Supplementary Document

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S1: Diagnostic criteria

Alzheimer's disease (**A**); behavioural variant frontotemporal dementia (**B**); primary progressive aphasia (**C**); dementia with Lewy bodies (**D**)

S1a.

Diagnostic criteria for AD - *Adapted from: McKhann, 2011*
Core clinical criteria for all dementia: Impairments interfere with daily functioning, represent a decline from previous functioning, and are not explained by delirium or major psychiatric disorder. Impairments in a minimum of 2 domains: ability to acquire new information, reasoning, judgement, visuospatial ability, language, personality/function.
Probable AD: Insidious onset & evidence of worsening of cognition. History & examination shows typical amnestic presentation including learning & recall impairments with evidence of cognitive dysfunction in at least one other cognitive domain, *or* non-amnestic presentation (language, visuospatial or executive dysfunction).
Possible AD: Atypical course meets core criteria but with sudden onset or insufficient detail of progressive decline, *or* etiologically mixed presentation meets core criteria but with evidence of cerebrovascular disease, DLB, or other neurological disease.
Probable/possible AD with biomarker evidence of AD pathophysiology: ↓ CSF $A\beta_{42}$, ↑ total tau & p-tau, ↓ FDG-PET uptake, & atrophy in temporal lobe and medial parietal cortex. (Recommended for research purposes)

S1b.

Diagnostic criteria for bvFTD - *Adapted from: Rascovsky, 2011*
Symptoms: Behavioural disinhibition, apathy/inertia, loss of sympathy, perseverative/stereotyped or compulsive/ritualistic behaviours, hyperorality/dietary changes, executive or visuospatial dysfunction.
Imaging: Frontal and/or anterior temporal atrophy on MRI/CT. Frontal and/or anterior temporal hypoperfusion or hypometabolism on SPECT/PET.
Possible bvFTD: 3 or more symptoms present. *Probable bvFTD*: Criteria for possible bvFTD with one of the imaging results. *Definitive bvFTD*: histopathological confirmation or presence of known pathogenic mutation.

S1c.

Diagnostic criteria for primary progressive aphasias - *Adapted from: Gorno-Tempini, 2011*		
Logopenic PPA (lvPPA)	**Semantic PPA (svPPA)**	**Nonfluent PPA (nfvPPA)**
Core symptoms: Impaired single word retrieval & sentence/phrase repetition.	**Core symptoms:** Impaired confrontation naming & single word comprehension.	**Core symptoms:** Agrammatism, effortful speech with sound errors (apraxia).
Other features: Phonologic errors, spared single-word comprehension, spared motor speech, absence of frank agrammatism.	**Other features:** Impaired object knowledge, surface dyslexia/dysgraphia, spared repetition, spared speech production.	**Other features:** Impaired comprehension of complex sentences, spared single word comprehension, spared object knowledge.
Imaging: Predominant left posterior perisylvian/parietal atrophy *or* hypoperfusion/ hypometabolism on SPECT/PET.	**Imaging**: Predominant anterior temporal lobe atrophy or hypoperfusion/ hypometabolism on SPECT/PET.	**Imaging:** Predominant left posterior fronto-insular atrophy on MRI, or hypoperfusion/ hypometabolism on SPECT/PET.
Clinical diagnosis: both core features & at least 3 of other features present. *Imaging supported diagnosis*: both imaging criteria required.	*Clinical diagnosis*: both core features & at least 2 of the other features present. *Imaging supported diagnosis*: both imaging criteria required.	*Clinical diagnosis*: both core features & at least 3 of the other features present. *Imaging supported diagnosis*: both imaging criteria required.
Definitive diagnosis: clinical diagnosis with histopathological evidence or presence of known pathogenic mutation.		

S1d.

Diagnostic criteria for DLB - *Adapted from: McKieth, 2017*
Core clinical features: Fluctuating cognition, visual hallucinations, REM sleep behaviour disorder, one or more feature of parkinsonism (bradykinesia, rest tremor, or rigidity).
Supportive clinical features: Sensitivity to antipsychotic agents, postural instability, repeated falls, syncope, dysautonomia, hyposmia, hypersomnia, apathy, depression, delusions, anxiety.
Indicative biomarkers: ↓ dopamine transporter uptake in basal ganglia on SPECT/PET, ↓ uptake in ^{123}Iodine-MIBG myocardial scintigraphy, REM sleep without atonia shown through polysomnography.
Supportive biomarkers: Preserved medial temporal lobe on CT/MRI, posterior slow-wave activity on EEG, reduced occipital activity, low uptake in SPECT/PET.
Possible DLB: 1 core feature without biomarker evidence or at least one biomarkers without core features. *Probable DLB*: 2 or more core features, with or without biomarker presence or one core feature with at least one biomarker. *Definitive DLB*: Histopathological confirmation or presence of known pathogenic mutation.

S2: Summary of database search strategy

June 2019

Syntax used for FTD and AD search
Scopus search (search 1)
TITLE-ABS-KEY ("FTD" OR "frontotemporal dementia" OR "frontotemporal lobar degeneration") AND TITLE-ABS-KEY ("fluid" OR "CSF" OR "cerebrospinal fluid" OR "urine" OR "urinary" OR "blood" OR "plasma" OR "serum" OR "saliva") AND TITLE-ABS-KEY ("biomarker" OR "biomarkers" OR "marker") AND ALL ("Alzheimer's disease") AND NOT ("amyotrophic lateral sclerosis" OR "ALS" OR "motor neuron disease" OR "MND")
→ **Search yielded 288 results**
PubMed search (search 2)
("Frontotemporal Dementia"[Mesh]) AND ("Fluid" OR "CSF" OR "cerebrospinal fluid" OR "urine" or "urinary" OR "blood" OR "plasma" OR "serum" OR "saliva") AND ("Biomarker" OR "markers" OR "biomarkers") NOT ("ALS" or "amyotrophic lateral sclerosis") AND ("Alzheimer's disease")
→ **Search yielded 52 results**
Syntax used for DLB and AD search
Scopus search (search 3)
TITLE-ABS-KEY ("Dementia with Lewy bodies") AND TITLE-ABS-KEY ("Fluid" OR "CSF" OR "cerebrospinal fluid" OR "urine" OR "urinary" OR "blood" OR "plasma" OR "serum" OR "saliva") AND TITLE-ABS-KEY ("Biomarker" OR "markers" OR "biomarkers") AND ALL ("Alzheimer's disease")
→ **Search yielded 186 results**
PubMed search (search 4)
("Dementia with Lewy bodies") AND ("Fluid" OR "CSF" OR "cerebrospinal fluid" OR "urine" or "urinary" OR "blood" OR "plasma" OR "serum" OR "saliva") AND ("Biomarker" OR "markers" OR "biomarkers") AND ("Alzheimer's disease")
→ **Search yielded 88 results**
TOTAL = 614

S3: Definitions of diagnostic accuracy measures

Adapted from: Xia, 2013

Sensitivity: This is the percentage of true positive subjects with the disease of interest in a total of subjects with the disease. It relates to the potential of the test to recognise subjects with the disease.

Specificity: This is the proportion of subjects without the disease with a negative result in a total of subjects without the disease, hence describes the ability of the test to recognise subjects without the disease.

ROC graphs: These are plotted based on the values of sensitivity and specificity at individual cut-offs. The shape of a ROC curve and area under the curve (AUC) allows us to estimate the discriminatory power of a test. The closer the curve is to the upper left-hand corner, and the larger the AUC, the better the discriminatory power of the test. AUC can have any value between 0 and 1, with 1 indicating a perfect diagnostic test.

The relationship between the AUC values and diagnostic accuracy are as follows:

0.5-0.6 = fail

0.6-0.7 = poor

0.7-0.8 = fair

0.8-0.9 = good

0.9-1.0 = excellent

S4: Reasons for article exclusions

Initial screening of titles & abstracts (**A**); secondary full-text screening against the inclusion criteria for 135 potentially eligible articles (including 10 from additional sources) (**B**)

S4a.

Reasons for exclusion	**Search 1** 223/288 excluded	**Search 2** 43/52 excluded	**Search 3** 137/186 excluded	**Search 4** 86/88 excluded
AD specific	15	-	5	2
FTD specific	18	1	-	-
PD specific	-	-	5	-
DLB specific	1	-	13	4
Post-mortem	5	1	16	5
Non-human/in vitro analysis	1	-	3	-
Editorials/opinion/commentaries	6	-	-	-
Imaging reviews/articles	44	8	19	8
Other disorders (e.g. HIV dementia, CJD, PD, HD, normal pressure hydrocephalus)	13	3	7	-
Genetics/pathophysiology	13	4	11	4
Clinical symptoms/cognitive testing	17	5	6	4
Techniques/assays	13	3	10	2
Case study/report	10	-	3	-
Reviews	41	4	16	10
Treatment	11	-	5	1
Not relevant to review	13	-	-	-
Full text unavailable	2	-	-	-
Duplicates	-	14	18	46
Total articles remaining → 125				

S4b.

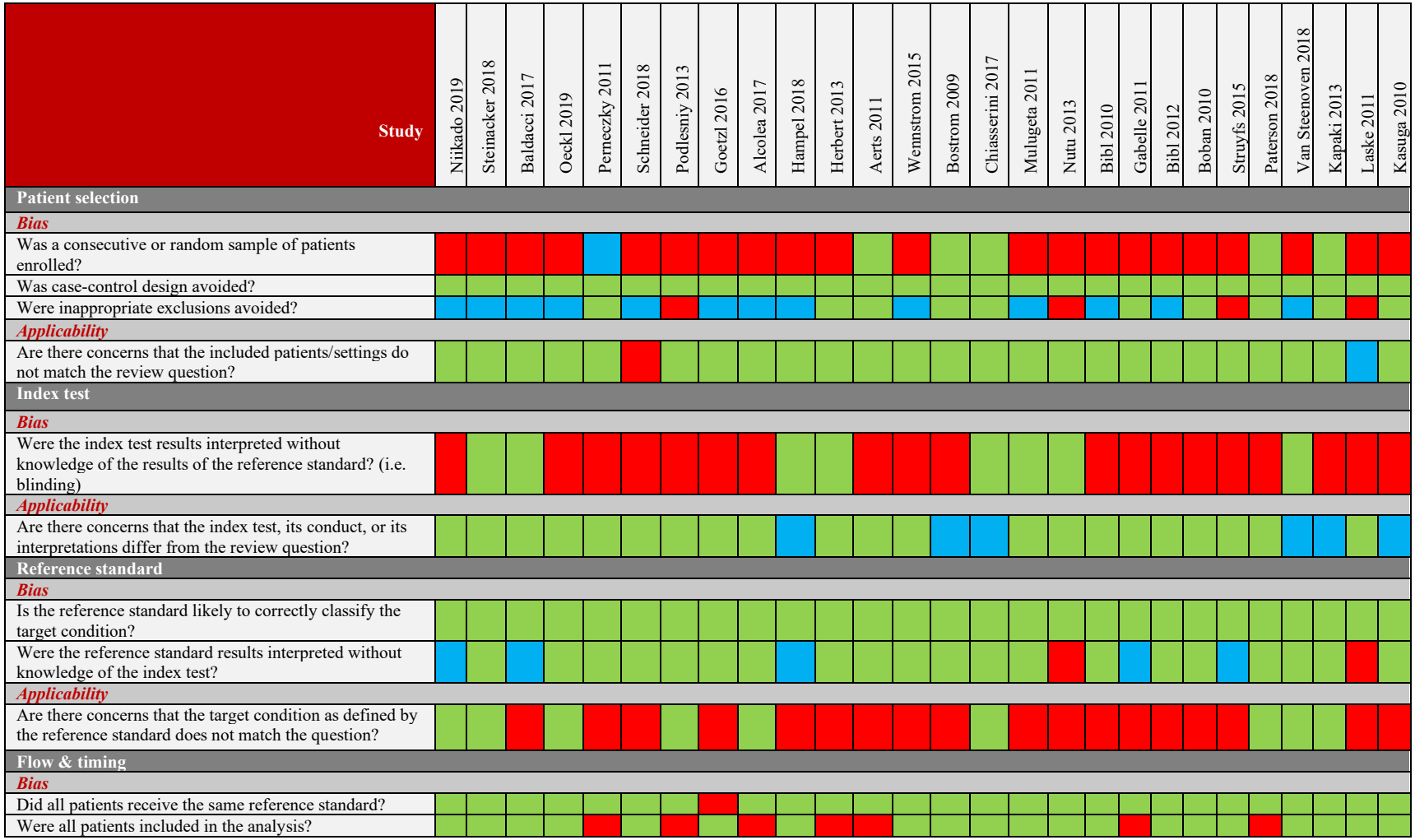
Study	Reason for exclusion
1. Lista, Toschi (2017)[a]	Aim was to use NfL to discriminate groups across the AD pathophysiology spectrum
2. Landqvist (2013)	No diagnostic accuracy assessment
3. Magdalinou (2015)	Lund-Manchester criteria for FTD
4. Ishiki (2016)	No diagnostic accuracy assessment
5. Goetzl, Mustapic (2016)	No diagnostic accuracy assessment
6. Lista, Toschi (2017)[b]	No diagnostic accuracy assessment
7. Perneczky (2013)	No diagnostic accuracy assessment
8. Alexopoulos (2012)	Lund-Manchester criteria for FTD
9. Spies (2009)	No diagnostic accuracy assessment
10. Muller (2016)	No diagnostic accuracy assessment
11. Sorensen (2016)	Patients grouped into AD and "other dementias"
12. Kortvelyessy (2015)	No diagnostic accuracy assessment
13. Morenas-Rodriguez (2016)	No diagnostic accuracy assessment
14. Heywood (2018)	No diagnostic accuracy assessment
15. Craig-Shapiro (2010)	No diagnostic accuracy assessment
16. Del Campo (2018)	Post-mortem
17. Busse (2017)	No diagnostic accuracy assessment
18. Gibbons (2015)	No diagnostic accuracy assessment
19. Khoonsari (2019)	Diagnostic accuracy for AD vs "non-AD"
20. Salza (2015)	Lund-Manchester criteria for FTD
21. Ikeuchi (2010)	No diagnostic accuracy assessment
22. Lang (2017)	Small sample sizes (FTD=6)
23. Muller (2015)	No diagnostic accuracy assessment
24. Pan (2016)	Inconsistent diagnostic criteria for FTD
25. Bradley-Whitman (2015)	Does not compare diagnostic accuracy between AD and FTD
26. Kapogiannis (2015)	No diagnostic accuracy assessment for FTD vs AD
27. Goetzl (2015)	No diagnostic accuracy assessment for FTD vs AD
28. Abraham (2011)	Patients grouped into AD and "other dementias"
29. Woolley (2014)	No diagnostic accuracy assessment
30. Woolley (2012)	No diagnostic accuracy assessment
31. Wellington (2016)	Lund-Manchester criteria for FTD
32. Goossens (2017)	Inconsistent diagnostic criteria for FTD
33. Timmer (2015)	No diagnostic accuracy assessment
34. Tarawneh (2011)	Patients grouped into AD and "other dementias"
35. Klafki (2009)	Small sample sizes (FTD=2)
36. Vinceti (2017)	No diagnostic accuracy assessment
37. Dumurgier (2015)	Patients grouped into AD and "other dementias"
38. Lewczuk (2015)	Patients grouped into AD and "other dementias"
39. Ulusu (2015)	Patients grouped into AD and "other dementias"
40. Knapskog (2016)	Patients grouped into AD and "other dementias"
41. Shea (2013)	Patients grouped into AD and "other dementias"
42. Spies, Slats (2010)	Full text unavailable
43. Spies, Claassen (2010)	Patients grouped into AD and "other dementias"
44. Kester (2010)	Patients grouped into AD and "other dementias"
45. Sorensen (2013)	No diagnostic accuracy assessment
46. Skillback (2015)	Lund-Manchester criteria for FTD & no diagnostic accuracy assessment
47. Balasa (2014)	No diagnostic accuracy assessment
48. Carrechio (2011)	GRN-mutation carrier specific FTD
49. Kaerst (2014)	No diagnostic accuracy assessment
50. Schoonenboom (2012)	No diagnostic accuracy assessment
51. Santos (2012)	Patients grouped into AD and "other dementias"
52. Nutu (2013)	No diagnostic accuracy assessment
53. Wennstrom (2013)	No diagnostic accuracy assessment
54. Parnetti (2011)	No diagnostic accuracy assessment for AD vs DLB
55. Reesink (2010)	Full text unavailable
56. Maetzler (2011)	No diagnostic accuracy assessment
57. Llorens (2017)	Post-mortem
58. Wennstrom, Hall (2015)	No diagnostic accuracy assessment
59. Wennstrom (2014)	No diagnostic accuracy assessment
60. King (2018)	No diagnostic accuracy assessment
61. Nielsen (2012)	Full text unavailable
62. Parnetti (2009)	No diagnostic accuracy assessment
63. Prikrylova (2016)	Dubois/IWG-2 diagnostic criteria for AD
64. Wennstrom (2012)	No diagnostic accuracy assessment
65. Schultz (2009)	No diagnostic accuracy assessment
66. Josviak (2017)	No diagnostic accuracy assessment
67. Esteras (2013)	No diagnostic accuracy assessment for AD vs DLB

68. Maetzler (2012)	No AD patient group
69. Gironi (2011)	No diagnostic accuracy assessment
70. Janelidze (2017)	Geser diagnostic criteria for DLB
71. Koyama (2016)	No diagnostic accuracy assessment
72. Llorens (2015)	No diagnostic accuracy assessment for AD vs DLB
73. Skillback (2017)	No diagnostic accuracy assessment
74. Mulugeta (2011)	No diagnostic accuracy assessment
75. Babic leko (2016)	Small sample sizes (DLB=5)
76. Luo (2013)	Dubois/IWG-2 diagnostic criteria for AD
77. Janssens (2018)	Diagnostic accuracy for DLB & PDD vs AD (not DLB & AD)
78. Janelidze, Zetterberg (2016)	No diagnostic accuracy assessment for AD vs DLB
79. Falgas (2019)	Small sample sizes (FTD=5)
80. Ventriglia (2013)	No diagnostic accuracy assessment
81. Ohrfelt (2009)	No diagnostic accuracy assessment
82. Scherling (2014)	No diagnostic accuracy assessment
83. Janelidze, Hertze (2016)	Diagnostic accuracy for AD vs "non-AD"
84. Boutoleau (2012)	Diagnostic accuracy for AD vs "non-AD"
85. Bostrom (2009)	No diagnostic accuracy assessment
86. Noguchi-Shinohara (2009)	No diagnostic accuracy assessment
87. Bousiges (2016)	Ethical approval not stated
88. Bousiges (2018)	Ethical approval not stated
89. Alcolea (2014)	No diagnostic accuracy assessment for AD vs FTD
90. Suzuki (2015)	Diagnostic accuracy for DLB vs "non-DLB" (not AD specifically)
91. Abraham (2011)	Extracted twice – excluded already (duplicate)
92. De Rino (2012)	Only on AD core biomarkers
93. Vergallo (2017)	Only on AD core biomarkers
94. De Souza (2011)	Only on AD core biomarkers
95. Ewers (2015)	Only on AD core biomarkers
96. Andersson (2011)	Only on AD core biomarkers
97. Van Harten (2011)	Meta-analysis
98. Mishima (2016)	Meta-analysis
99. Biemans (2016)	No diagnostic accuracy assessment for AD vs FTD or AD vs DLB
100. Denk (2018)	Dubois/IWG-2 diagnostic criteria for AD
101. Fiandaca (2012)	No diagnostic accuracy assessment for novel biomarker
102. Verwey (2010)	No diagnostic accuracy assessment for novel biomarker
103. Slaets (2014)	Post-mortem
104. Mollenhauer (2011)	Diagnostic accuracy assessment for synucleinopathy vs non-synucleinopathy disorders
105. Koehler (2013)	Diagnostic accuracy assessment not given for AD vs DLB
106. Bougea (2018)	Diagnostic accuracy for DLB vs AD & PDD (not DLB & AD)
107. Hall (2012)	Diagnostic accuracy for DLB & PDD vs AD (not DLB & AD)
108. Hansson (2014)	Diagnostic accuracy for DLB & PDD vs AD (not DLB & AD)

S5: Full results of quality assessment

Table used to record answers to QUADAS-2 signalling questions (**A**); tabular display of QUADAS-2 results (**B**); risk of bias and applicability concern scores for individual studies based on QUADAS-2 answers (**C**)

S5a.



S5b.

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Niikado 2019	☹	☹	?	☺	☺	☺	☺
Steinacker 2018	☹	☺	☺	☺	☺	☺	☺
Alcolea 2017	☹	☹	☺	☹	☺	☺	☺
Hampel 2018	☹	☺	?	☺	☺	?	☹
Paterson 2018	☺	☹	☺	☹	☺	☺	☺
Goetzl 2016	☹	☹	☺	☹	☺	☺	☹
Baldacci 2017	☹	☺	?	☺	☺	☺	☹
Oeckl 2019	☹	☹	☺	☺	☺	☺	☺
Schneider 2018	☹	☹	☺	☺	☺	☺	☹
Podlesniy 2013	☹	☹	☺	☹	☺	☺	☺
Perneczky 2011	?	☹	☺	☹	☺	☺	☹
Gabelle 2011	☹	☹	?	☹	☺	☺	☹
Struyfs 2015	☹	☹	?	☺	☺	☺	☹
Bibl 2012	☹	☹	☺	☺	☺	☺	☹
Boban 2010	☹	☹	☺	☺	☺	☺	☹
Van Steenoven 2018	☹	☺	☺	☺	☺	?	☺
Kapaki 2013	☺	☹	☺	☺	☺	?	☺
Kasuga 2010	☹	☹	☺	☺	☺	?	☹
Chiasserini 2017	☺	☺	☺	☺	☺	?	☺
Laske 2011	☹	☹	☹	☺	?	☺	☹
Bibl 2010	☹	☹	☺	☺	☺	☺	☹
Mulugeta 2011	☹	☺	☺	☺	☺	☺	☹
Nutu 2013	☹	☺	☹	☺	☺	☺	☹
Herbert 2014	☹	☺	☺	☹	☺	☺	☹
Aerts 2011	☺	☹	☺	☹	☺	☺	☹
Wennstrom 2015	☹	☹	☺	☺	☺	☺	☹
Bostrom 2009	☺	☹	☺	☺	☺	?	☹
High risk	21	19	2	8	0	0	18
Low risk	5	8	20	19	26	22	9
Unclear risk	1	0	5	0	1	5	0

☺Low Risk ☹High Risk ? Unclear Risk

S5c.

Risk of bias
Low: Steinacker, 2018, Van Steenoven, 2018, Kapaki, 2013, Chiasserini, 2017, Mulugeta, 2011, Bostrom, 2009 (**6**)
Low-medium (unclear): Hampel, 2018, Baldacci, 2017 (**2**)
Medium: Paterson, 2018, Oeckl, 2019, Schneider, 2018, Bibl, 2012, Boban, 2010, Kasuga, 2010, Bibl, 2010, Nutu, 2013, Herbert, 2014, Aerts, 2011, Wennstrom, 2015 (**11**)
Medium-high (unclear): Niikado, 2019, Perneczky, 2011, Struyfs, 2015 (**3**)
High: Alcolea, 2017, Goetzl, 2016, Podlesniy, 2013, Gabelle, 2011, Laske, 2011 (**5**)
Applicability concerns
Low: Niikado, 2019, Steinacker, 2018, Alcolea, 2017, Paterson, 2018, Oeckl, 2019, Podlesniy, 2013 (**6**)
Some: Baldacci, 2017, Goetzl, 2016, Schneider, 2018, Perneczky, 2011, Gabelle, 2011, Struyfs, 2015, Bibl, 2012, Boban, 2010, Van Steenoven, 2018, Kapaki, 2013, Kasuga, 2010, Chiasserini, 2017, Bibl, 2010, Mulugeta, 2011, Nutu, 2013, Herbert, 2014, Aerts, 2011, Wennstrom, 2015, Bostrom, 2009 (**19**)
High: Hampel, 2018, Laske, 2011 (**2**)
Scores were given to each study depending on the number of domains in which there was risk of bias or applicability concern. In a study with risk of bias in one domain, an overall low risk was given, if in two domains, a medium risk was given, and if in three, a high risk of bias was given. Studies were considered to have low applicability concerns if there were no concerns in any domain. If there was concern to one, it was considered to have some applicability concerns, and if in more than one, it was considered to have high applicability concerns.

S6: Novel amyloid peptides: full results

Study		Struyfs 2015 (S)		Bibl 2012 (B)		Gabelle 2011 (G)		Paterson 2018 (P)	
Study design		Single-centre cross-sectional study		Single-centre cross-sectional study		Multi-centre cross-sectional study		Single-centre cross-sectional study	
Country		Belgium		Germany		France		UK	
Method		Electrochemiluminescence assay		Aβ SDS-PAGE/immunoblot		Electrochemiluminescence assay		Electrochemiluminescence assay	
AD (F|M)	FTD (F|M)	**49** (31|18)	**17** (?)[N]	**22** (12|10)	**17** (8|9)[N]	**52** (26|26)	**34** (14|20)[N]	**156** (90|66)	**45** (18|27)[R]
Mean (SD) age in years		77 (70-82)*	70 (66-73)*	70.8 (8.6)	62 (5.7)	68.51 (9.28)	64.91 (10.5)	62.5 (57-68)*	61 (57-66)*

Table 1a: Details of studies that measured amyloid peptides in AD & FTD (*above*)

N = Behavioural FTD phenotype diagnosed using Neary (1998) criteria.
R = bvFTD group diagnosed using Rascovsky (2011) criteria.

Paterson (2018) included Aβ42/Aβ40 diagnostic accuracy only for AD vs bvFTD and not for AD vs PNFA.

Table 1b: Results from studies for each amyloid peptide biomarker measured (*right*)

**Median (interquartile range).*
AUC values (area under curve) for amyloid peptides or ratios to distinguish AD & FTD.
c = ng/mL value from study was converted to pg/mL.
↑ = Higher in this group compared to other group(s) & controls.
↓ = Lower in this group compared to other group(s) & controls.

Study	Biomarker mean (SD) pg/mL		Diagnostic accuracy
	AD	FTD	
Aβ38			
S	2174 (1598-2880)*	1607 (1235–2212)*	AUC = 0.685
G	1278 (686)	942 (350) ↓	AUC = 0.64
Aβ40			
S	6023 (4616-8447)*	4564 (3348–5799)*	AUC = 0.687
G	8330 (4218)	6612 (2152) ↓	AUC = 0.61
Aβ38 / Aβ40			
S	0.35 (0.31–0.38)*	0.35 (0.30–0.37)*	AUC = 0.541
G	7.37 (2.99)	7.41 (1.88)	AUC = 0.51
Aβ42 / Aβ40			
S	0.07 (0.06–0.09)* ↓	0.14 (0.09–0.17)*	AUC = 0.830
B	0.122 (0.05) ↓	0.22 (0.103)	AUC = 0.797
G	20.51 (9.87)	10.43 (6.02) ↑	AUC = 0.85
P	0.043 (0.036–0.053)* ↓	0.083 (0.072-0.094)*	AUC = 0.86
Aβ42 / Aβ38			
S	0.21 (0.17–0.26)* ↓	0.39 (0.24–0.48)*	AUC = 0.815
B	0.327 (0.168) ↓	0.727 (0.317)	AUC = 0.917
G	2.95 (1.23)	1.47 (1.01) ↑	AUC = 0.87
Aβ37			
S	701 (556-894)*	523 (384–706)* ↓	AUC = 0.720
Aβ42 / Aβ37			
S	0.66 (0.51–0.76)* ↓	01.17 (0.74–1.50)*	AUC = 0.851
Aβ2-42			
B	91 (54)[c] ↓	188 (97)[c]	AUC = 0.859
Aβ2-42 / 1-38			
B	0.04 (0.017) ↓	0.118 (0.05)	AUC = 0.929
Aβ2-42 / 1-40			
B	0.014 (0.009) ↓	0.04 (0.015)	AUC = 0.929

Study		Struyfs 2015 (S)		Paterson 2018 (P)		Bibl 2010 (B)		Nutu 2013 (N)		Mulugeta 2011 (M)	
Study design		Single-centre cross-sectional study		Single-centre cross-sectional study		Multi-centre cross-sectional study		Single-centre cross-sectional study		Multi-centre cross-sectional study	
Country		Belgium		UK		Germany		Sweden		Norway & Sweden	
Method		Electrochemi-luminescence assay		Electrochemi-luminescence assay		Aβ SDS-PAGE/immunoblot		Electrochemi-luminescence assay		Electrochemi-luminescence assay	
AD (F|M)	DLB (F|M)	**49** (31|18)	**17** (?)	**156** (90|66)	**20** (5|15)	**45** (27|18)	**15** (3|12)	**48** (35|13)	**51** (18|33)	**30** (18|12)	**23** (7|16)
Mean (SD) age in years		77 (70-82)*	77 (73-81)*	62.5 (57-68)*	70 (68-75)*	70.9 (9.2)	71.4 (7.6)	79 (74–80)*	75 (70–81)*	75.5 (11.3)	74 (10.8)

Table 2a: Details of the studies that measured amyloid peptides in AD & DLB (*above*)

Table 2b: Results from studies for each amyloid peptide biomarker measured (*right*)

**Median (interquartile range) AUC values (area under curve) for individual amyloid peptides or ratios to distinguish AD & DLB. c = ng/mL value from study was converted to pg/mL.*

↑= Higher in this group compared to other group(s) & controls.

↓= Lower in this group compared to other group(s) & controls.

Study	Biomarker mean (SD) pg/mL		Diagnostic accuracy
	AD	DLB	
Aβ38			
S	2174 (1598-2880)*	1353 (1024–1968)* ↓	AUC = 0.745
Aβ40			
S	6023 (4616-8447)*	4487 (3766–8005)* ↓	AUC = 0.630
N	3,517 (3,002–3,898)*	3,003 (2,466–3,452)* ↓	AUC = 0.69
A1-40 ox			
B	880 (270)c	1270 (700)c ↑	AUC = 0.908
Aβ38 / Aβ40			
S	0.35 (0.31–0.38)	0.27 (0.24–0.33) ↓	AUC = 0.826
Aβ42 / Aβ40			
S	0.07 (0.06–0.09)* ↓	0.13 (0.08–0.17)*	AUC = 0.753
P	0.043 (0.036–0.053)* ↓	0.055 (0.047–0.089)*	AUC = 0.73
N	0.09 (0.07–0.10)* ↓	0.13 (0.09–0.20)*	AUC = 0.759
Aβ42 / Aβ38			
S	0.21 (0.17–0.26)* ↓	0.51 (0.28–0.60)*	AUC = 0.843
M	0.46 (0.29) ↓	0.66 (0.34)	AUC = 0.765
Aβ37			
S	701 (556-894)*	483 (369–758)* ↓	AUC = 0.725
Aβ42 / Aβ37			
S	0.66 (0.51–0.76)*	1.22 (0.83–1.72)* ↑	AUC = 0.832

S7: Soluble amyloid precursor protein: full results

Study	Fluid	Study design / Country / Method	AD sample (F|M) / FTD sample (F|M)	Mean age in years (SD)	Biomarker Mean (SD) ng/mL Diagnostic accuracy
Soluble APP					
Alcolea 2017	CSF	Multi-centre cross-sectional study	**72** (44|28)	70.8 (7.8)	**sAPPβ**: 1,015.5 (346.7) ↑
		Spain	bvFTD = **68** (27|41)[R]	64.8 (9.7)	546.6 (243.3)
		Commercial ELISA	nfvPPA = **23** (11|12)[GT]	67.7 (7.0)	639.6 (296.5)
			svPPA = **19** (9|10)[GT]	67.4 (9.94)	596.9 (233.8)
					AUC = 0.86
Perneczky 2011	CSF	Single-centre prospective study	**21** (12|9)[**]	67.95 (8.81)	**sAPPβ**: 1200.29 (452.40) ↑
		Germany	**16** (8|8)[N]	63.63 (6.08)	630.32 (258.93)
		Commercial ELISA			***sAPPβ & tau* → AUC = 0.92**
Gabelle 2011	CSF	Multi-centre cross-sectional study	**52** (26|26)	68.51 (9.28)	**sAPPα *(units?)***: 25043 (7129) ↑ / **sAPPβ *(units?)***: 39407 (8813) ↑
		France	**34** (14|20)[N]	64.91 (10.5)	22523 (6032) / 34895 (8699)
		Electrochemi-luminescence assay			**AUC = 0.61** / **AUC = 0.67**

Studies that measured soluble amyloid precursor protein (sAPP) in FTD & AD

[R] = bvFTD group diagnosed using Rascovsky (2011) criteria.
[GT] = PPA group diagnosed using Gorno-Tempini (2011) criteria.
[N] = Behavioural FTD phenotype diagnosed using Neary (1998) criteria.
**MCI-AD group (MCI patients that developed AD).

Alcolea (2017) also recruited CBS & PSP (*not shown*) diagnosed using Armstrong (2013) and Litvan (1996) criteria.
AUC values (area under curve) for sAPP alone or in combination with another biomarker to distinguish AD & FTD.
***(units?)** = no units given.*
↑ = Higher in this group compared to other group(s) & controls.

S8: Neurofilament light chain: full results

Study	Fluid	Study design / Country / Method	AD sample (F|M) / FTD sample (F|M)	Mean age in years (SD)	Biomarker Mean (SD) pg/mL Diagnostic accuracy
N f L					
Niikado 2019	CSF	Single-centre cross-sectional study	**14** (7|7)	71 (53-81)*	1335 (432.9)
		Argentina	**13** (9|4)[R]	58 (39–70)*	2609.5 (1684.9) ↑
		Commercial ELISA			**AUC = 0.736**
Steinacker 2018	Serum	Multi-centre prospective cohort	**26** (11|15)	67 (8.1)	32.3 (15.8)
		Germany	**74** (30|44)[R]	63.7 (9.2)	49.0 (35.2) ↑
		Simoa technology			**AUC = 0.676**
Alcolea 2017	CSF	Multi-centre cross-sectional study	**72** (44|28)	70.8 (7.8)	**NfL**: 1,051.8 (395.4); **NfL/sAPPβ**: 1.1 (0.8)
		Spain	bvFTD = **68** (27|41)[R]	64.8 (9.7)	2,174.4 (2394.9) ↑ ; 5.2 (7.1) ↑
		Commercial ELISA	nfvPPA = **23** (11|12)[GT]	67.7 (7.0)	2,042.4 (1617.3) ↑ ; 2.9 (2.5) ↑
			svPPA = **19** (9|10)[GT]	67.4 (9.94)	2,394.4 (1388.1) ↑ ; 3.7 (2.7) ↑
					AUC = 0.67 ; **AUC = 0.85**
Hampel 2018	CSF	Multi-centre cross-sectional study	**35** (24|11)	73 (68–76)*	1483 (1180–1844)* ↑
		Germany, Sweden, France	**9** (5|4)[N]	73 (70–74)*	1022 (693–1435)*
		Commercial ELISA			***t-tau & NfL*** → **AUC = 0.7959** ***Aβ1-42, p-tau & NfL*** → **AUC = 0.796**
Paterson 2018	CSF	Single-centre cross-sectional study	**156** (90|66)	62.5 (57-68)*	1191.5 (857.6–1584.0)*
		UK	**17** (9|8)[GT]	65 (61-69)*	1974.9 (1627.7–3490.5)* ↑
		Commercial ELISA			***(AD vs PNFA)*** → **AUC = 0.84**

Studies that measured NfL in AD & FTD

[R] = bvFTD group diagnosed using Rascovsky (2011) criteria.
[GT] = PPA group diagnosed using Gorno-Tempini (2011) criteria.
[N] = Behavioural FTD phenotype diagnosed using Neary (1998) criteria.
Alcolea (2017) also recruited CBS & PSP (*not shown*), diagnosed using Armstrong (2013) and Litvan (1996) criteria.
Paterson (2018) included NfL diagnostic accuracy only for AD vs PNFA and not for AD vs bvFTD.
**Median (interquartile range).*
AUC values (area under curve) for NfL alone or in combination with other biomarkers to distinguish AD & FTD.
↑ = Higher in this group compared to other group(s) & controls.

S9: α-synuclein: full results

Study	Fluid	Study design / Country / Method	AD sample (F|M) / DLB sample (F|M)	Mean age in years (SD)	Biomarker Mean (SD) pg/mL Diagnostic accuracy
O - α - s y n					
Van Steenoven 2018	CSF	Single-centre cross-sectional study	**35** (2|33)	67.8 (6.3)	89 (30)
		Netherlands	**41** (6|35)	66.5 (6.1)	108 (34) ↑
		In-house ELISA			***o-α-syn with t-tau*** → **AUC = 0.84**
α - s y n					
Kapaki 2013	CSF	Single-centre cross-sectional study	**18** (10|8)	71.3 (8.6)	92.1 (42.4)
		Greece	**16** (4|12)	72.7 (5.8)	174 (103.5) ↑
		In-house ELISA			**AUC = 0.73**
Kasuga 2010	CSF	Single-centre cross-sectional study	**31** (18|13)	67.9 (12.3)	12200 (5800)[c] ↑
		Japan	**34** (21|13)	75.8 (10.7)	8200 (4200)[c]
		In-house ELISA			**Se = 72.4%** **Sp = 61.8%**
Chiasserini 2017	CSF	Multi-centre cross-sectional study	**48** (25|23)	70.9 (9.6)	2450.8 (871.24) ↑
		Germany, Belgium, Italy	**40** (13|27)	73.1 (6.3)	1751.1 (1105.3)
		Commercial ELISA			**AUC = 0.78**
Laske 2011	Serum	Cross-sectional study	**80** (50|30)	71.9 (8.1)	7000 (4000)[c]
		Germany	**40** (20|20)	71.3 (6.6)	4700 (3300)[c] ↓
		Commercial ELISA			**AUC = 0.723**

Studies that measured α-synuclein in AD & DLB

AUC values (area under curve), or Se (sensitivity) & Sp (specificity) for individual markers or in combination with other biomarkers to distinguish AD & DLB.

c = ng/mL value from study was converted to pg/mL.

↑ = Higher in this group compared to other group(s) & controls.

↓ = Lower in this group compared to other group(s) & controls.

S10: YKL-40: full results

Study	Fluid	Study design / Country / Method	AD sample (F|M) / FTD sample (F|M)	Mean age in years (SD)	Biomarker Mean (SD) ng/mL Diagnostic accuracy
YKL-40					
Baldacci 2017	CSF	Multi-centre cross-sectional study	**35** (24|11)	73 (68–76)*	146 (119–177)*↑
		Germany, Sweden, France	**9** (5|4)[N]	73 (70–74)*	114 (98–120)*
		Commercial ELISA			**AUC = 0.71**
Hampel 2018	CSF	Multi-centre cross-sectional study	**35** (24|11)	73 (68–76)*	146 (119–177)*↑
		Germany, Sweden, France	**9** (5|4)[N]	73 (70–74)*	114 (98–120)*
		Commercial ELISA			***Aβ1-42, t-tau, p-tau & YKL-40*** → **AUC = 0.7956** ***Aβ1-42, p-tau & YKL-40*** → **AUC = 0.813**
Alcolea 2017	CSF				**YKL-40** / **sAPPβ/YKL-40**
		Multi-centre cross-sectional study	**72** (44|28)	70.8 (7.8)	280.3 (47.6) / 3.7 (1.3)↑
		Spain	bvFTD = **68** (27|41)[R]	64.8 (9.7)	253.6 (69.1) / 2.4 (1.2)
		Commercial ELISA	nfvPPA = **23** (11|12)[GT]	67.7 (7.0)	287.5 (59.0)↑ / 2.3 (1.0)
			svPPA = **19** (9|10)[GT]	67.4 (9.94)	287.1 (49.9) / 1.9 (0.9)
					AUC = 0.55 / **AUC = 0.84**

Studies that measured YKL-40 in FTD & AD

[R] = bvFTD group diagnosed using Rascovsky (2011) criteria.
[GT] = PPA group diagnosed using Gorno-Tempini (2011) criteria.
[N] = Behavioural FTD phenotype diagnosed using Neary (1998) criteria.
Alcolea (2017) also recruited CBS & PSP (*not shown*), diagnosed using Armstrong (2013) and Litvan (1996) criteria.
**median (interquartile range).*
AUC values (area under curve) provided for biomarker alone or in combination with another biomarker to differentiate AD & FTD.
↑ = Higher in this group compared to other group(s) & controls.

S11: Synaptic proteins: full results

Study	Fluid	Study design / Country / Method	AD sample (F|M) / FTD sample (F|M)	Mean age in years (SD)	Biomarker Median (IQR) pg/mL Diagnostic accuracy				
Synaptic proteins									
Hampel 2018	CSF	Multi-centre cross-sectional study	**35** (24|11)	73 (68–76)*	**Neurogranin**				
		Germany, Sweden, France	**9** (5|4)[N]	73 (70–74)*	468 (300–692)* ↑				
		In-house ELISA			125 (125–192)*				
					Aβ1-42, neurogranin & YKL-40 → AUC = 0.802				
Goetzl 2016	Plasma	Multi-centre cross-sectional study	**12** (6|6)	74.4 (6.84)	**Synapto-tagmin**	**Synapto-podin**	**Synapto-physin**	**Neurogranin**	**GAP43**
					36,555 ± 4682**	1299 ± 116**	240 ± 47.1**	232 ± 56.5**	1863 ± 140**
		USA	**16** (4|12)[R]	63.6 (7.27)	83,307 ± 11,154** ↑	3145 ± 372** ↑	8541 ± 1157** ↑	1117 ± 227** ↑	4515 ± 630** ↑
		Commercial ELISA			**AUC = 0.85**	**AUC = 0.94**	**AUC = 1**	**AUC = 0.88**	**AUC = 1**

Studies that measured synaptic proteins in FTD & AD

[N] = Behavioural FTD phenotype diagnosed using Neary (1998) criteria.

[R] = bvFTD group diagnosed using Rascovsky (2011) criteria.

***mean ± standard error of the mean.*

AUC values (area under curve) provided for biomarker alone or in combination with another biomarker to differentiate AD & FTD.

↑ = Higher in this group compared to other group(s) & controls.

S12: Other novel biomarkers measured in FTD: full results

Study	Fluid	Study design / Country / Method	AD sample (F|M) / FTD sample (F|M)	Mean age in years (SD)	Biomarker Median (IQR) pg/mL Diagnostic accuracy
GFAP					
Oeckl 2019	Serum	Multi-centre cross-sectional (pilot) study	**28** (19|9)	71 (67–78)*	376 (294–537)* ↑
		Germany	**35** (15|20)[R]	64 (56–71)*	211 (166–263)*
		Simoa technology			**AUC = 0.85**
miRNA					
Schneider 2018	CSF	Multi-centre cross-sectional study	**13** (5|8)	-	miR-632 expression significantly ↓ in FTD group compared to AD
		UK, Canada, Sweden, Italy & Netherlands	**17** (4|13) [R/GT/B]	-	
		qRT-PCR			**AUC = 0.88**
mtDNA					
Podlesniy 2013	CSF	Single-centre cross-sectional study	**13** (8|5)	64 (2)	mtDNA content significantly ↓ in AD compared to FTLD group
		Spain	**15** (8|7)[N1]	61 (2)	
		qRT-PCR			**AUC = 0.98**
P-tau199					
Boban 2010	CSF	Multi-centre cross-sectional study	**27** (11|16)	66.8 (8.53)	46.2 (34.2-58.1)* ↑
		Croatia & Germany	**25** (11|14)[N2]	66.4 (8.1)	28.7 (22.2-43.25)*
		Commercial ELISA			**AUC = 0.801**

Other biomarkers measured in FTD & AD

[R] = bvFTD group diagnosed using Rascovsky (2011) criteria.

[R/GT/B] = FTD group including bvFTD, nfvPPA, svPPA & ALS diagnosed using Rascovsky (2011), Gorno-Tempini (2011), and Brooks (1994).

[N1] = FTLD group diagnosed using Neary (1998) criteria including FTD, PNFA, and SD.

[N1] = FTLD group diagnosed using Neary (1998) criteria including FTD and PNFA.

**median (interquartile range).*

AUC values (area under curve) provided for individual biomarkers to distinguish AD & FTD.

↑ = Higher in this group compared to other group(s) & controls.

↓ = Lower in this group compared to other group(s) & controls.

S13: Other novel biomarkers measured in DLB: full results

Study	Fluid	Study design / Country / Method	AD sample (F|M) / DLB sample (F|M)	Mean age in years (SD)	Biomarker Median (IQR) pg/mL Diagnostic accuracy
MHPG					
Herbert 2014	CSF	Single-centre cross-sectional study	**64** (51|13)	73.1 (8.3)	50.0 (12.8)* *(nmol/L)*
		Netherlands	**14** (4|10)	72.4 (8.0)	38.9 (12.6)* *(nmol/L)* ↓
		Liquid chromatography			***MHPG with Aβ1-42, t-tau, p-tau*** → **AUC = 0.85**
Aerts 2011	CSF	Multi-centre cross-sectional study	**45** (11|34)	71.6 (9.4)	~ 49.0 (15-85) *(nmol/L)*
		Netherlands	**23** (5|18)	71.6 (9.3)	~ 35.0 (15-79) *(nmol/L)* ↓
		Liquid chromatography			***MHPG*** → **AUC = 0.81** ***MHPG with Aβ1-42, t-tau, p-tau*** → **AUC = 0.99**
YKL-40					
Wennstrom 2015	CSF	Single-centre cross-sectional study	**49** (37|12)	77.1 (6.0)	~ 260 (240-320) ↑
		Sweden	**36** (20|16)	74.6 (5.7)	~ 220 (170-260)
		Commercial ELISA			**AUC = 0.736**
FABP3					
Chiasserini 2017	CSF	Multi-centre cross-sectional study	**48** (25|23)	70.9 (9.6)	896.1 (514.07)* ↑
		Germany, Belgium, Italy	**40** (13|27)	73.1 (6.3)	836.3 (450.6)*
		Commercial ELISA			***FAPB3*** → **AUC = 0.54** ***FAPB3 & α-syn*** → **AUC = 0.92**
sAPPβ					
Paterson 2018	CSF	Single-centre cross-sectional study	**156** (90|66)	62.5 (57-68)*	202200 (151200-352800)[c]
		UK	**20** (5|15)	70 (68-75)*	138000 (115000-175200)[c] ↓
		Electrochemi-luminescence assay			**AUC = 0.73**
Metals					**Cu** / **Ca** / **Mg**
Bostrom 2009	CSF	Single-centre cross-sectional study	**174** (122|52)	74 (52-86)*	17.8 (9-109) *(μg/L)* / 49.9 (41.5–67.2) *(mg/L)* / 27.5 (23.4–35.5) *(mg/L)*
		Sweden	**29** (12|17)	74 (54-84)*	20.7 (14-140.2) *(μg/L)* ↑ / 56.2 (45.2–67.6) *(mg/L)* ↑ / 32.6 (26.8–38.8) *(mg/L)* ↑
		Mass spectrometry			**AUC = 0.66** / **AUC = 0.84** / **AUC = 0.92**

Other novel biomarkers measured in AD & DLB

**mean (SD).*

AUC values (area under curve) for individual biomarkers or in combination with other biomarkers to distinguish AD & DLB.

~ approximate values based on reading from scatter or box plots.

c = ng/mL value from study was converted to pg/mL.

↑ = Higher in this group compared to other group(s) & controls.

↓ = Lower in this group compared to other group(s) & controls.

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