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Review article

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Molecular biomarkers for vascular cognitive impairment and dementia

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Supplementary Table 1 | Proteins and peptides as biomarkers of vascular cognitive impairment and dementia.

Analyte	Compartment	Evidence for use as biomarker			
		Diagnostic	**Risk**	**Monitoring or prognostic**	**Pharmacodynamic**
Endothelial dysfunction					
ICAM-1	Serum or plasma	NA	Associated with WMHs[1] and SBIs[1]	NA	Associated with outcome[2,3]
VCAM-1	Serum or plasma	Distinguish from healthy controls[4]	Associated with WMHs[5]	Associated with memory composite score[5]	Associated with outcome[2,3]
E-selectin	Serum or plasma	NA	Associated with WMHs[4] and lacunes[4]	NA	Associated with outcome[2,3]
ADMA	Serum or plasma	Distinguish from healthy controls[6]	Associated with WMHs[7,8], lacunes[7,8] and SBIs[9]	Associated with verbal memory[10]	NA
MR-proADM	Serum or plasma	NA	Associated with WMHs[11]	Associated with word and letter fluency test scores[11]	NA
PlGF	Serum or plasma	Distinguish from healthy controls[12]	Associated with WMHs[13]	Associated with CDR scale[13] scores	NA
	CSF	Distinguish from healthy controls[12]	NA	NA	NA

Blood–brain barrier breakdown					
MMP-2	Serum or plasma	NA	NA	Associated with scores on tests of attention, executive function, language[12]	NA
	CSF	Distinguish from healthy controls[12]	NA	NA	NA
MMP-3	Serum or plasma	Distinguish from healthy controls[14]	NA	NA	Associated with outcome[15]
MMP-9	Serum or plasma	NA	NA	Associated with MoCA score[16]	Associated with outcome[15]
	CSF	Distinguish from AD[17,18] or healthy controls[17,18]	NA	NA	NA
TIMP-1	CSF	Distinguish from AD[17] or healthy controls[17]	NA	NA	NA
TIMP-4	Serum or plasma	NA	Associated with WMHs[19]	NA	Associated with outcome[15]
albumin	CSF–serum quotient	Distinguish from AD[20,21] or healthy controls[21]	NA	NA	NA
MMP-2	CSF–serum quotient	Distinguish from healthy controls[14,22]	NA	NA	NA

Oxidative stress					
Lp-PLA2	Serum or plasma	NA	Associated with WMHs[1,23] and SBIs[1]	NA	NA
MDA	Serum or plasma	Distinguish from AD[24]	NA	NA	NA
Inflammation					
IL-6	Serum or plasma	Distinguish from healthy controls[25]	Associated with WMHs[26]	Associated with FAB score[27]	Associated with outcome[2,3]
	CSF	Distinguish from AD[28]	NA	NA	NA
IL-1β	Serum or plasma	Distinguish from healthy controls[29]	NA	NA	Associated with outcome[2]
IL-18	Serum or plasma	Distinguish from healthy controls[30]	Associated with WMHs[31]	Associated with FAB score[27]	NA
CRP, hs-CRP	Serum or plasma	Diagnosis of VCID[25,32,33]	Associated with WMHs[34,35] and lacunes[36]	Associated with FAB scores[27] and performance on tests of verbal fluency[10]	Associated with outcome[3]
TNF-α	Serum or plasma	Distinguish from healthy controls[12,29,37]	NA	NA	Associated with outcome[2,3]
VEGF	Serum or plasma	NA	Associated with SBIs[38]	NA	Associated with outcome[2]
	CSF	Distinguish from healthy controls[39]	NA	Associated with MMSE score[40]	NA

VEGF-A	Serum or plasma	Diagnosis of VCID[41], distinguish from healthy controls[12]	NA	NA	NA
VEGF-C	Serum or plasma	Distinguish from healthy controls[12]	NA	NA	NA
	CSF	Distinguish from AD[12]	NA	NA	NA
TGF-β	Serum or plasma	Distinguish from healthy controls[30]	NA	NA	NA
	CSF	Distinguish from healthy controls[39]	NA	NA	NA
RAGE	Serum or plasma	NA	NA	Associated with cognitive impairment after stroke[42]	NA
BDNF	Serum or plasma	NA	NA	NA	Associated with outcome[43]
IGF-1	Serum or plasma	Diagnosis of VCID[44], distinguish from healthy controls[45,46]	NA	NA	NA
NGF	CSF	Distinguish from healthy controls[40]	NA	NA	NA
LCN2	CSF	Distinguish from AD or healthy controls[47]	NA	NA	NA

Clotting pathway dysfunction					
Fibrinogen	Serum or plasma	Diagnosis of VCID[48], distinguish from AD[49]	Associated with WMHs[50] and lacunes[50]	NA	NA
D-dimer	Serum or plasma	Diagnosis of VCID[51], distinguish from AD[49] or healthy controls[52]	NA	NA	NA
vWF	Serum or plasma	Distinguish from healthy controls[52,53]	Associated with WMHs[54]	NA	Associated with outcome[15]
TM	Serum or plasma	Distinguish from healthy controls[55]	Associated with SVD severity[55]	NA	NA
PAI-1	Serum or plasma	Diagnosis of VCID[48], distinguish from healthy controls[52]	NA	NA	NA
Serum or plasma					
NfL	Serum or plasma	Distinguish from healthy controls[56]	Associated with WMHs[57], lacunes[57] and CMBs[57]	Associated with performance on tests of processing speed[57,58], executive function[57] and global cognition[59]	NA
	CSF	Distinguish from healthy controls[60,61]	Associated with WMHs[61-63]	Associated with MMSE score[60,64]	NA
GFAP	Serum or plasma	Distinguish from healthy controls[65,66]	NA	Associated with performance on TMT-A/B[63]	NA

AD, Alzheimer disease; ADMA, asymmetric dimethylarginine; BDNF, brain-derived neurotrophic factor; CDR, Clinical Dementia Rating; CMBs, cerebral microbleeds; CSF, cerebrospinal fluid; CRP, C-reactive protein; FAB, Frontal Assessment Battery; GFAP, glial fibrillary acidic protein; hs-CRP, high-sensitivity CRP; IGF, insulin-like growth factor; IL, interleukin; LCN2, lipocalin 2; Lp-PLA2, lipoprotein-associated phospholipase A2; MDA, malondialdehyde; MMP, matrix metalloproteinase; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MR-proADM, mid-regional pro-adrenomedullin; NA, none available; NGF, nerve growth factor; NfL, neurofilament light chain; PAI, plasminogen activator inhibitor; PlGF, placental growth factor; RAGE, receptor for advanced glycation end products; SBI, silent brain infarct; SVD, small vessel disease; TGF, transforming growth factor; TIMP, tissue inhibitors of metalloproteinase; TM, thrombomodulin; TMT, Trail Making Test; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; VCID, vascular cognitive impairment and dementia; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor; WMH, white matter hyperintensity.

Supplementary Table 2 | Metabolites and lipids as biomarkers of vascular cognitive impairment and dementia.

Analyte	Compartment	Evidence for use as biomarker			
		Diagnostic	**Risk**	**Prognostic**	**Clinical**
Metabolites					
Homocysteine	Serum or plasma	Distinguish from AD[67], healthy controls[67-73]	Associated with WMHs[74], SBIs[75] and CMBs[76]	Associated with MMSE[76,77], mRS[77] scores	NA
24S-OH-Cholesterol	Serum or plasma	Distinguish from healthy controls[78,79]	NA	NA	NA
Lipids					
Total-cholesterol	Serum or plasma	Distinguish from healthy controls[80]	NA	NA	NA
HDL–cholesterol	Serum or plasma	NA	NA	NA	NA
LDL–cholesterol	Serum or plasma	Distinguish from healthy controls[80]	NA	NA	NA
Triglyceride	Serum or plasma	NA	NA	NA	NA
Ceramide	Serum or plasma	Distinguish from healthy controls[81]	NA	NA	NA
oxLDL	Serum or plasma	Diagnosis of VCID[73]	NA	NA	NA

24S-OH-Chol, 24S-hydroxycholesterol; AD, Alzheimer disease; CMBs, cerebral microbleeds; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MMSE, Mini-Mental State Examination; mRS, modified Rankin Scale; oxLDL, oxidized low density lipoprotein; SBI, silent brain infarct; VCID, vascular cognitive impairment and dementia; WMH, white matter hyperintensity.

Supplementary Table 3 | MicroRNAs and exosome-microRNAs as biomarkers of vascular cognitive impairment and dementia.

Analyte	Compartment	Evidence for use as biomarker			
		Diagnostic	**Risk**	**Prognostic**	**Clinical**
MicroRNAs					
miR-130b-3p	Serum or plasma	Distinguish from healthy controls[82]	NA	NA	NA
miR-10b-3p	Serum or plasma	Distinguish from healthy controls[82]	NA	NA	NA
miR-146a	Serum or plasma	Distinguish from AD[83]	NA	NA	NA
miR-222	Serum or plasma	Distinguish from healthy controls[60]	NA	NA	NA
miR-29a	Serum or plasma	Distinguish from healthy controls[82,84]	NA	Associated with MMSE score[82]	NA
Exosome-microRNAs					
exo-miR-154-5p	Serum or plasma	Distinguish from healthy controls[85]	NA	NA	NA
exo-miR-223-3p	Serum or plasma	Distinguish from healthy controls[86]	NA	NA	NA

AD, Alzheimer disease; exo-miR, exosomal miRNA; miR, microRNA; NA, none available; MMSE, Mini-Mental State Examination; VCID, vascular cognitive impairment and dementia.

Supplementary Table 4 | Biomarker panels for differential diagnosis of vascular cognitive impairment and dementia and risk of small vessel disease.

Analyte panel	Evidence for use as biomarker panel	
	Diagnostic	**Risk**
Serum or plasma		
Fibrinogen, FVIII and PAI-1	Diagnosis of VCID[48]	NA
ICAM-1, P-selectin, CD40 ligand, platelet factor-4 and homocysteine	NA	Associated with WMHs[87]
hs-CRP, IL-1α, IL-6 and TNF	NA	Associated with lacunes[87]
CSF		
Phospho-tau, total tau, $A\beta_{1-42}$, NfL	Distinguishes from AD[88]	NA
$A\beta_{1-42}$, total tau, phospho-tau, MBP, TIMP-1, NfL and MMP-9	Distinguishes from AD[17]	NA
CSF, serum and imaging		
BBB permeability, MMP-2 index	Distinguishes Binswanger disease from other type of VCID[89]	NA

Aβ, amyloid-β; AD, Alzheimer disease; BBB, blood-brain barrier; CSF, cerebrospinal fluid; FVIII; factor VIII; hsCRP, high-sensitivity C-reactive protein; ICAM, intercellular adhesion molecule; IL, interleukin; MBP, myelin basic protein; MMP, matrix metalloproteinase; NA, none available; NfL, neurofilament light chain; PAI, plasminogen activator inhibitor; SVD, small vessel disease; TIMP, tissue inhibitors of metalloproteinase; TNF, tumor necrosis factor; VCID, vascular cognitive impairment and dementia; WMH, white matter hyperintensity.

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