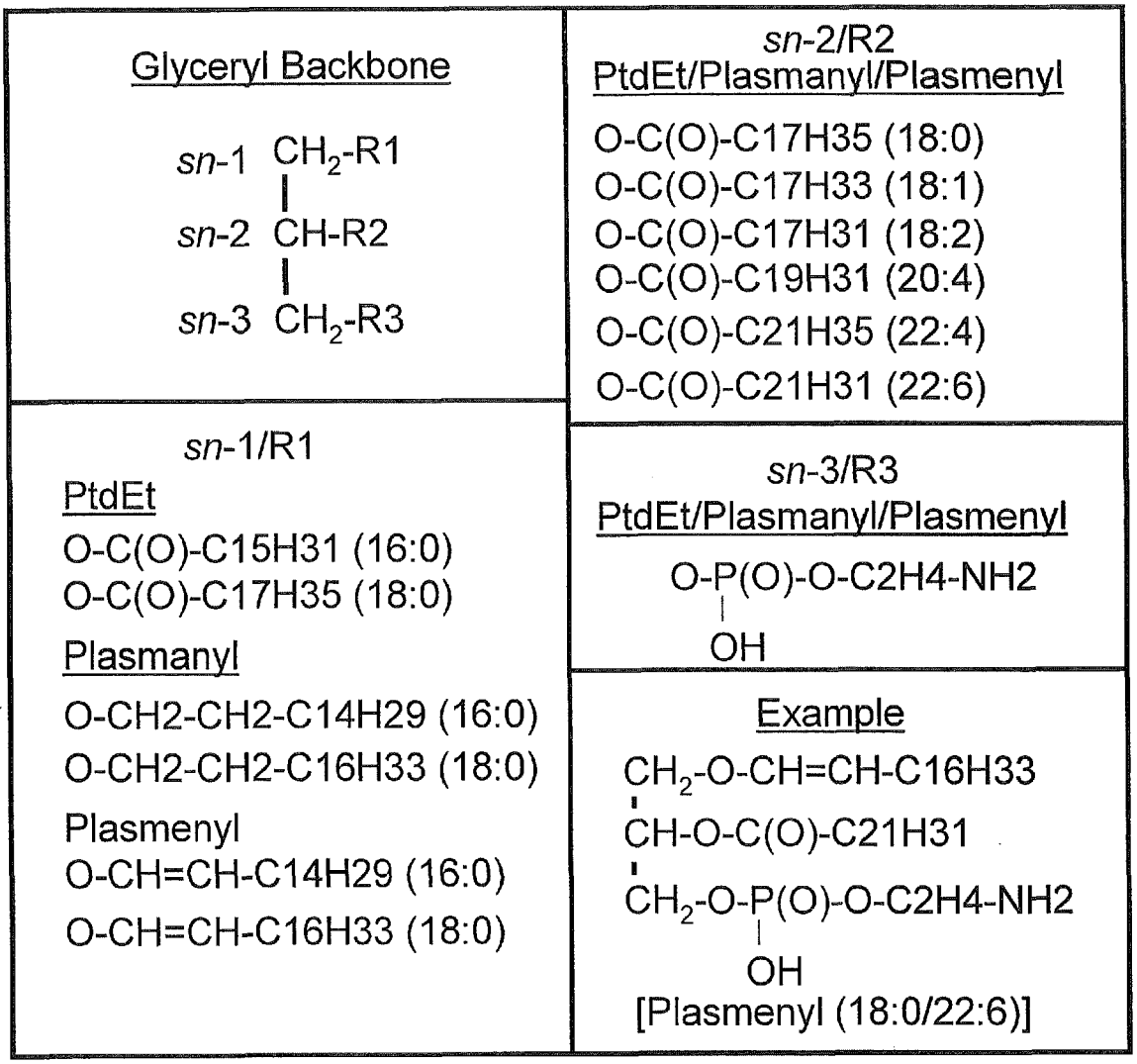

Glyceryl Backbone
sn-1 CH2-R1
sn-2 CH-R2
sn-3 CH2-R3
sn-2/R2
PtdEt/Plasmanyl/Plasmenyl
O-C(O)-C17H35 (18:0)
O-C(O)-C17H33 (18:1)
O-C(O)-C17H31 (18:2)
O-C(O)-C19H31 (20:4)
O-C(O)-C21H35 (22:4)
O-C(O)-C21H31 (22:6)
sn-1/R1
PtdEt
O-C(O)-C15H31 (16:0)
O-C(O)-C17H35 (18:0)
Plasmanyl
O-CH2-CH2-C14H29 (16:0)
O-CH2-CH2-C16H33 (18:0)
Plasmenyl
O-CH=CH-C14H29 (16:0)
O-CH=CH-C16H33 (18:0)
sn-3/R3
PtdEt/Plasmanyl/Plasmenyl
O-P(O)-O-C2H4-NH2
OH
Example
CH2-O-CH=CH-C16H33
CH-O-C(O)-C21H31
CH2-O-P(O)-O-C2H4-NH2
OH
[Plasmenyl (18:0/22:6)]

Fig. 20

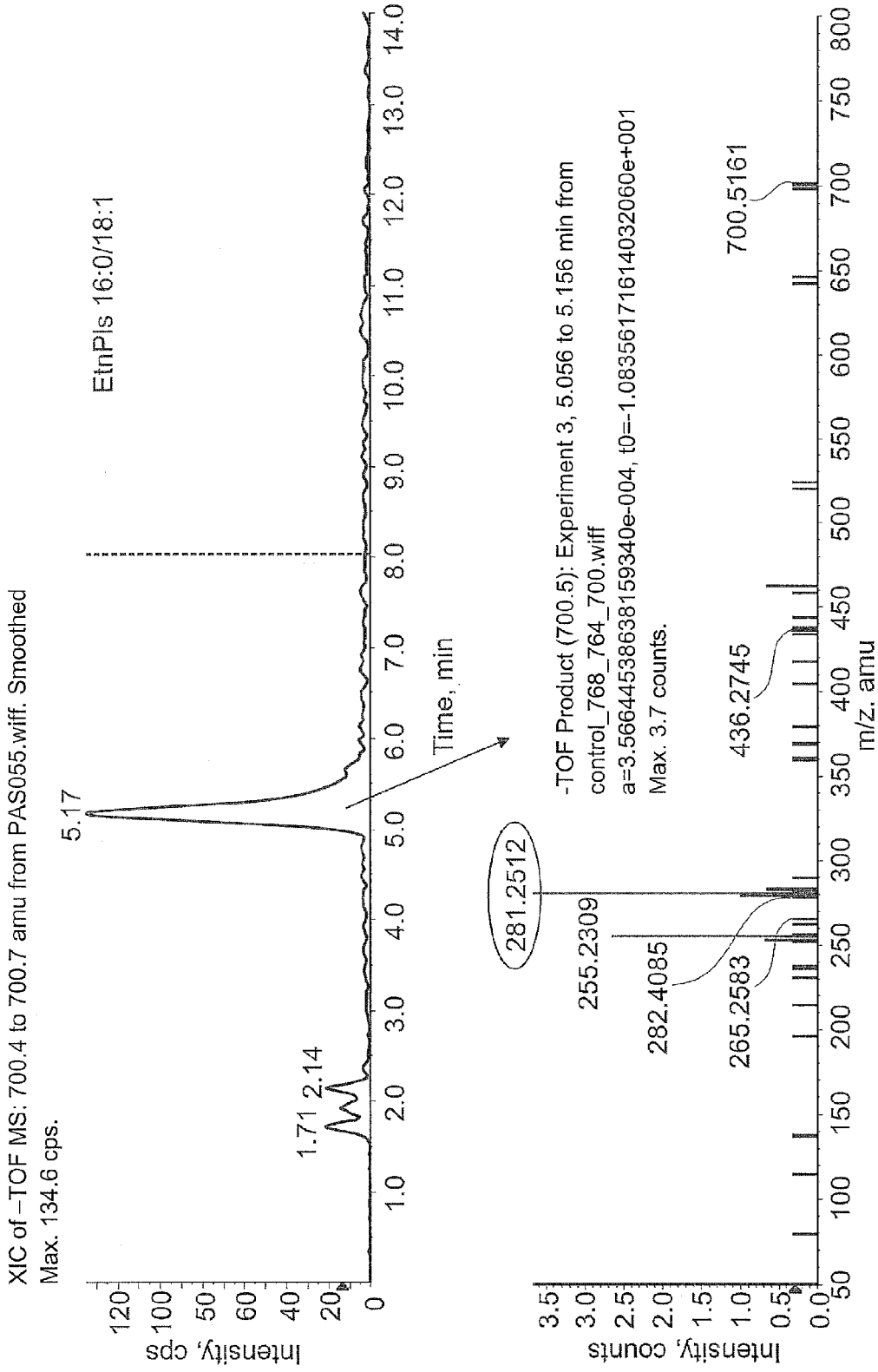

XIC of –TOF MS: 700.4 to 700.7 amu from PAS055.wiff. Smoothed
Max. 134.6 cps.
EtnPls 16:0/18:1
5.17
1.71
2.14
Intensity, cps
Time, min
-TOF Product (700.5): Experiment 3, 5.056 to 5.156 min from
control_768_764_700.wiff
a=3.566445386381593 40e-004, t0=-1.083561716140320 60e+001
Max. 3.7 counts.
281.2512
255.2309
282.4085
265.2583
436.2745
700.5161
Intensity, counts
m/z, amu

Fig. 21

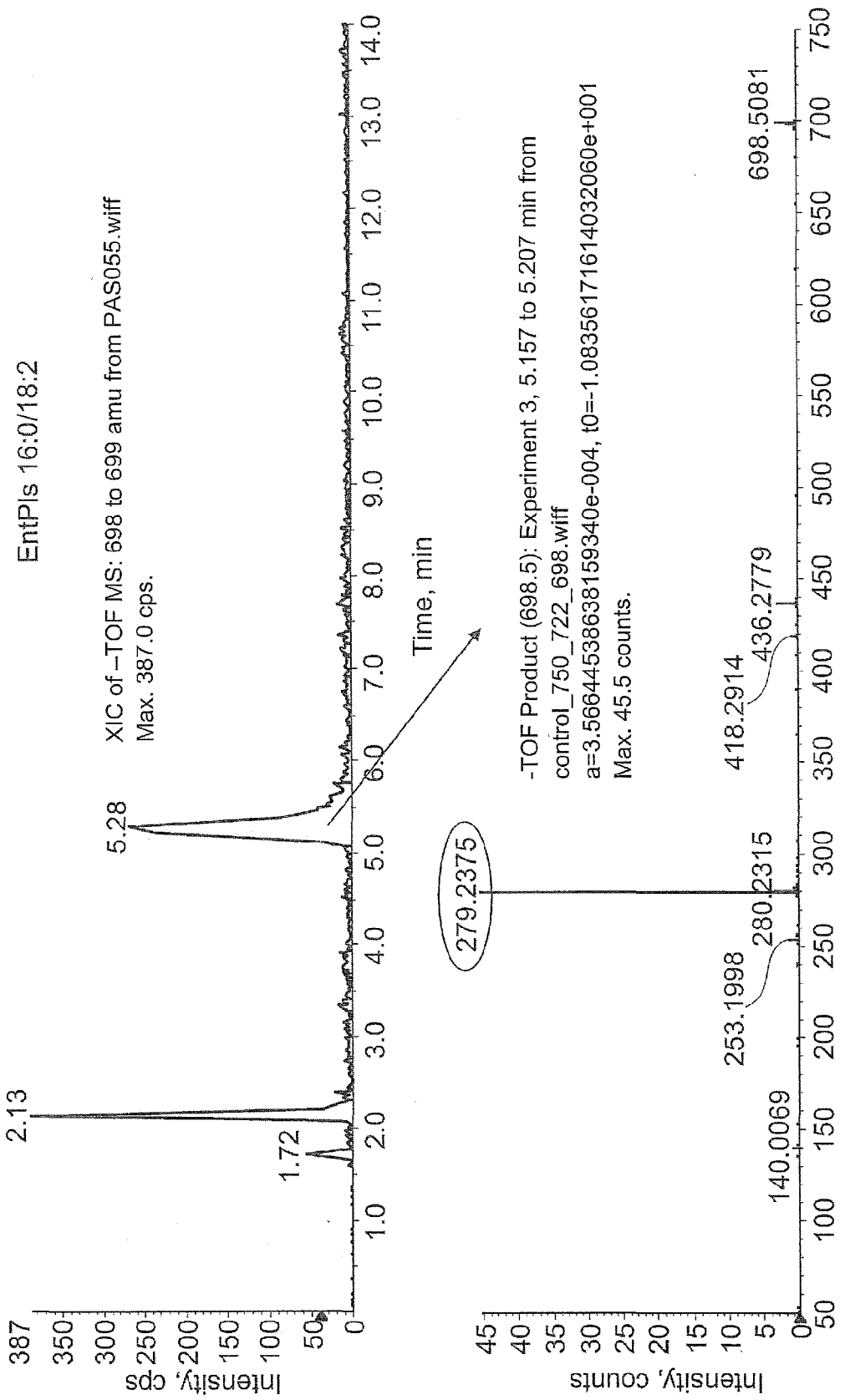

EntPls 16:0/18:2
XIC of –TOF MS: 698 to 699 amu from PAS055.wiff
Max. 387.0 cps.
Intensity, cps
Time, min
2.13
1.72
5.28
-TOF Product (698.5): Experiment 3, 5.157 to 5.207 min from
control_750_722_698.wiff
a=3.56644538638159340e-004, t0=-1.08356171614032060e+001
Max. 45.5 counts.
Intensity, counts
m/z, amu
279.2375
253.1998
280.2315
140.0069
418.2914
436.2779
698.5081

Fig. 22

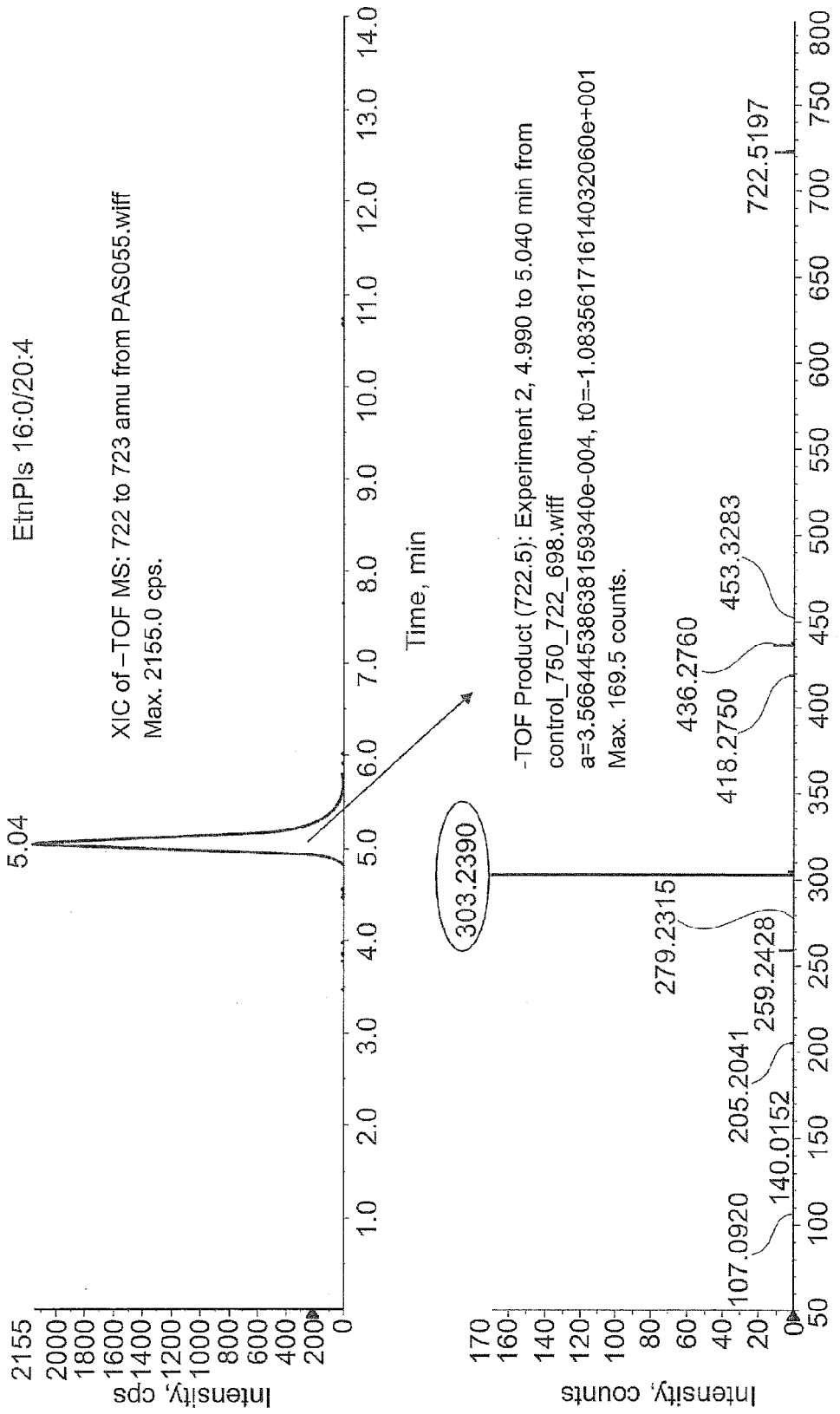

EtnPls 16:0/20:4
XIC of -TOF MS: 722 to 723 amu from PAS055.wiff
Max. 2155.0 cps.
5.04
Intensity, cps
Time, min
-TOF Product (722.5): Experiment 2, 4.990 to 5.040 min from
control_750_722_698.wiff
a=3.566445386381593 40e-004, t0=-1.083561716140320 60e+001
Max. 169.5 counts.
303.2390
279.2315
259.2428
205.2041
140.0152
107.0920
436.2760
418.2750
453.3283
722.5197
Intensity, counts
m/z, amu

Fig. 23

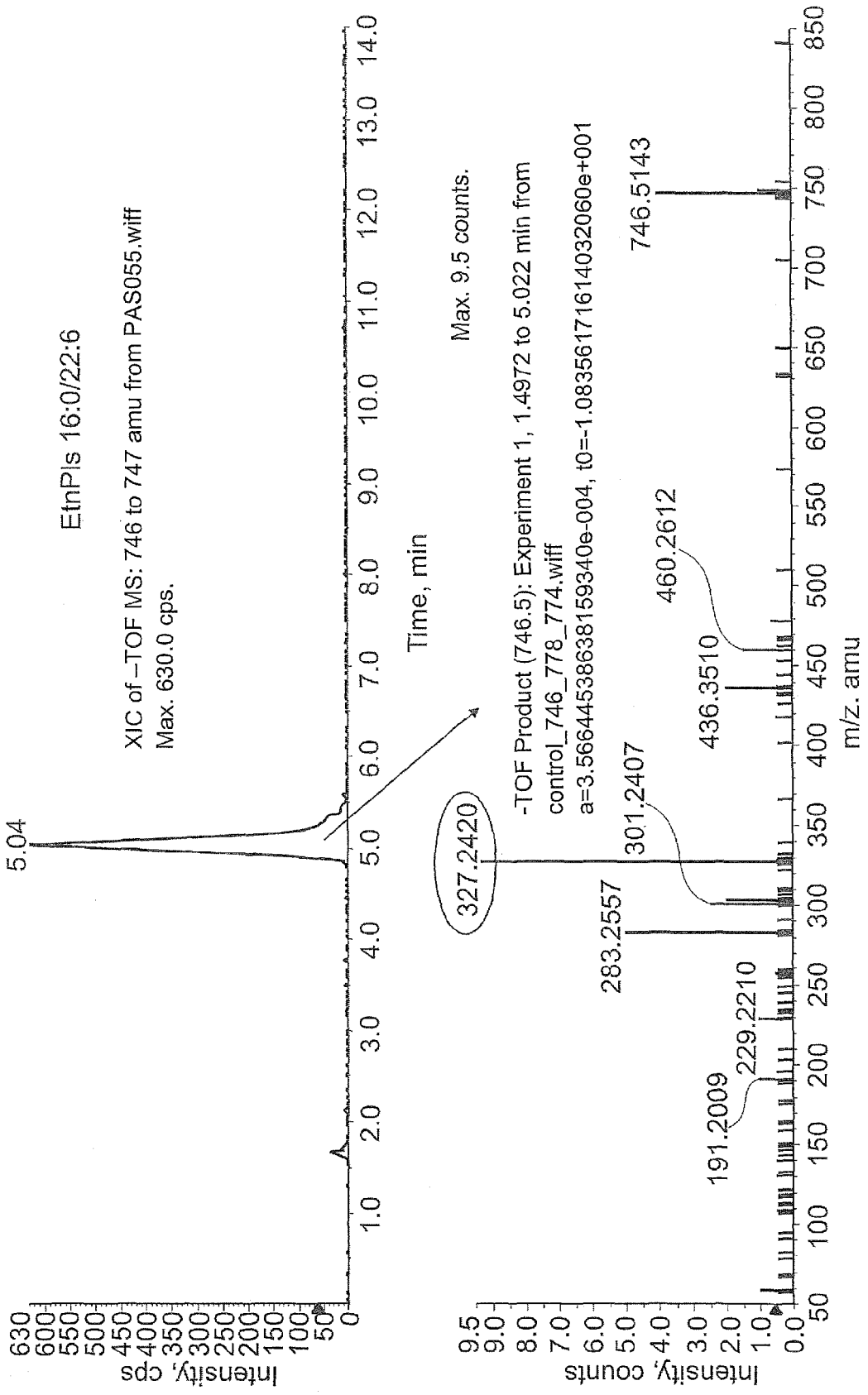

EtnPls 16:0/22:6
XIC of –TOF MS: 746 to 747 amu from PAS055.wiff
Max. 630.0 cps.
5.04
Intensity, cps
Time, min
-TOF Product (746.5): Experiment 1, 1.4972 to 5.022 min from control_746_778_774.wiff
a=3.566445386381593 40e-004, t0=-1.083561716140320 60e+001
Max. 9.5 counts.
327.2420
301.2407
283.2557
191.2009
229.2210
436.3510
460.2612
746.5143
Intensity, counts
m/z, amu

Fig. 24

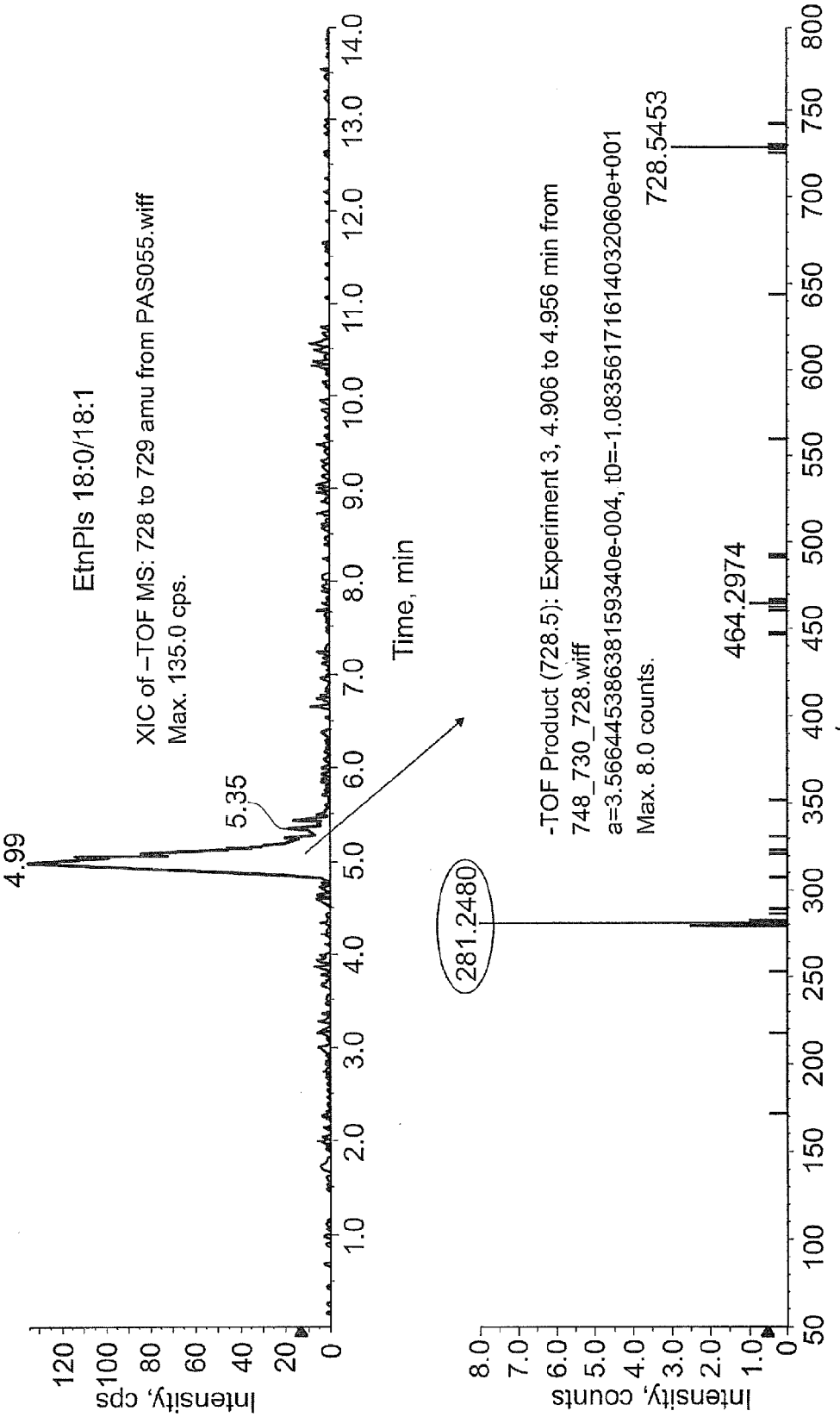

EtnPls 18:0/18:1
XIC of -TOF MS: 728 to 729 amu from PAS055.wiff
Max. 135.0 cps.
4.99
5.35
Intensity, cps
Time, min
-TOF Product (728.5): Experiment 3, 4.906 to 4.956 min from
748_730_728.wiff
a=3.56644538638159340e-004, t0=-1.08356171614032060e+001
Max. 8.0 counts.
281.2480
464.2974
728.5453
Intensity, counts
m/z, amu

Fig. 25

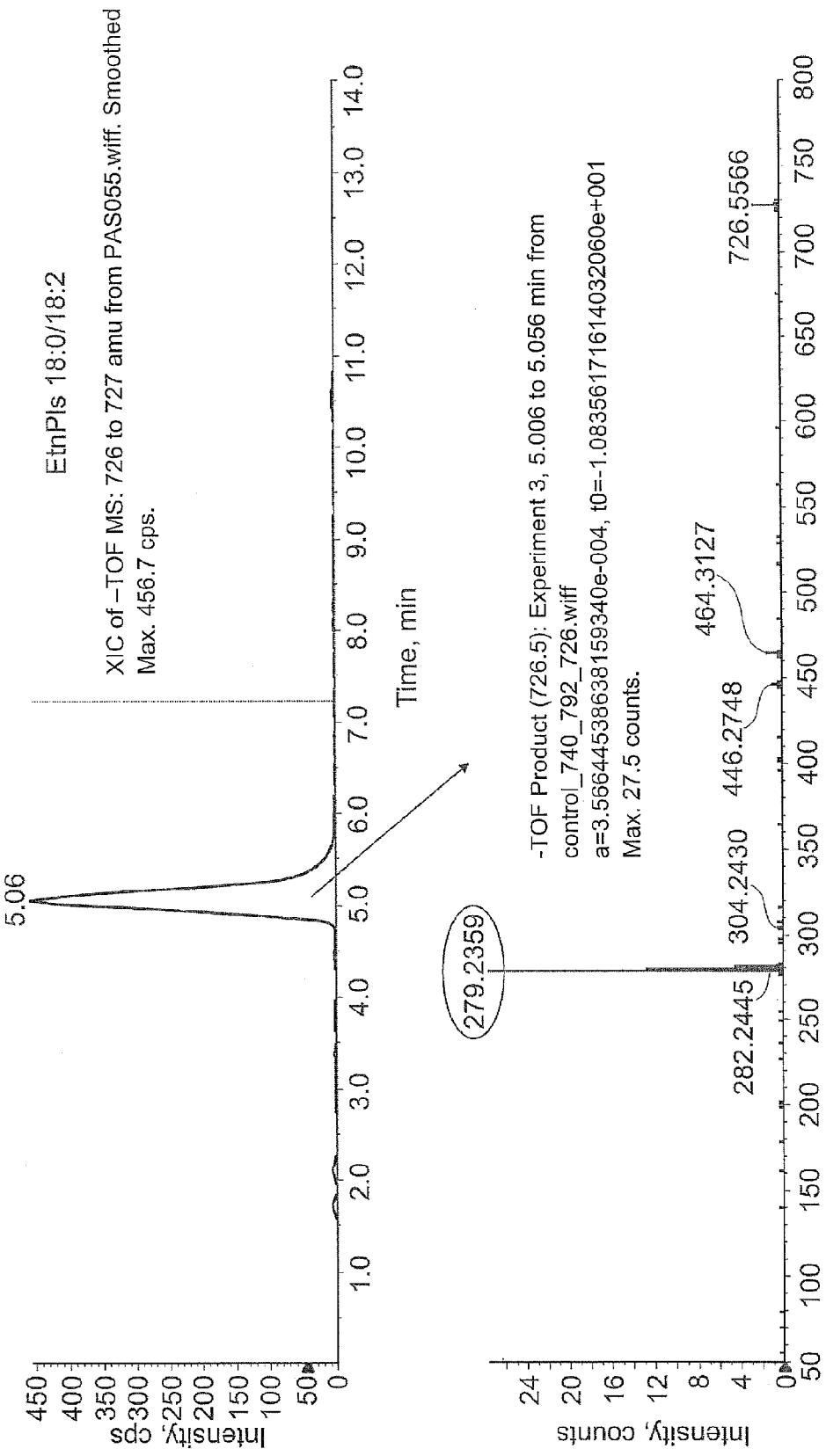

EtnPls 18:0/18:2
XIC of -TOF MS: 726 to 727 amu from PAS055.wiff. Smoothed
Max. 456.7 cps.
5.06
Intensity, cps
Time, min
-TOF Product (726.5): Experiment 3, 5.006 to 5.056 min from
control_740_792_726.wiff
a=3.56644538638159340e-004, t0=-1.08356171614032060e+001
Max. 27.5 counts.
279.2359
282.2445
304.2430
446.2748
464.3127
726.5566
Intensity, counts
m/z, amu

Fig. 26

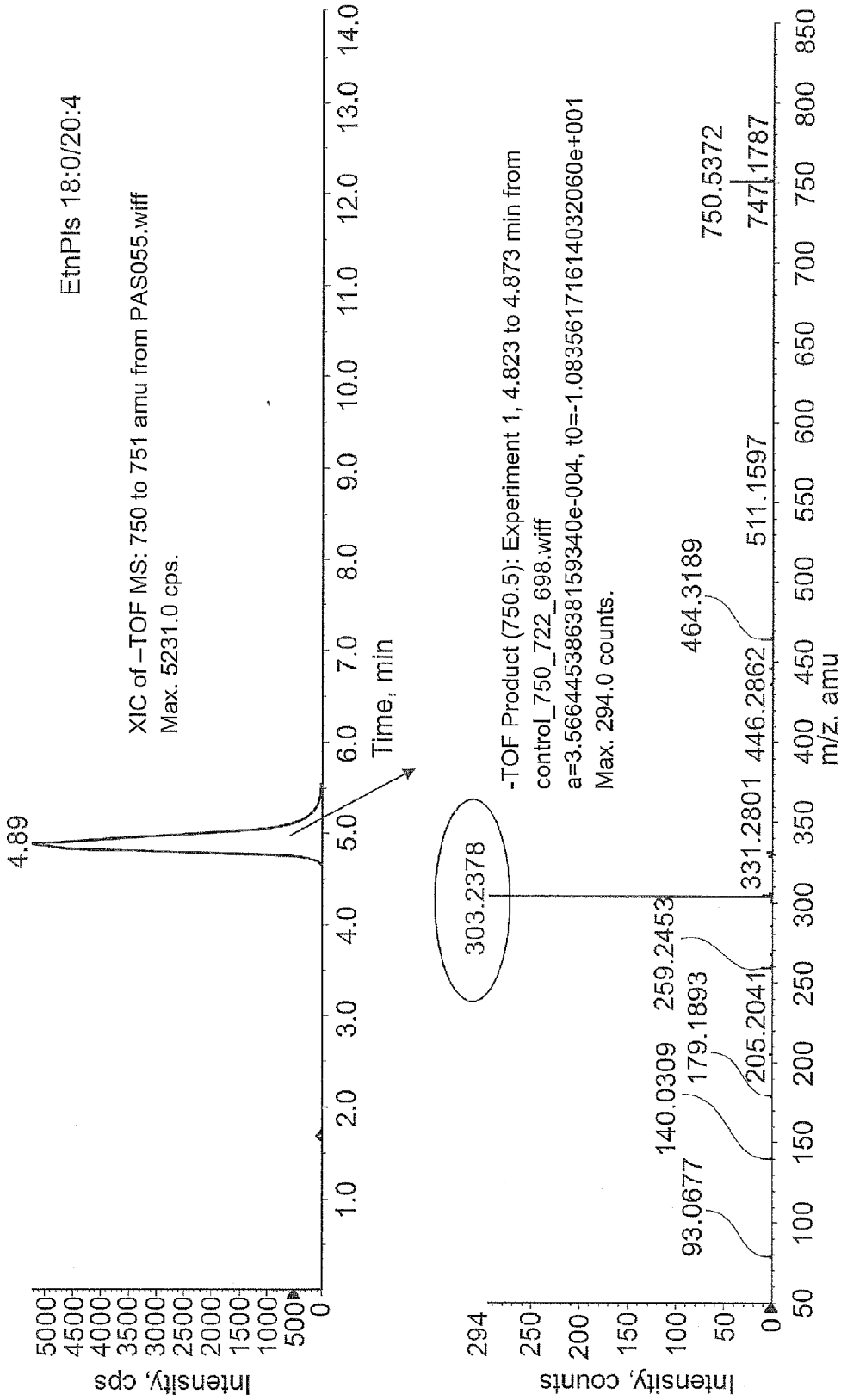

EtnPls 18:0/20:4
XIC of –TOF MS: 750 to 751 amu from PAS055.wiff
Max. 5231.0 cps.
4.89
Intensity, cps
Time, min
-TOF Product (750.5): Experiment 1, 4.823 to 4.873 min from control_750_722_698.wiff
a=3.56644538638159340e-004, t0=-1.08356171614032060e+001
Max. 294.0 counts.
303.2378
331.2801
446.2862
464.3189
511.1597
750.5372
747.1787
259.2453
205.2041
179.1893
140.0309
93.0677
Intensity, counts
m/z, amu

Fig. 27

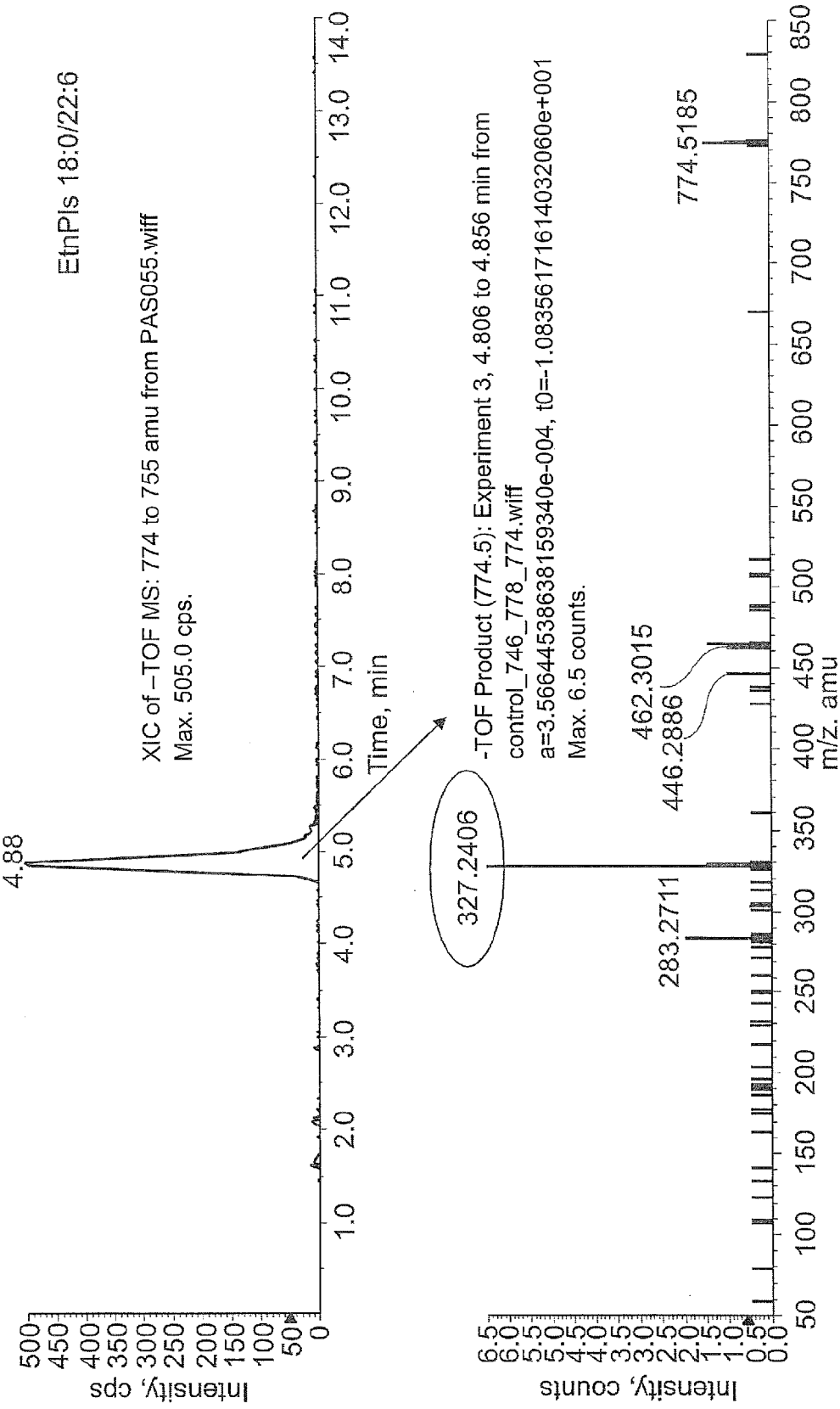

EtnPls 18:0/22:6
XIC of –TOF MS: 774 to 755 amu from PAS055.wiff
Max. 505.0 cps.
4.88
Intensity, cps
Time, min
-TOF Product (774.5): Experiment 3, 4.806 to 4.856 min from
control_746_778_774.wiff
a=3.56644538638159340e-004, t0=-1.08356171614032060e+001
Max. 6.5 counts.
327.2406
283.2711
462.3015
446.2886
774.5185
Intensity, counts
m/z, amu

Fig. 28

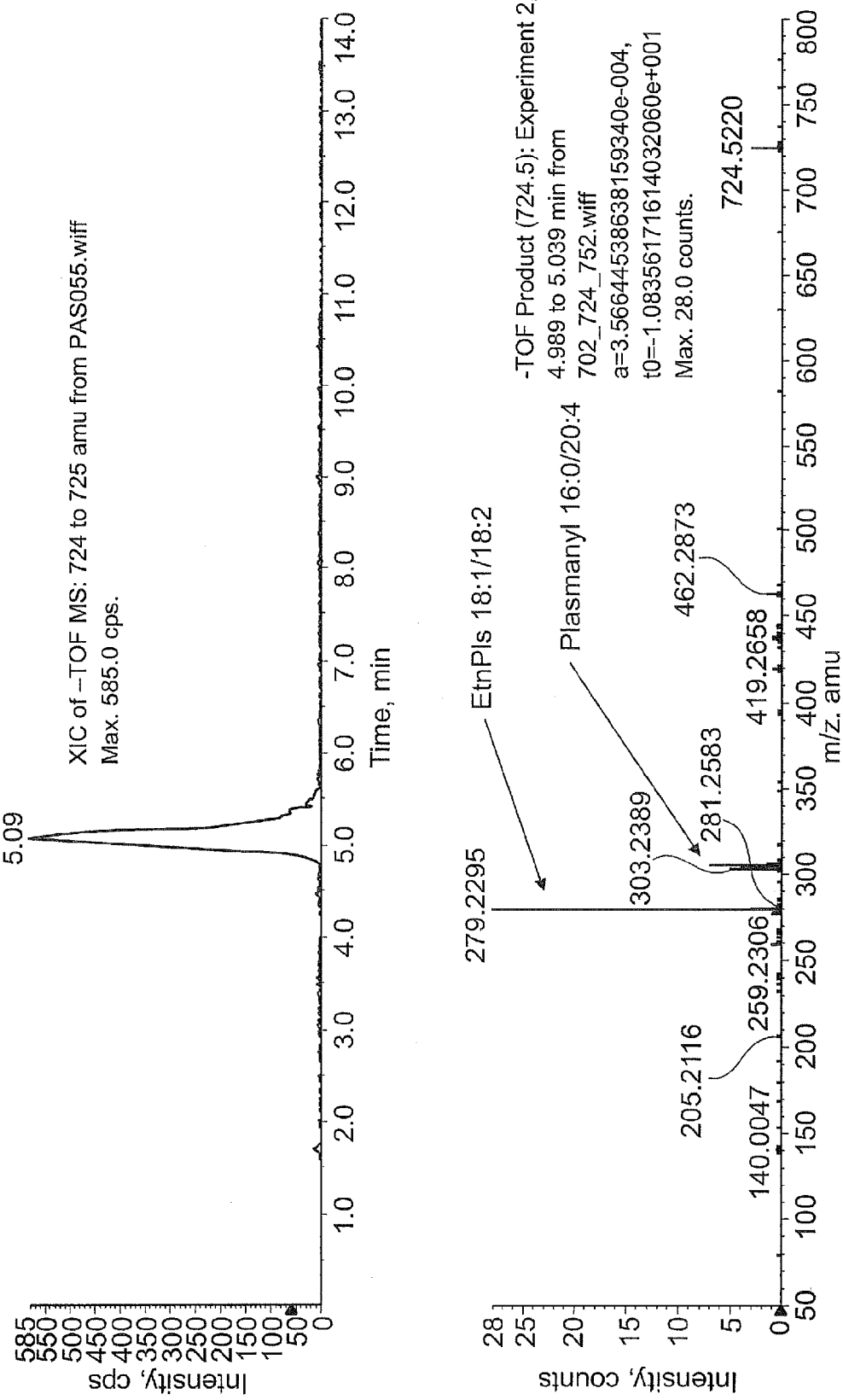

XIC of –TOF MS: 724 to 725 amu from PAS055.wiff
Max. 585.0 cps.
5.09
Intensity, cps
Time, min
-TOF Product (724.5): Experiment 2, 4.989 to 5.039 min from 702_724_752.wiff
a=3.56644538638159340e-004, t0=-1.08356171614032060e+001
Max. 28.0 counts.
EtnPls 18:1/18:2
Plasmanyl 16:0/20:4
279.2295
303.2389
281.2583
462.2873
724.5220
419.2658
259.2306
205.2116
140.0047
Intensity, counts
m/z, amu

Fig. 29

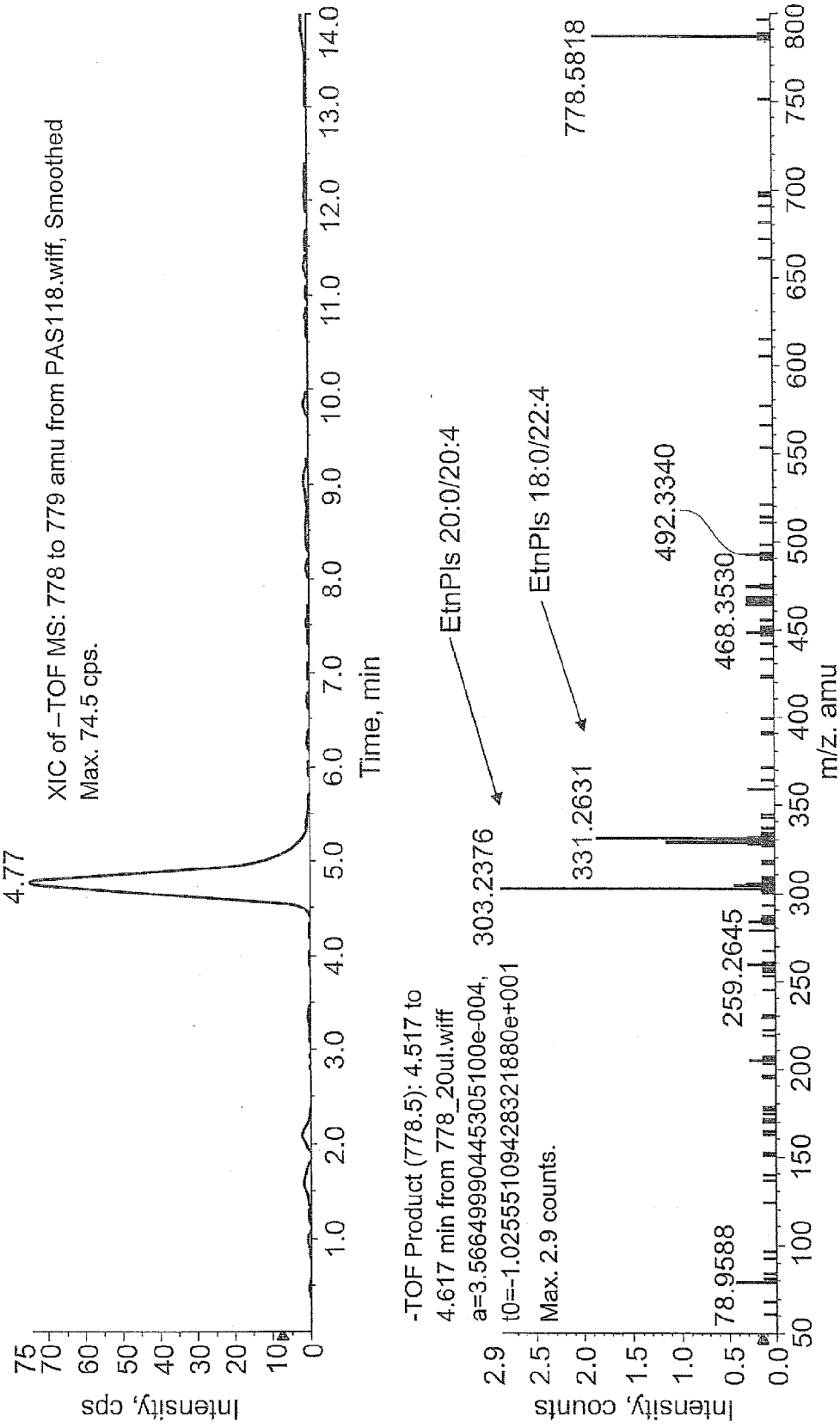

XIC of –TOF MS: 778 to 779 amu from PAS118.wiff, Smoothed
Max. 74.5 cps.
4.77
Intensity, cps
Time, min
-TOF Product (778.5): 4.517 to
4.617 min from 778_20ul.wiff
a=3.56649990445305100e-004,
t0=-1.02555109428321880e+001
Max. 2.9 counts.
EtnPls 20:0/20:4
EtnPls 18:0/22:4
303.2376
331.2631
492.3340
468.3530
778.5818
259.2645
78.9588
Intensity, counts
m/z, amu

Fig. 30

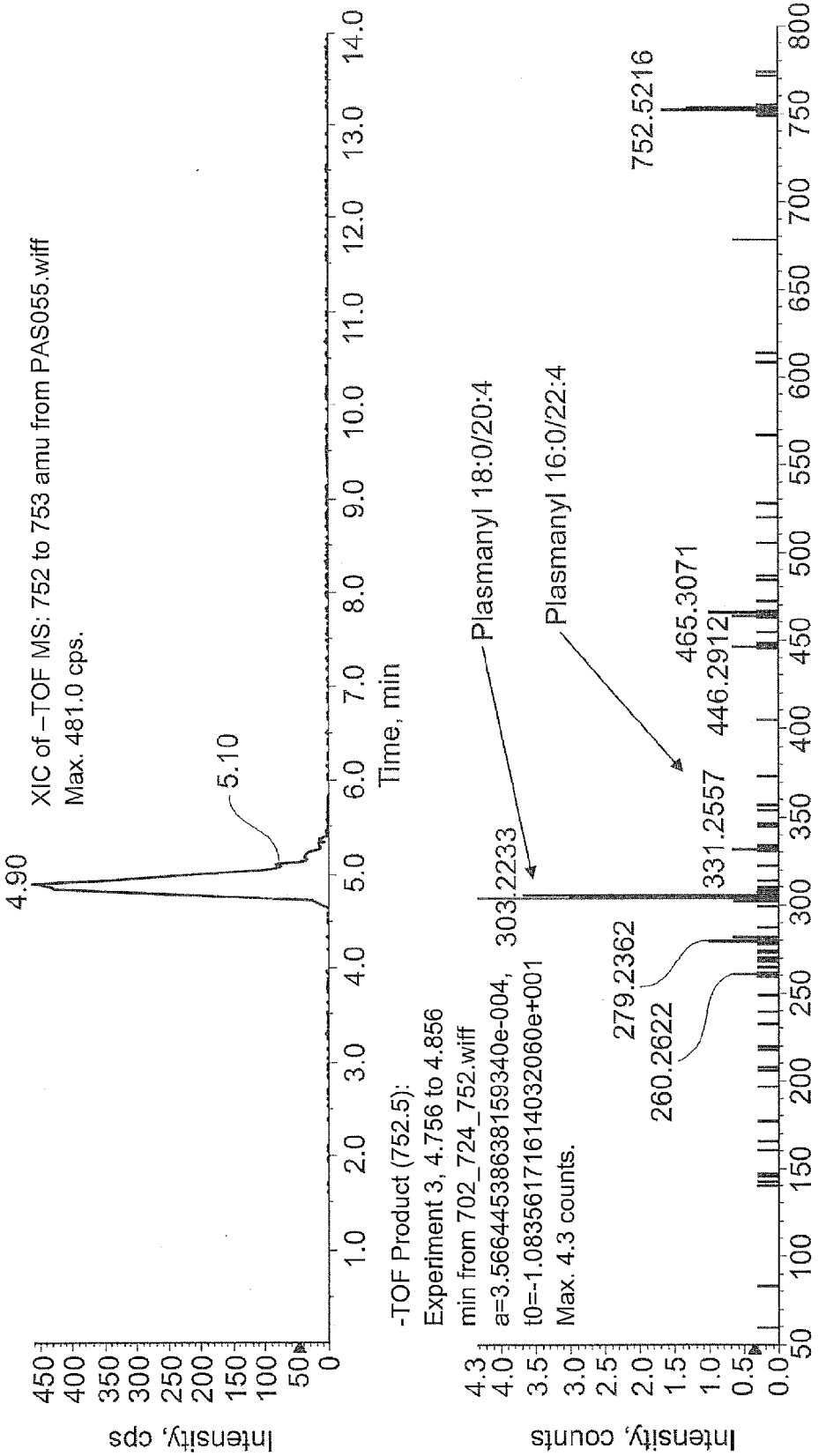

XIC of –TOF MS: 752 to 753 amu from PAS055.wiff
Max. 481.0 cps.
4.90
5.10
Intensity, cps
Time, min
-TOF Product (752.5):
Experiment 3, 4.756 to 4.856
min from 702_724_752.wiff
a=3.56644538638159340e-004,
t0=-1.08356171614032060e+001
Max. 4.3 counts.
303.2233
Plasmanyl 18:0/20:4
Plasmanyl 16:0/22:4
279.2362
260.2622
331.2557
446.2912
465.3071
752.5216
Intensity, counts
m/z, amu

Fig. 31

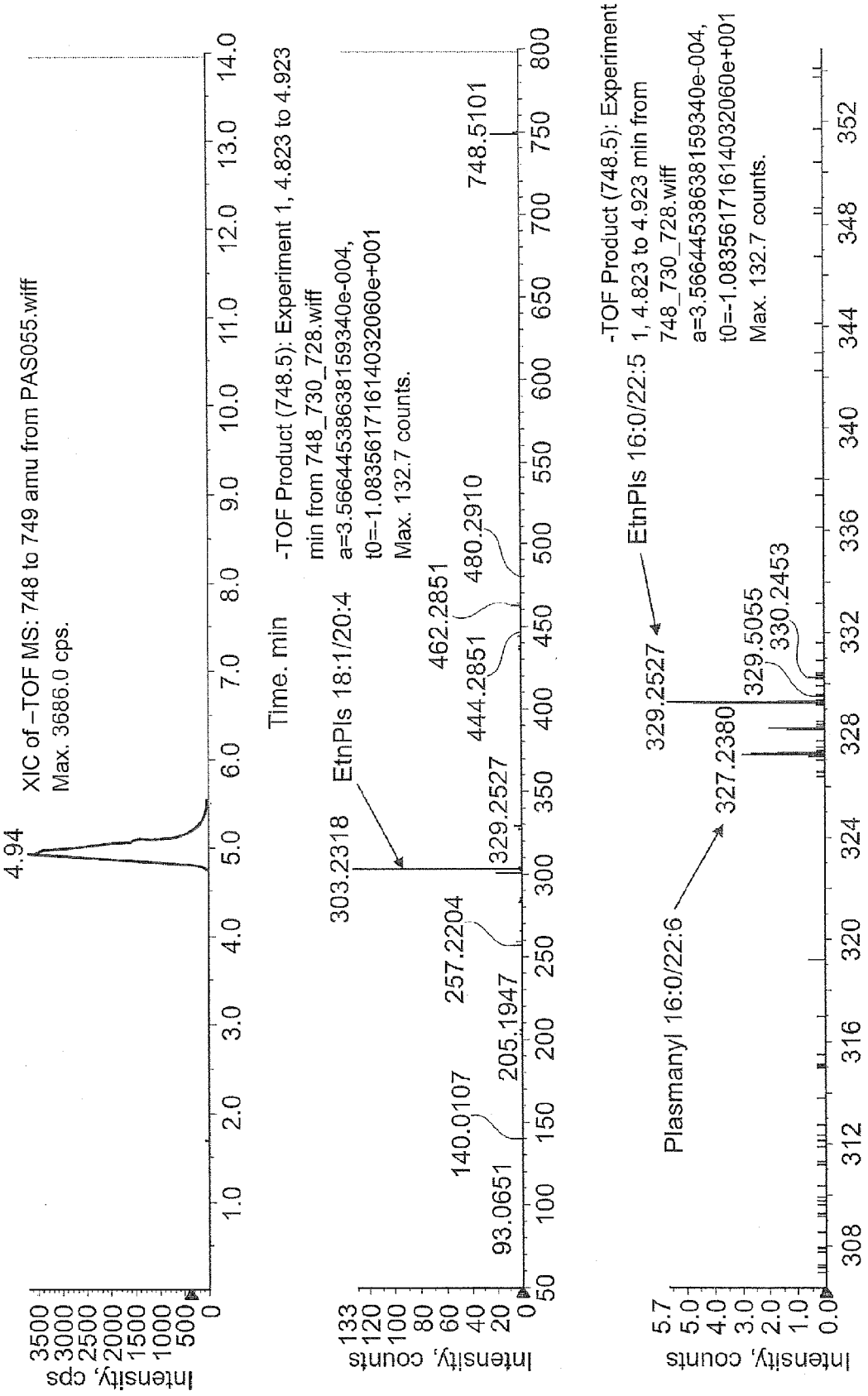

XIC of –TOF MS: 748 to 749 amu from PAS055.wiff
Max. 3686.0 cps.
4.94
Intensity, cps
Time. min
-TOF Product (748.5): Experiment 1, 4.823 to 4.923 min from 748_730_728.wiff
a=3.56644538638159340e-004, t0=-1.08356171614032060e+001
Max. 132.7 counts.
EtnPls 18:1/20:4
303.2318
329.2527
444.2851
462.2851
480.2910
748.5101
257.2204
205.1947
140.0107
93.0651
Intensity, counts
-TOF Product (748.5): Experiment 1, 4.823 to 4.923 min from 748_730_728.wiff
a=3.56644538638159340e-004, t0=-1.08356171614032060e+001
Max. 132.7 counts.
EtnPls 16:0/22:5
329.2527
Plasmanyl 16:0/22:6
327.2380
329.5055
330.2453
Intensity, counts

Fig. 32

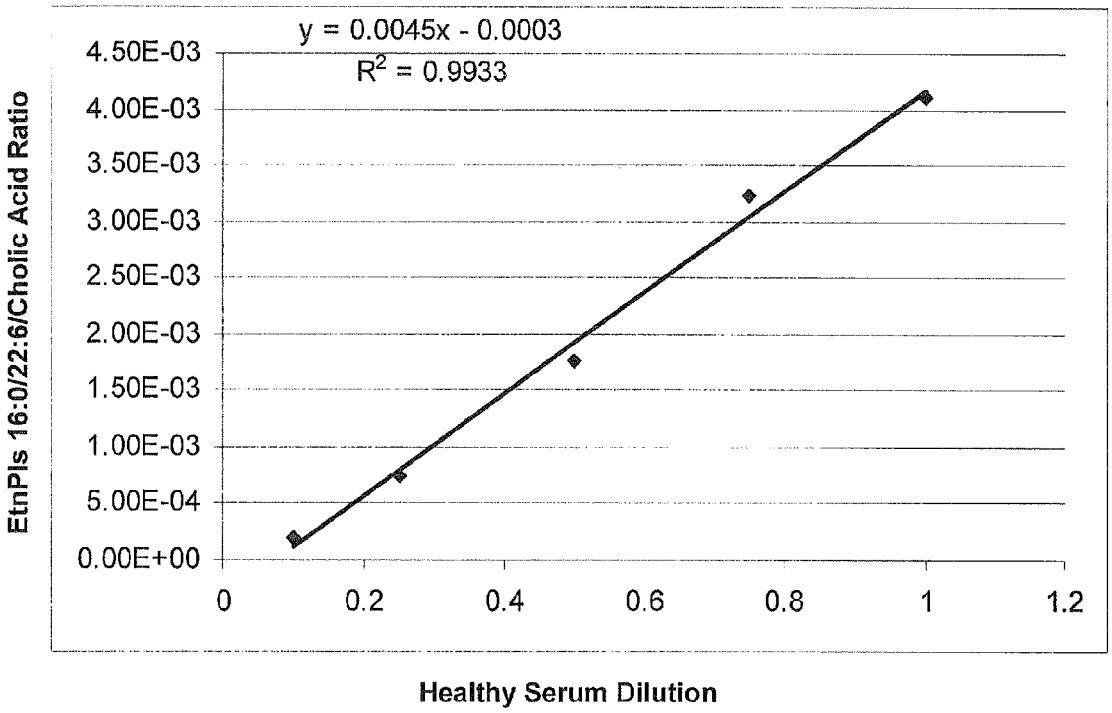

y = 0.0045x - 0.0003
R2 = 0.9933
4.50E-03
4.00E-03
3.50E-03
3.00E-03
2.50E-03
2.00E-03
1.50E-03
1.00E-03
5.00E-04
0.00E+00
0
0.2
0.4
0.6
0.8
1
1.2
EtnPls 16:0/22:6/Cholic Acid Ratio
Healthy Serum Dilution

Fig. 33

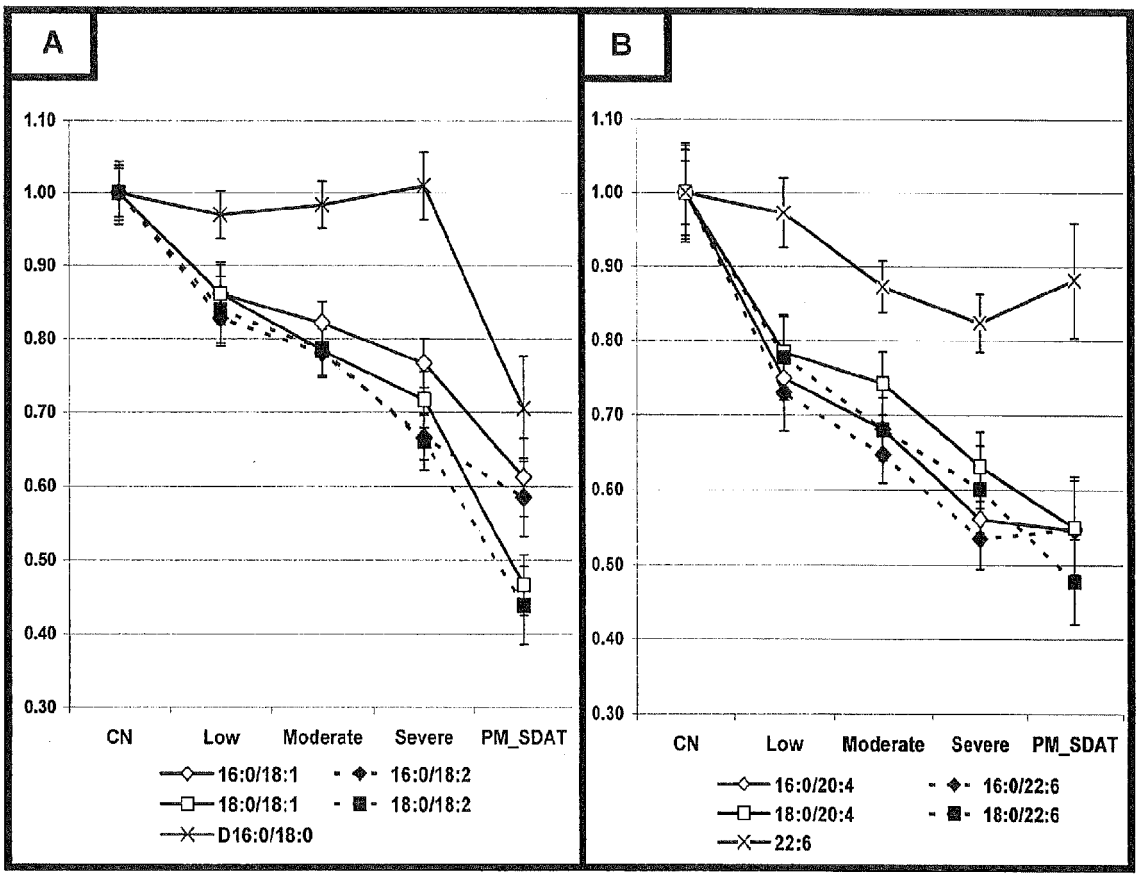

A
1.10
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
CN
Low
Moderate
Severe
PM_SDAT
16:0/18:1
16:0/18:2
18:0/18:1
18:0/18:2
D16:0/18:0
B
1.10
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
CN
Low
Moderate
Severe
PM_SDAT
16:0/20:4
16:0/22:6
18:0/20:4
18:0/22:6
22:6

Fig. 34

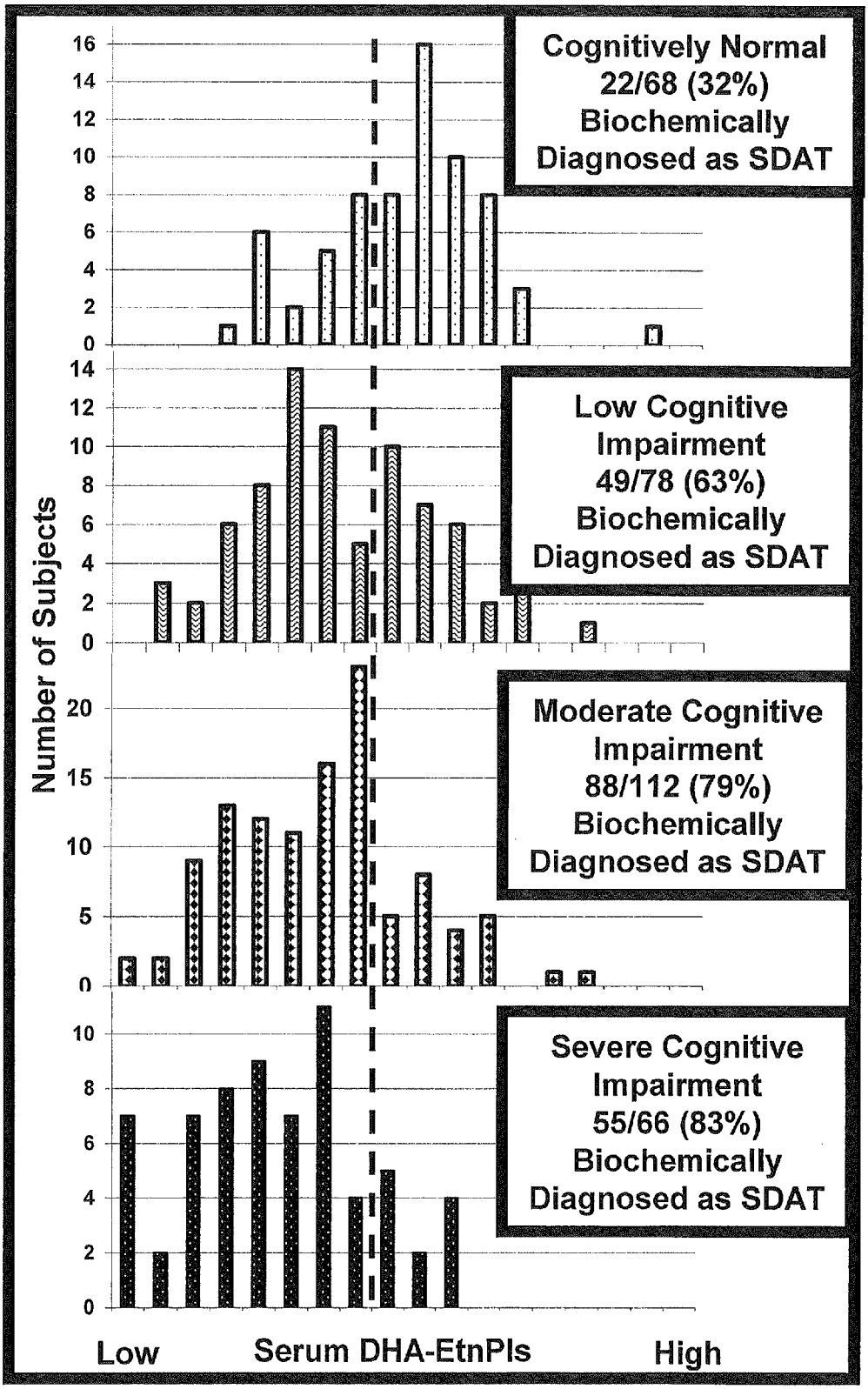

Cognitively Normal
22/68 (32%)
Biochemically
Diagnosed as SDAT
Low Cognitive
Impairment
49/78 (63%)
Biochemically
Diagnosed as SDAT
Moderate Cognitive
Impairment
88/112 (79%)
Biochemically
Diagnosed as SDAT
Severe Cognitive
Impairment
55/66 (83%)
Biochemically
Diagnosed as SDAT
Number of Subjects
Low
Serum DHA-EtnPls
High

Fig. 35

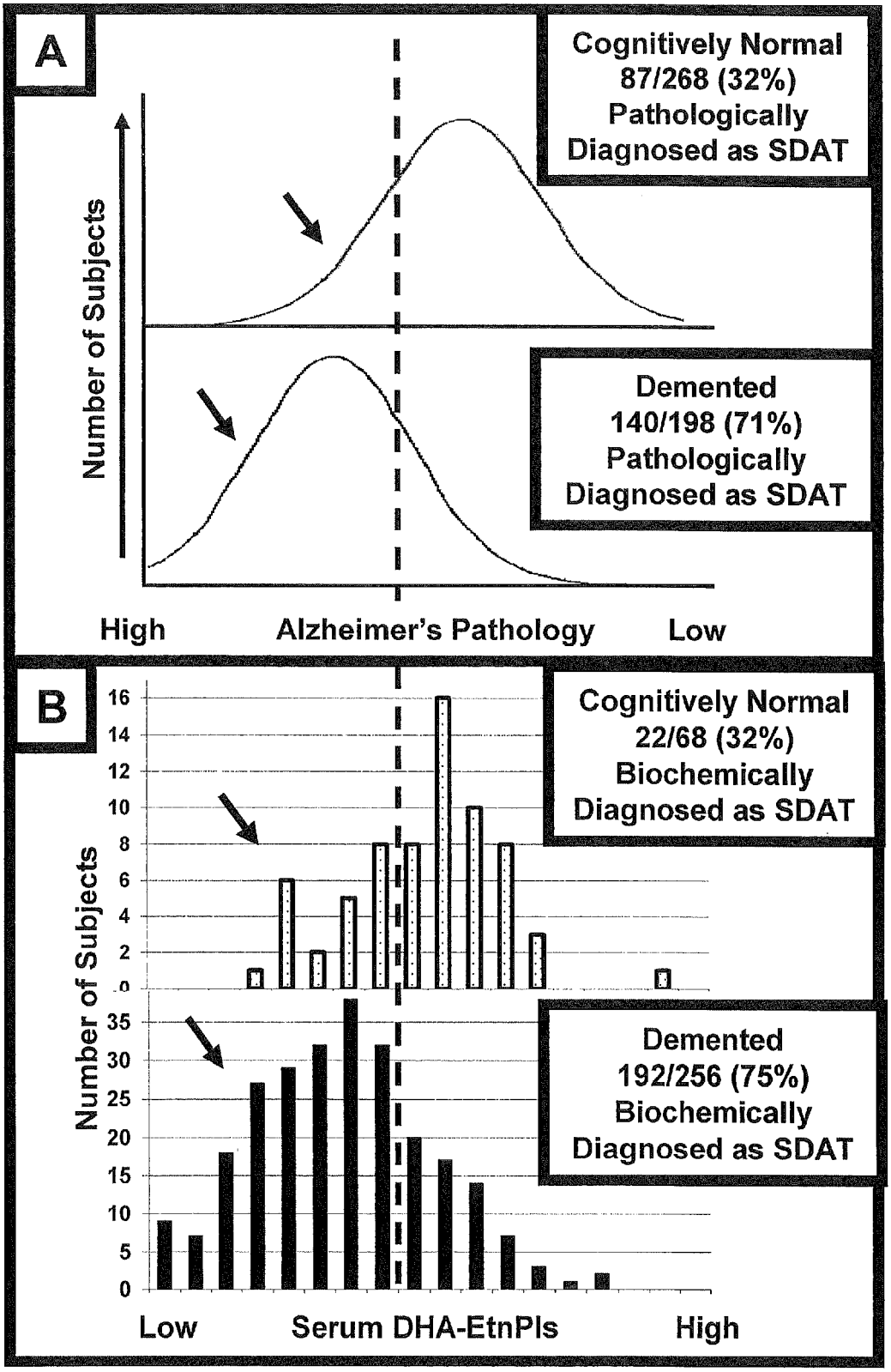

A
Cognitively Normal
87/268 (32%)
Pathologically
Diagnosed as SDAT
Number of Subjects
Demented
140/198 (71%)
Pathologically
Diagnosed as SDAT
High
Alzheimer's Pathology
Low
B
Cognitively Normal
22/68 (32%)
Biochemically
Diagnosed as SDAT
16
14
12
10
8
6
4
2
0
Number of Subjects
35
30
25
20
15
10
5
0
Demented
192/256 (75%)
Biochemically
Diagnosed as SDAT
Low
Serum DHA-EtnPls
High

Fig. 36

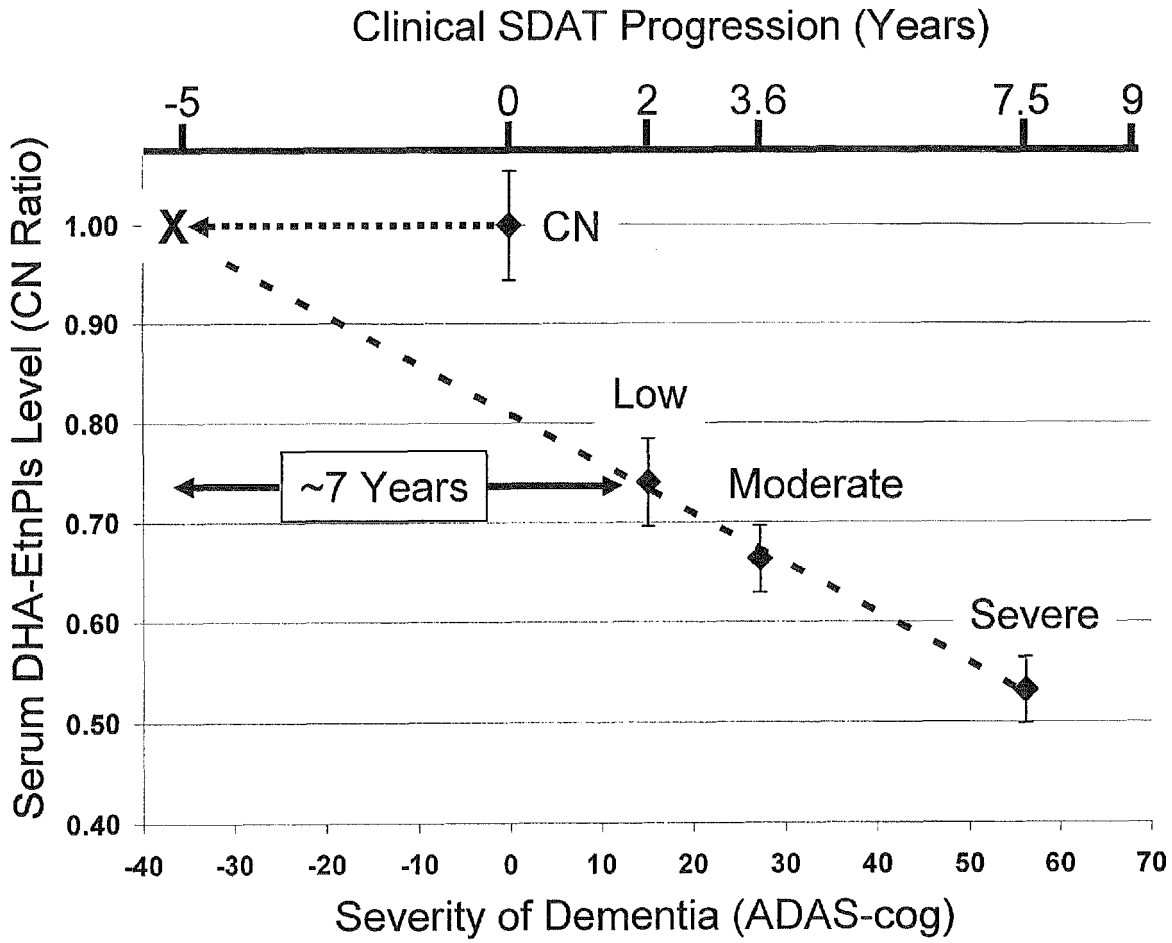

Clinical SDAT Progression (Years)
-5
0
2
3.6
7.5
9
Serum DHA-EtnPls Level (CN Ratio)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
CN
Low
Moderate
Severe
~7 Years
-40
-30
-20
-10
0
10
20
30
40
50
60
70
Severity of Dementia (ADAS-cog)

Fig. 37

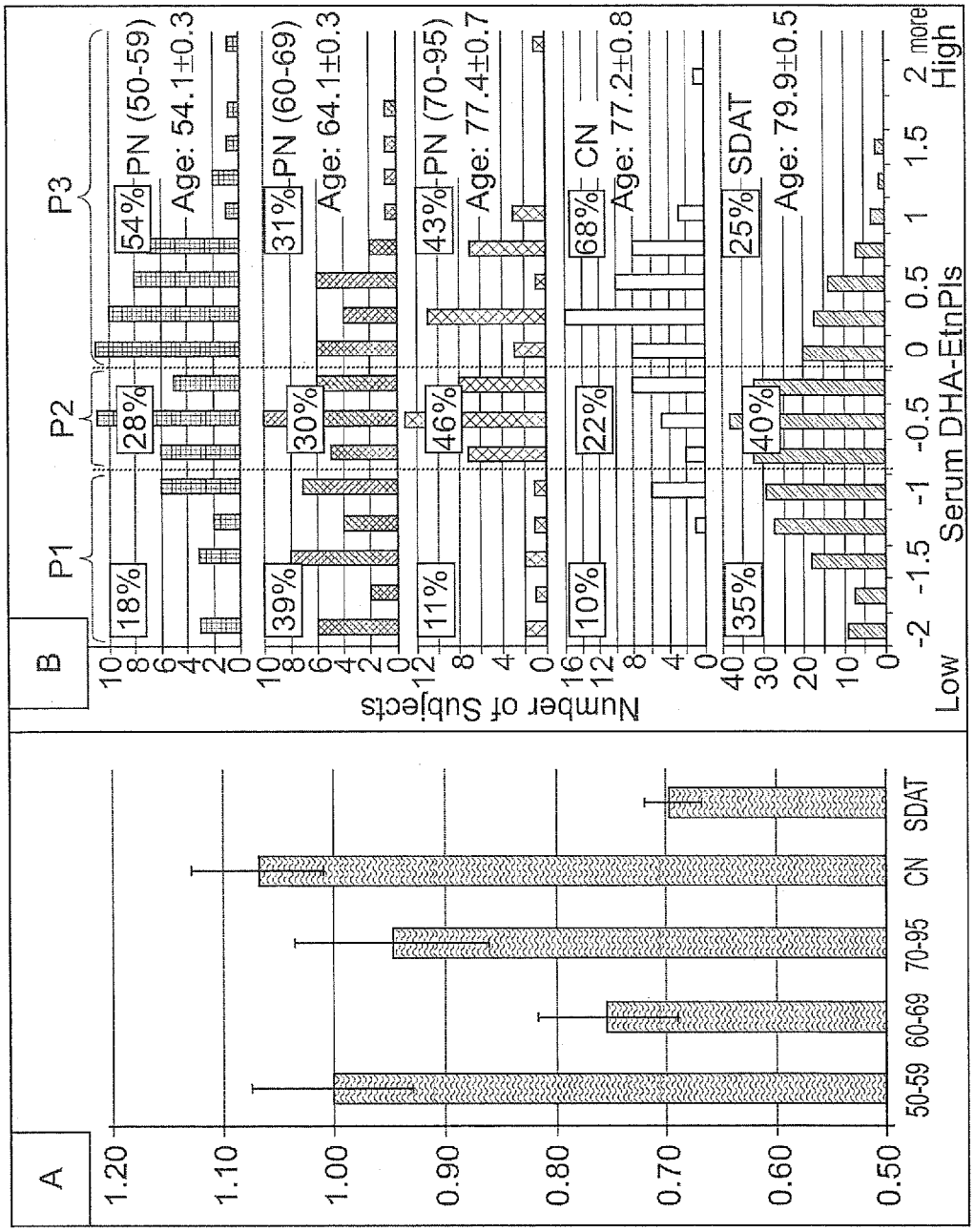

A
B
P1
P2
P3
1.20
1.10
1.00
0.90
0.80
0.70
0.60
0.50
50-59
60-69
70-95
CN
SDAT
Number of Subjects
18%
28%
54%
PN (50-59)
Age: 54.1±0.3
39%
30%
31%
PN (60-69)
Age: 64.1±0.3
11%
46%
43%
PN (70-95)
Age: 77.4±0.7
10%
22%
68%
CN
Age: 77.2±0.8
35%
40%
25%
SDAT
Age: 79.9±0.5
-2
-1.5
-1
-0.5
0
0.5
1
1.5
2 more
Low
Serum DHA-EtnPls
High

Fig. 38

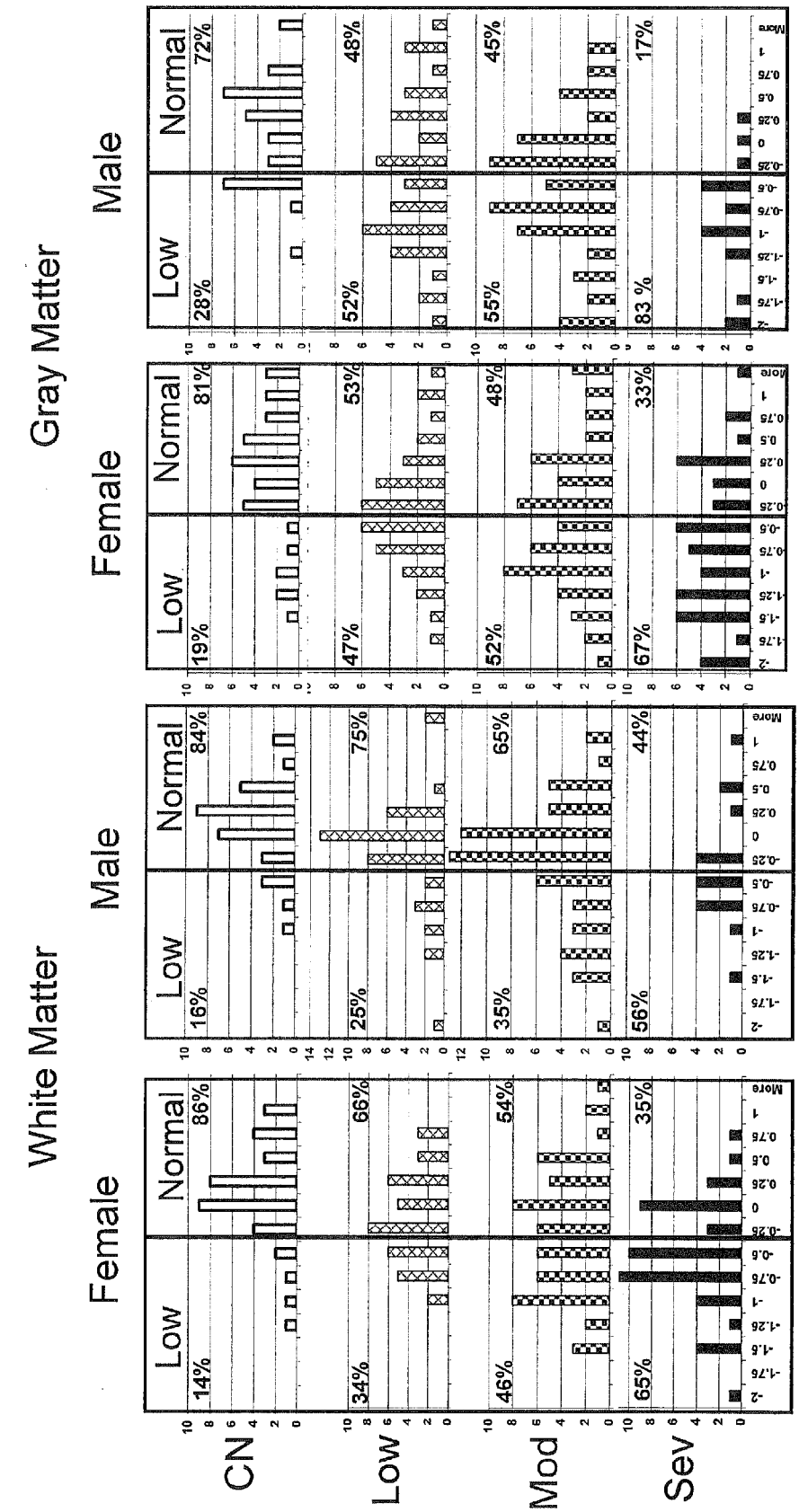

White Matter
Gray Matter
Female
Male
Female
Male
Low
Normal
CN
Low
Mod
Sev
14%
86%
16%
84%
19%
81%
28%
72%
34%
66%
25%
75%
47%
53%
52%
48%
46%
54%
35%
65%
52%
48%
55%
45%
65%
35%
56%
44%
67%
33%
83 %
17%
-2
-1.75
-1.5
-1.25
-1
-0.75
-0.5
-0.25
0
0.25
0.5
0.75
1
More

Fig. 39

REFERENCES CITED IN THE DESCRIPTION

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摘要

本發明涉及一個方法，其用於診斷病人的非阿爾茨海默氏症的癡呆，患有非阿爾茨海默氏症的癡呆風險 。該方法包括利用高分辨質譜法來分析病人血液樣本從而獲得準確的質量強度數據；b）把準確質量強度數據與由一個或多過一個參考樣本得出的相應數據作出比較，從而確定準確質量強度的增加或減少；以及c）利用所述準確質量強度的增加或減少來診斷所述病人的非阿爾茨海默氏症的癡呆，患有非阿爾茨海默氏症的癡呆的風險 。