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APPENDIX. SUPPLEMENTARY DATA TO:

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Modern Approaches to the Diagnosis of Cognitive Impairment and Alzheimer's Disease: A Narrative Literature Review.

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The appendix is posted as it was supplied by the authors.

Table S1. Characteristics of the studies included in the review

№	Title	Author	Year	Country	Type of study	Methods	Result
1	Cerebrospinal fluid biomarkers for Alzheimer's disease: current limitations and recent developments	Henrik Zetterberg	2015	UK	Systematic review	Analysis of published data on specific CSF markers of AD.	Three CSF biomarkers of neuropathological signs of the Alzheimer's disease have been developed and confirmed; namely total tau (T-tau), phosphorylated tau (P-tau), and 42 amino acid form of β-amyloid (Aβ42) that reflect neurodegeneration, neurofibrillary tangles, and amyloid/senile plaques, respectively, and are among the new diagnostic criteria for the disease. Thanks to collaborative global studies, they have been largely successful, but there are a number of limitations that require further research and discussion. First, bias and random differences in biomarker measurements both within and between laboratories remain a problem. Secondly, known markers reflect only part of the pathology underlying Alzheimer's disease. There is a need for new markers of synaptic dysfunction, microglial activation, and protein aggregations, which often accompany plaques and tangles. Third, CSF markers do not reflect the anatomical location of any abnormal changes; CSF markers can be supplemented with high-resolution molecular imaging techniques.
2	Advances in the development of new biomarkers for Alzheimer's disease	Timofey O Klyucherev, Pawel Olszewski, Alena A Shalimova, Vladimir N Chubarev, Vadim V Tarasov, Misty M Attwood, Stina Syvänen, Helgi B Schiöth	2022	Sweden, Russia	Predictive study	MRI, (^{18}F)2-fluoro-2-deoxy-D-glucose PET, amyloid ligand PET, blood and CSF testing, OCT.	The most reliable strategy for detecting biomarkers (including microRNA) in blood is to use a combination of biomarkers, since this approach can increase accuracy and specificity in the diagnosis. One of the most promising trends for biomarkers is using them as real-time indicators to monitor the effect of disease-modifying therapies for AD in clinical trials. More than 182 phase II and III clinical trials of AD therapy are currently under way in the United States. ClinicalTrials.gov is a database where the effects of therapy are routinely monitored using CSF biomarkers and PET imaging. The use of plasma biomarkers such as Aβ 40, Aβ 42, P-Tau, and pro-inflammatory cytokines as additional tools for monitoring AD progression has begun in some studies (NCT03533257, NCT04228666, NCT04570644), and we expect this trend to continue. Blood-based biomarkers can reduce costs significantly in AD diagnosis compared to current diagnostic methods, allowing the use of low-cost diagnostic methods in a large number of people as the primary screening method. For example, such a strategy may include an approach involving a combination of several microRNAs. In particular, miR-125b, miR-146a, miR-9, and miR-103, the most frequently studied microRNAs, are the most promising diagnostic strategies for AD, and studies have demonstrated their high sensitivity and specificity.
3	Cerebrospinal fluid neurogranin: relation to cognition and neurodegeneration in Alzheimer's disease	Erik Portelius, Henrik Zetterberg, Tobias Skillbäck, Ulrika Törnqvist, Ulf Andreasson, John Q Trojanowski, Michael W Weiner, Leslie M Shaw, Niklas Mattsson, Kaj Blennow	2015	Sweden, UK, USA	Predictive study	AD patients with dementia (n=95), patients with mild cognitive impairment (n=173), patients without cognitive impairment (n=110). **Method:** CSF immunoassay, MRI, (^{18}F)2-fluoro-2-deoxy-D-glucose PET, MMSE, ADAS-Cog.	CSF neurogranin was elevated in AD patients with dementia ($p < 0.001$), progressive mild cognitive impairment ($p < 0.001$), and stable mild cognitive impairment ($p < 0.05$) compared with the control group, as well as in AD patients with dementia ($p < 0.01$) and progressive mild cognitive impairment ($p < 0.05$) compared with stable mild cognitive impairment. In the group with mild cognitive impairment, high baseline CSF levels of neurogranin predicted cognitive decline, as reflected by a decreased Mini-Mental State Examination score ($p < 0.001$) and an increased Alzheimer's Disease Assessment Scale-Cognitive Subscale score ($p < 0.001$) during clinical follow-up. In addition, high baseline levels of neurogranin in the cerebrospinal fluid in the mild cognitive impairment group correlated with longitudinal decline in cortical glucose metabolism ($p < 0.001$) and hippocampal volume ($p < 0.001$) during clinical follow-up. In addition, in the group with progressive mild cognitive impairment, elevated neurogranin levels in the cerebrospinal fluid were associated with accelerated deterioration in the Alzheimer's Disease Assessment Scale-Cognitive Subscale score ($\beta=0.0017$, $p=0.01$).

4	Cerebrospinal fluid synaptosomal-associated protein 25 is a key player in synaptic degeneration in mild cognitive impairment and Alzheimer's disease	Hua Zhang, Joseph Therriault, Min Su Kang, Kok Pin Ng, Tharick A Pascoal, Pedro Rosa-Neto, Serge Gauthier	2018	China, Canada, Singapore	Predictive study	139 subjects from the ADNI database. Cognitively normal individuals (n=52), subjects with mild cognitive impairment (n=22), subjects with progressive mild cognitive impairment (n=47), and subjects with dementia due to AD (n=18). **Method:** CSF analysis, effect of CSF SNAP-25 and SNAP-25/Aβ42 on conversion from MCI to AD.	CSF levels of SNAP-25 and SNAP-25/Aβ42 were elevated in patients with progressive cognitive impairment and AD compared with the control group, as well as in progressive cognitive impairment and AD compared with mild cognitive impairment. Cognitively normal subjects who deteriorated to cognitive impairment or AD at the time of the follow-up had an increased SNAP-25/Aβ42 ratio compared to non-progressive subjects. CSF SNAP-25, especially SNAP-25/Aβ42, offers diagnostic utility for pMCI and AD. CSF SNAP-25 and SNAP-25/Aβ42 significantly predicted slide from cognitive impairment to AD. In addition, an increased SNAP-25/Aβ42 ratio was associated with the rate of hippocampal atrophy with progressive cognitive impairment and the rate of change in cognitive impairment in the control group during the follow-up period.
5	Apolipoprotein B is a novel marker for early tau pathology in Alzheimer's disease	Cynthia Picard, Nathalie Nilsson, Anne Labonté, Daniel Auld, Pedro Rosa-Neto; Alzheimer's Disease Neuroimaging Initiative; Nicholas J, Henrik Zetterberg, Kaj Blennow, John C B Breitner, Sylvia Villeneuve, Judes Poirier	2022	Canada, Sweden, UK	Predictive study	400 participants aged 60 and over at increased risk of developing AD, 1,650 patients with memory loss from 31 centers across Canada. **Method:** CSF analysis, measurement of apoB protein levels and biomarkers of beta-amyloid (Aβ), t-tau and p-tau, synaptic markers GAP43, synaptotagmin 1, synaptosome-associated protein, 25kDa (SNAP-25) and neurogranin.	The concentrations of growth-associated protein 43 (GAP43), neurogranin, synaptosome-associated protein, 25kDa (SNAP25), and synaptotagmin 1 were lower in AD than in the controls ($p < 0.001$). The levels of exosomal biomarkers correlated with the levels in the cerebrospinal fluid (R2=0.540.70). The combination of exosomal biomarkers allowed one to detect AD 57 years before the onset of cognitive impairment (area under the curve=0.870.89).
6	Blood neuro-exosomal synaptic proteins predict Alzheimer's disease at the asymptomatic stage	Longfei Jia, Min Zhu, Chaojun Kong, Yana Pang, Heng Zhang, Qiongqiong Qiu, Cuibai Wei, Yi Tang, Qi Wang, Ying Li, Tingting Li, Fangyu Li, Qigeng Wang, Yan Li,Yiping Wei, Jianping Jia	2021	China	Predictive study	This study uses four datasets. Participants from the Beijing Center (n=82: 28 AD patients, 25 aMCI patients, and 29 healthy controls); Participants from other centers in Shandong, Guizhou, Henan, Hebei, Jilin, Guangxi, and Inner Mongolia Autonomous Region (n=216: 73 AD patients, 71 aMCI patients, and 72 healthy controls). The third group included 320 subjects (160 with pre-dementia, 160 without cognitive impairment). The fourth group included 62 subjects in the control group and 59 carriers of mutations, whose age ranged from 5 to 7 years. **Method:** blood test for exosomal enzymes, transmission electron microscopy (TEM), Western blot, CSF enzyme immunoassay.	The concentrations of growth associated protein 43 (GAP43), neurogranin, synaptosome-associated protein, 25kDa (SNAP25), and synaptotagmin 1 were lower in AD than in the controls ($p < 0.001$). The levels of exosomal biomarkers correlated with the levels in the cerebrospinal fluid (R2=0.540.70). The combination of exosomal biomarkers allowed one to detect AD 5-7 years before the onset of cognitive impairment (area under the curve = 0.870.89).

7	A meta-analysis on the levels of VILIP-1 in the CSF of Alzheimer's disease compared to normal controls and other neurodegenerative conditions	Ioannis A Mavroudis, Foivos Petridis, Symela Chatzikonstantinou, Eleni Karantali, Dimitris Kazis	2021	UK, Cyprus, Greece	Predictive study	Analysis of published data on the VILIP-1 levels in the CSF of patients with AD, the control group, patients with mild cognitive impairment and patients with dementia with Lewy bodies.	VILIP-1 levels were found to be significantly higher in AD compared with normal controls, but not with other groups, and, furthermore, they were significantly higher in patients with MCI worsening into AD than in patients with stable MCI.
8	Current trends in blood biomarker detection and imaging for Alzheimer's disease	Shun Hu, Changwen Yang, Haiming Luo	2022	China	Predictive study	Analysis of published data on the diagnosis of AD: blood biomarkers, enzyme immunoassay, imaging.	In the review, development trends in technology for detecting AD-associated blood biomarkers, including platforms for optoelectronic analysis, was discussed.
9	Classification accuracy of blood-based and neurophysiological markers in the differential diagnosis of Alzheimer's disease and frontotemporal lobar degeneration	Alberto Benussi, Valentina Cantoni, Jasmine Rivolta, Silvana Archetti, Anna Micheli, Nicholas Ashton, Henrik Zetterberg, Kaj Blennow, Barbara Borroni	2022	Italy, Sweden, UK	Predictive study	202 subjects. **Method**: analysis of plasma neurofilament light (NfL), glial fibrillar protein (GFAP), tau protein 181 (p-Tau 181), as well as the ratio of amyloid β42 to 40 (Aβ 142/140) an ultrasensitive single molecule matrix (Simoa) and TMS-derived neurophysiological parameters including SICI, ICF, LICI, and SAI were used.	There were significant differences in plasma NfL, the GFAP, and p-Tau 181 levels between the groups, but not in the Aβ 142/Aβ 140 ratio. To improve diagnostic accuracy, we adopted a two-step process reflecting the clinical judgement on clinical grounds. In the first step, NfL was the best single biomarker for classifying "cases" vs. "controls" (AUC 0.94, p <0.001), while in the second step, SAI was the best single biomarker for classifying AD vs. FTLD (AUC 0.96, p <0.001). The combination of several biomarkers has significantly increased the accuracy of the diagnosis. The best model for classifying "cases" vs. "controls" included the predictors p-Tau 181, GFAP, NfL, SICI, ICF, and SAI, resulting in an AUC of 0.99 (p <0.001). For the second step in classifying AD vs. FTD, the best model included a combination of Aβ 142/Aβ 140 ratio, p-Tau 181, SICI, ICF, and SAI, resulting in an AUC of 0.98 (p <0.001).
10	A population-based meta-analysis of circulating GFAP for cognition and dementia risk	Mitzi M Gonzales, Crystal Wiedner, Chen-Pin Wang, Qianqian Liu, Joshua C Bis, Zhiguang Li, Jayandra J Himali, Saptaparni Ghosh, Emy A Thomas, Danielle M Parent, Tiffany F Kautz, Matthew P Pase, Hugo J Aparicio, Luc Djoussé, Kenneth J Mukamal, Bruce M Psaty, William T Longstreth Jr, Thomas H Mosley Jr, Vilmundur Gudnason, Djass Mbangdadji, Oscar L Lopez, Kristine Yaffe, Stephen Sidney, R Nick Bryan, Ilya M Nasrallah, Charles S DeCarli, Alexa S Beiser, Lenore J Launer, Myriam Fornage, Russell P Tracy, Sudha Seshadri, Claudia L Satizabal	2022	USA	Predictive study	4,338 adults from four cohorts. **Method:** Analysis of circulating GFAP levels using the Simoa HD-1 Analyzer.	Meta-analyses have shown that higher circulating GFAP levels are associated with lower general cognitive ability (β=-0.09, [95% confidence interval [CI]: -0.15 to -0.03], p=0.005), but not with total brain or hippocampal volume (p >0.05). However, each standard deviation unit increase in log-transformed GFAP levels was significantly associated with a 2.5-fold increased risk of all-cause dementia (hazard ratio [RR]: 2.47 (95% CI: 1, 52-4.01) and dementia in Alzheimer's disease (RR: 2.54 [95% CI: 1.424.53]) during 15 years of follow-up.

11	Cerebrospinal fluid β-synuclein as a synaptic biomarker for preclinical Alzheimer's disease	Lorenzo Barba, Samir Abu Rumeileh, Giovanni Bellomo, Federico Paolini Paoletti, Steffen Halbgebauer, Patrick Oeckl, Petra Steinacker, Federico Massa, Lorenzo Gaetani, Lucilla Parnetti, Markus Otto	2023	Germany, Italy	Predictive study	75 patients with AD of varying severity, 35 patients from the control group. **Method:** analysis of the CSF levels of β-syn, α-syn, t-tau and NfL.	CSF β-syn, α-syn, t-tau were significantly elevated in pre-AD patients compared with the control group ($p < 0.0001$, $p = 0.02$ and $p = 0.0001$, respectively), while NfL only increased with dem-AD ($p = 0.001$). In pre-AD cases, t-tau concentrations were lower than those of MCI-AD ($p = 0.04$) and dem-AD ($p = 0.01$). CSF B-synuclein had the best diagnostic performance for the discrimination of pre-AD subjects from all controls (area under the curve, AUC=0.97) and SMC-Ctrl subjects (AUC=0.99).
12	β-Synuclein as a candidate blood biomarker for synaptic degeneration in Alzheimer's disease	Pablo Mohaupt, Marie-Laure Pons, Jerome Vialaret, Constance Delaby	2022	France	Predictive study	Analysis of published data on the use of β-synuclein in the diagnosis of AD	The switch from mass spectrometry to an immunodetection method increases the accessibility of β-synuclein quantification of β-synuclein in larger research groups. Its value as a marker for AD will have to be tested in cohorts and compared with blood markers such as pTau217 and pTau231, whose performance remains unmatched to date.
13	Relationship of serum beta-synuclein with blood biomarkers and brain atrophy	Patrick Oeckl, Sarah Anderl-Straub, Adrian Danek, Janine Diehl-Schmid, Klaus Fassbender, Klaus Fliessbach, Steffen Halbgebauer, Hans-Jürgen Huppertz, Holger Jahn, Jan Kassubek, Johannes Kornhuber, Bernhard Landwehrmeyer, Martin Lauer, Johannes Prudlo, Anja Schneider, Matthias L Schroeter, Petra Steinacker, Alexander E Volk, Matias Wagner, Juliane Winkelmann, Jens Wiltfang, Albert C Ludolph, Markus Otto	2022	Germany	Predictive study	patients (n=374) recruited between 2011 and 2018 within the German FTLD consortium. **Method:** comparison of serum beta-synuclein immunoprecipitation — mass spectrometry (IP-MS) with blood markers p-tau181 and neurofilament light in the German FTLD consortium cohort (n=374), its correlation with brain atrophy (MRI) and cognitive scores	Serum beta-synuclein was increased in AD but not in frontotemporal lobar degeneration (FTLD) syndromes. Beta-synuclein correlated with atrophy in temporal brain structures and was associated with cognitive impairment. Serum p-tau181 showed the most specific changes in AD but the lowest correlation with structural alterations. NfL was elevated in all diseases and correlated with frontal and temporal brain atrophy.
14	Visinin-like protein 1 levels in blood and CSF as emerging markers for Alzheimer's and other neurodegenerative diseases	Steffen Halbgebauer, Petra Steinacker, Daniel Riedel, Patrick Oeckl, Sarah Anderl-Straub, Jolina Lombardi, Christine A F von Arnim, Magdalena Nagl, Armin Giese, Albert C Ludolph, Markus Otto	2022	Germany	Predictive study	Paired CSF and serum samples from 234 patients, 73 patients with AD, 18 patients with the behavioral variant of frontotemporal dementia (bvFTD), 26 patients with Parkinson's disease, 20 patients with amyotrophic lateral sclerosis (ALS), 22 patients with Creutzfeldt-Jakob disease (CJD), and 75 patients with non-neurodegenerative control (Con). **Method:** analysis of CSF and serum VILIP-1, compared with the main biomarkers of AD.	CSF and serum VILIP-1 levels were correlated weakly ($r = 0.32$ (CI: 0.200.43), $p < 0.0001$). VILIP-1 concentrations in CSF and serum were elevated in AD compared to Con ($p < 0.0001$ and $p < 0.01$) and CJD ($p < 0.0001$ for CSF and serum), and an increase in CSF was observed already in early AD stages ($p < 0.0001$). In the discrimination of AD versus Con, we could demonstrate a strong diagnostic potential for CSF VILIP-1 alone (area under the curve (AUC): 0.87), CSF VILIP-1/CSF Abeta 142 (AUC: 0.98), and serum VILIP-1/CSF Abeta 142 ratio (AUC: 0.89).

15	Certification of visinin-like protein-1 (VILIP-1) certified reference material by amino acid-based and sulfur-based liquid chromatography isotope dilution mass spectrometry	Yang Zang, Xirui Zhou, Mengyun Pan, Yanli Lu, Hangrui Liu, Jinping Xiong, Liuxing Feng	2023	China	Predictive study	Development and certification of the VILIP-1 CRM solution using amino acid-based isotope dilution mass spectrometry (AA-ID-MS) and sulfur-based isotope dilution inductively coupled plasma mass spectrometry (ID-ICP-MS).	In this work, VILIP-1 solution CRM with a certified value and uncertainty of 39.82±1.52 μg·g-1 was developed and certified using amino acid-based isotope dilution mass spectrometry (AA-ID-MS) and sulfur-based isotope dilution inductively coupled plasma mass spectrometry (ID-ICP-MS). VILIP-1 CRM shows excellent homogeneity and can be stable for at least 7 days at -20°C and 12 months at -70°C. The developed VILIP-1 CRM can be used to assign value to secondary calibrators and clinical matrix CRMs, showing prospects in early diagnosis and disease monitoring for AD.
16	A new generation of AD biomarkers: 2019 to 2021	Jade Hawksworth, Esperanza Fernández, Kris Gevaert	2022	Belgium	Predictive study	Analysis of plasma and cerebrospinal fluid for beta-amyloid-42 (Aβ42), total tau (t-tau), and phosphorylated tau (p-tau). In addition, several proteins have been identified as likely proxies for neurodegeneration, including neurofilament light (NfL), synaptosomal-associated protein 25 (SNAP-25), and neurogranin (NRGN).	Several proteins have been identified as likely proxies for neurodegeneration, including neurofilament light (NfL), synaptosomal-associated protein 25 (SNAP-25), and neurogranin (NRGN).
17	Blood Analytes as Biomarkers of Mechanisms Involved in Alzheimer's Disease Progression	Andrea Baldini, Alberto Greco	2022	Italy	Predictive study	90 patients with AD. **Method:** analysis of 277 tests (both complete blood count and blood chemistry, including blood tests with immunoinflammatory and oxidative markers).	Statistical results show an inverse significant relationship between four analytes (high-density cholesterol, total cholesterol, iron, and ferritin) and AD severity. Furthermore, the Reactome database suggests that such analytes may be involved in pathways that change as AD progresses. Indeed, the identified blood markers include molecules that reflect the heterogeneous pathogenic mechanisms of AD. The combination of such blood analytes may be an early indicator of AD progression and represent useful therapeutic targets.
18	Large-scale plasma proteomic profiling identifies a high-performance biomarker panel for Alzheimer's disease screening and staging	Yuanbing Jiang, Xiaopu Zhou, Fanny C Ip, Philip Chan, Yu Chen, Nicole C H Lai, Kit Cheung, Ronnie M N Lo, Estella P S Tong, Bonnie W Y Wong, Andrew L T Chan, Vincent C T Mok, Timothy C Y Kwok, Kin Y Mok, John Hard, Henrik Zetterberg, Amy K Y Fu, Nancy Y Ip	2022	China, UK, Sweden	Predictive study	97 Hong Kong Chinese over 60 who attended the Queen Elizabeth Hospital from February 2018 to March 2020. **Method:** Plasma proteome analysis for a panel of 1,160 proteins.	We identified 429 proteins that were dysregulated in the plasma of AD patients. We selected 19 "hub proteins" representative of the AD plasma protein profile, which formed the basis of a scoring system that accurately classified clinical AD (area under the curve =0.9690–0.9816) and associated endophenotypes. Moreover, specific hub proteins exhibit disease stage-dependent dysregulation, which can delineate AD stages.

19	An accurate fully automated panel of plasma biomarkers for Alzheimer's disease	Sebastian Palmqvist, Erik Stomrud, Nicholas Cullen, Shorena Janelidze, Ekaterina Manuilova, Alexander Jethwa, Tobias Bittner, Udo Eichenlaub, Ivonne Suridjan, Gwendlyn Kollmorgen, Matthias Riepe, Christine A F von Arnim, Hayrettin Tumani, Klaus Hager, Fedor Heidenreich, Niklas Mattsson-Carlgren, Henrik Zetterberg, Kaj Blennow, Oskar Hansson	2022	Sweden, Germany, Switzerland, UK, China	Predictive study	Two cohorts of participants with available CSF and blood samples (n=920): Group A + (n=32 healthy, n=106 mild cognitive impairment and n=89 with AD), and BioFINDER-1 (n=461 healthy, n=232 with mild cognitive impairment). **Method**: plasma Aβ42, Aβ40, p-tau181, p-tau217, ApoE4, NfL, and GFAP immunoassay.	The best biomarker for discriminating Aβ-positive versus Aβ-negative participants was Aβ42/Aβ40 (are under the curve [AUC] 0.830.87). Combining Aβ42/Aβ40, p-tau181, and ApoE4 improved the AUCs significantly (0.90 to 0.93; p <0.01). Adding additional biomarkers had marginal effects (ΔAUC ≤0.01). In BioFINDER, p-tau181, p-tau217, and ApoE4 predicted AD dementia within 6 years in CU (AUC 0.88) and p-tau181, p-tau217, and Aβ42/Aβ40 in MCI (AUC 0.87).
20	A Novel Panel of Plasma Proteins Predicts Progression in Prodromal Alzheimer's Disease	Daniella Castro Araújo, Adriano Alonso Veloso, Karina Braga Gomes, Leonardo Cruz de Souza, Nivio Ziviani, Paulo Caramelli	2022	Brazil	Predictive study	379 patients with mild cognitive impairment, 176 of whom were diagnosed with AD. **Method:** analysis of 12 plasma proteins (ApoB, calcitonin, C-peptide, CRP, IGFBP-2, interleukin-3, interleukin-8, PARC, serotransferrin, THP, TLSP 1-309 and TN-C)	We developed a machine learning-based panel composed of 12 plasma proteins (ApoB, calcitonin, C-peptide, CRP, IGFBP-2, interleukin-3, interleukin-8, PARC, serotransferrin, THP, TLSP 1-309, and TN-C) which yielded an AUC of 0.91, accuracy of 0.91, sensitivity of 0.84, and specificity of 0.98 for predicting the risk of MCI patients deteriorating into dementia due to AD in a horizon of up to four years.
21	Prognosis of Alzheimer's Disease Using Quantitative Mass Spectrometry of Human Blood Plasma Proteins and Machine Learning	Alexey S Kononikhin, Natalia V Zakharova, Savva D Semenov, Anna E Bugrova, Alexander G Brzhozovskiy, Maria I Indeykina, Yana B Fedorova, Igor V Kolykhalo, Polina A Strelnikova, Anna Yu Ikonnikova, Dmitry A Gryadunov, Svetlana I Gavrilova, Evgeny N Nikolaev	2022	Russia	Predictive study	Analysis of 149 non-depleted EDTA plasma samples (MHRC, Russia) of patients with AD (using the BAK 125 kit (MRM Proteomics Inc., n=47), mild cognitive impairment (MCI, n=36), vascular dementia (n=8), frontotemporal dementia (n=15), and an elderly control group (n=43, Canada). **Method:** plasma protein quantitation using the BAK 125 kit.	Statistical analysis revealed a significant decrease in the levels of afamin, apolipoprotein E, biotinidase, and serum paraoxonase/arylesterase 1 associated with AD. Different machine-learning training algorithms were performed to identify the protein panels and build corresponding classifiers for the AD prognosis. Machine learning revealed 31 proteins that are important for AD differentiation and mostly include previously reported CBs. The best performing classifiers reached 80% accuracy, 79.4% sensitivity, and 83.6% specificity and were capable of assessing the risk of developing AD over the next 3 years for patients with MCI.
22	Neuroinflammation in frontotemporal dementia	Fiona Bright, Eryn L Werry, Carol Dobson-Stone, Olivier Piguet, Lars M Ittner, Glenda M Halliday, John R Hodges, Matthew C Kiernan, Clement T Loy, Michael Kassiou, Jillian J Kril	2019	Australia	Predictive study	Analysis of published data on the neuroinflammatory mechanisms in frontotemporal dementia.	This review discusses specific evidence of neuroinflammatory mechanisms in FTD and describes how advances in our understanding of these mechanisms, in FTD as well as in other neurodegenerative diseases, might facilitate the development and implementation of diagnostic tools and disease-modifying treatments for FTD.

23	Neuroinflammation: A Potential Risk for Dementia	Md Afroz Ahmad, Ozaifa Kareem, Mohammad Khushtar, Md Akbar, Md Rafiul Haque, Ashif Iqubal, Md Faheem Haider, Faheem Hyder Pottoo, Fatima S Abdulla, Mahia B Al-Haidar, Noora Alhajri	2022	India, Saudi Arabia, UAE	Predictive study	Analysis of published data and the role of inflammation in neurodegenerative processes.	In this review, the association of inflammation with dementia is discussed (Figure 3). In AD, deposition of the amyloid β-protein alone can cause an inflammatory response that leads to memory impairment and disease progression. Despite the chance that the deposition of the amyloid β-protein will precede "cognitive deficits" or "clinical manifestation" by decades, it can be speculated that endogenous or exogenous factors can alter the natural immunogenic response mounted by exposure of microglia to amyloid β-protein. Therefore, ecologically adjustable risk factors of AD, including obesity, traumatic brain damage, and systemic inflammation, can cause dementia through the continued neuroinflammatory drive.
24	The IL-1β phenomena in neuroinflammatory diseases	Andrew S Mendiola, Astrid E Cardona	2018	USA	Predictive study	Analysis of published data and the impact of IL-1β in dementia	Recent research in the areas of neuroinflammation in MS, AD, and DR supports the notion that a combination of approaches may provide success in ameliorating and perhaps reversing neuronal damage via utilization of IL-1β blocking strategies, targeting vascular damage, and cellular infiltration to CNS tissues. Experimental models will continue to be valuable tools to test the balance of IL-1β in the CNS in health and disease. Efforts to understand how to target IL-1 signaling in both immune and resident CNS cells still continue with the purpose of applying efficacious IL-1 modulatory therapies to treat not only neuroinflammatory disorders, but also inflammatory diseases that involve systemic and peripheral tissues.
25	Neurobiological Highlights of Cognitive Impairment in Psychiatric Disorders	Anna Morozova,Yana Zorkina, Olga Abramova, Olga Pavlova, Konstantin Pavlov, Kristina Soloveva, Maria Volkova, Polina Alekseeva, Alisa Andryshchenko, Georgiy Kostyuk, Olga Gurina, and Vladimir Chekhonin	2022	Russia	Predictive study	Analysis of data on molecular biological markers that are associated with neuroinflammation and cognitive impairment.	Plasma biomarkers, including neurotrophic factors, pro-inflammatory cytokines, and oxidative stress markers, are persistently elevated in a significant proportion of patients with cognitive dysfunction and, thus, may be crucial symptoms. In addition, these plasma markers certainly depend on the DNA sequences of the genes and transcription mechanisms. Moreover, environmental factors such as lifestyle, diet, unhealthy lifestyles, and stress levels regulate gene transcription via epigenetic mechanisms of DNA and histone methylation and acetylation. The genetic basis of mental disorders is complex and still poorly understood. There is a paucity of data on the neuroinflammatory processes of mental disorders associated with cognitive impairment and how they contribute to their development, progression, and persistence.
26	Neuroinflammation and Proinflammatory Cytokines in Epileptogenesis	Alireza Soltani Khaboushan, Niloufar Yazdanpanah, Nima Rezaei	2022	Iran	Predictive study	Analysis of publications on the role of neuroinflammation and its primary mediators, including IL-1β, IL-1α, IL-6, IL-17, IL-18, TNF-α, and interferon-γ (IFN-γ) in the pathophysiology of epilepsy.	Epileptic seizures are associated with increased levels of PICs, particularly interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), which underscores the impact of neuroinflammation and PICs on the hyperexcitability of the brain and epileptogenesis.
27	Immunological variants of amnestic mild cognitive impairment	I K Malashenkova, S A Krynskiy, N A Hailov, D P Ogurtsov, E I Chekulaeva, E V Ponomareva, S I Gavrilova, N A Didkovsky	2020	Russia	Predictive study	100 patients diagnosed with mild cognitive impairment, 45 patients with AD in the stage of mild-to-mild dementia and 40 subjects without cognitive impairment (control group). **Method:** determination of the concentration of key cytokines, C-reactive protein, circulating immune complexes, and immunoglobulins (Ig A, M, G) in blood serum by ELISA, determination of the main lymphocyte subpopulations by flow cytometry.	Four main immunological variants of mild cognitive impairment syndrome, associated with clinical prognosis, have been identified. The identified changes in the immune parameters are important for further studies seeking to assess the impact of viral and bacterial infections, as well as intestinal microflora imbalance, on the clinical prognosis in patients with various immunological variants of mild cognitive impairment syndrome.

28	Nerve growth factor in the psychiatric brain	Stefania Ciafrè, Giampiero Ferraguti, Paola Tirassa, Angela Iannitelli, Massimo Ralli, Antonio Greco, George N Chaldakov, Pamela Rosso, Elena Fico, Marisa Patrizia Messina, Valentina Carito, Luigi Tarani, Mauro Ceccanti, Marco Fiore	2020	Italy, Bulgaria	Predictive study	A study of the association of the nerve growth factor (NGF) and its TrkA receptor and their neurotrophic, metabotropic and/or immunotrophic effects in the pathogenesis of neurodegenerative diseases, including Alzheimer's disease and psychiatric disorders (eg. depression and schizophrenia).	Long-running studies have recognized the important trophic and homeostatic role of NGF, which exhibits its modulating functions in the endocrine, nervous, adipose, and immune systems. Thanks to increased knowledge about the molecular mechanisms of action of this small and versatile peptide, further research could help develop effective brain treatment strategies for many clinical fields, including neurodegeneration, neuroinflammation, and neuroadipocrinology.
29	The Nerve Growth Factor Metabolic Pathway Dysregulation as Cause of Alzheimer's Cholinergic Atrophy	Sonia Do Carmo, Benjamin Kannel, A Claudio Cuello	2021	Canada, UK	Predictive study	Literature review on the dependence of neuronal atrophy on NGF in Alzheimer's disease	In this review, we highlight the existence of an entire CNS metabolic pathway explaining the activity-dependent release of proNGF, along with a cluster of molecules which, in highly coordinated fashion, provoke the conversion of the NGF precursor molecule to its mature and trophic active form in the extracellular space, in proximity to their cognate receptors located in cholinergic synaptic terminals. The mNGF rapidly binds to these receptors to be internalized and retrogradely transported to the neuronal soma to fulfill its trophic functions. The function of the remnant unbound mNGF in the extracellular space is terminated by the proteolytic degradation effected by matrix metalloproteases.
30	Nerve growth factor (NGF) pathway biomarkers in Down syndrome prior to and after the onset of clinical Alzheimer's disease: A paired CSF and plasma study	Rowan Pentz, M. Florencia Iulita, Adriana Ducatenzeiler, Laura Videla, Bessy Benejam, María Carmona-Iragui, Rafael Blesa, Alberto Lleó, Juan Fortea, A. Claudio Cuello	2021	Canada, Spain, UK	Predictive study	37 patients who consented to blood and cerebrospinal fluid collection and 16 subjects from the control group. **Method:** neurological and neuropsychological examination, evaluation of AD CSF biomarkers (beta-amyloid [Aβ] 42/Aβ40, total tau [t-tau] and phosphorylated tau [p-tau]).	ProNGF and MMP-3 were elevated, while tPA was decreased in the plasma from individuals with DS. CSF from individuals with DS showed elevated proNGF, neuroserpin, MMP-3, and MMP-9. ProNGF and MMP-9 in CSF differentiated DSAD from aDS (area under the curve =0.86, 0.87). NGF pathway markers associated with CSF amyloid beta and tau and differentiated by sex.
31	Gene- and Gender-Related Decrease in Serum BDNF Levels in Alzheimer's Disease	Daniela Piancatelli, Anna Aureli, Pierluigi Sebastiani, Alessia Colanardi, Tiziana Del Beato, Lorenza Del Cane, Patrizia Sucapane, Carmine Marini, Silvia Di Loreto	2022	Italy	Predictive study	110 patients (79 with AD and 31 with MCI), control group – 58 subjects. **Method:** A study of the relationship between serum BDNF levels and some major polymorphisms of both BDNF genes (Val66Met, rs6265; C270T, rs56164415) and molecules potentially involved in inflammation (IL-1 family, including IL-1α rs1800587; IL-1β rs1143627; IL-38 rs6743376), in oxidative stress and mitochondrial damage or protection (APOE rs7412 and rs429358, FOXO3A rs2802292, SIRT3 rs11555236, GLO1 rs1049346 and SOD2 rs4880) were investigated in patients with AD or MCI, to determine potential predictive risk associations.	Serum levels of BDNF were detected in 71 patients diagnosed with AD, 31 with MCI, and 32 age-matched controls, using an enzyme-linked immunosorbent assay (ELISA) (ab99978 Abcam, Cambridge, UK). The sensitivity of the test was <80 pg/mL.

32	Brain-Derived Neurotropic Factor in Neurodegenerative Disorders	Abdallah Mohammad Ibrahim, Lalita Chauhan, Aditi Bhardwaj, Anjali Sharma, Faizana Fayaz, Bhumika Kumar, Mohamed Alhashmi, Noora AlHajri, Md Sabir Alam, Faheem Hyder Pottoo	2022	Saudi Arabia, India, UAE	Predictive study	The role of BDNF in the treatment and as a biomarker of AD risk.	BDNF is one of the neurotrophic factors that modulate its function through the TrkB receptor. It plays an important role in the central nervous system, forming and maintaining a healthy neuronal environment, which is most prominently reflected in cognitive and memory functions. A decrease in BDNF activity has been associated with the aging process and neurodegenerative disorders. The role of BDNF in the treatment and as a disease biomarker should be carefully explored in future studies.
33	Association of plasma brain-derived neurotrophic factor with Alzheimer's disease and its influencing factors in Chinese elderly population	Fuqiang Qian, Jian Liu, Hongyu Yang, Haohao Zhu, Zhiqiang Wang, Yue Wu	2022	China	Predictive study	Analysis of published data on the relationship between BDNF levels and neurodegenerative diseases.	BDNF levels in DAT patients were higher than those in CNC and MCI patients ($P < 0.01$). BDNF levels significantly correlated with CDR, MMSE, and clinical diagnosis ($P < 0.001$). Age, education, occupation, and sample source had significant effects on BDNF differences among the CNC, MCI, and DAT groups ($P < 0.001$). BDNF first decreased and then increased with cognitive impairment in the ApoE4-negative group ($P < 0.05$).
34	Neurotrophin-3 Promotes the Neuronal Differentiation of BMSCs and Improves Cognitive Function in a Rat Model of Alzheimer's Disease	Zhongrui Yan, Xianjing Shi, Hui Wang, Cuiping Si, Qian Liu, and Yifeng Du	2021	China	Predictive study	A sample of rats with AD. **Method:** Evaluation of *in vitro* and *in vivo* effects of NT-3 on BMSC differentiation in neurons and the recovery of cognitive function after BMSC transplantation in AD rats.	The protein level of NT-3 in BMSCs approximately doubled after gene transduction with lentivirus ($P < 0.001$). Successful interference of NT-3 expression in BMSCs was also confirmed, and the efficiency of lentivirus-mediated interference was more than 70% ($P < 0.001$). Neuron-like morphologic changes were more pronounced in the NT-3 overexpression group than in the vector control group, whereas silencing of NT-3 expression attenuated the morphologic changes. Immunostaining of NSE, NF-200, and neuronal class III β-tubulin in BMSCs was performed to further demonstrate differentiated neurons. NT-3 overexpression enhanced the expressions of NSE, NF-200, and neuronal class III β-tubulin in BMSCs, whereas silencing of NT-3 resulted in weaker staining for NSE, NF-200, and neuronal class III β-tubulin. The levels of total and nuclear β-catenin in BMSCs were increased significantly by NT-3 overexpression, compared with the vector group ($P < 0.001$). However, silencing of NT-3 remarkably down-regulated the levels of total and nuclear β-catenin ($P < 0.01$). Immunostaining of β-catenin in BMSCs further confirmed that the expression of the β-catenin protein was increased by NT-3 overexpression but decreased by NT-3 silencing. Compared with the BMSC group, the NT-3 level in brain tissue was increased in the NT-3-BMSC group ($P < 0.001$) but decreased in the sh-NT-3-BMSC group ($P < 0.01$). On day 3 of training, the latencies were decreased in the BMSC and NT-3-BMSC groups compared with the PBS group. However, there was no difference in latency between the sh-NT-3-BMSC group and PBS group. On day 4 of training, the decrease in latency was more obvious in the NT-3-BMSC group than in the BMSC group, whereas the sh-NT-3-BMSC group and PBS group showed little difference in latency. On day 5 of training, the latencies in the BMSC, NT-3-BMSC, and sh-NT-3-BMSC groups were decreased significantly compared with the PBS group, but there were no differences between the three BMSC groups. On day 3 of training, the latencies were decreased in the BMSC and NT-3-BMSC groups compared with the PBS group (Figure 5C). However, there was no difference in latency between the sh-NT-3-BMSC group and PBS group. On day 4 of training, the decrease in latency was more obvious in the NT-3-BMSC group than in the BMSC group, whereas the sh-NT-3-BMSC group and PBS group showed little difference in latency. On day 5 of training, the latencies in the BMSC, NT-3-BMSC, and sh-NT-3-BMSC groups were decreased significantly compared with the PBS group, but there were no differences between the three BMSC groups. The levels of total and nuclear β-catenin in brain tissue were increased significantly in the BMSC group compared with the PBS group ($P < 0.05$), and the levels were further up-regulated in the NT-3-BMSC group ($P < 0.001$) but down-regulated in the sh-NT-3-BMSCgroup ($P < 0.01$). The expressions of NSE and NF-200 in brain tissue were higher in the NT-3-BMSC group than in the BMSC group. However, NSE and NF-200 expression was suppressed in the sh-NT-3-BMSC group.

35	NT-4/5 antagonizes the BDNF modulation of corticostriatal transmission: Role of the TrkB.T1 receptor	Francisco M. Torres-Cruz, Israel César Vivar-Cortés, Isaac Moran, Ernesto Mendoza, Victor Gómez-Pineda, Francisco García-Sierra, and Elizabeth Hernández	2019	Mexico	Predictive study	Male mice C57BL/6 (ENVIGO, Mexico) at the age of 35 days. Mice were housed in groups of five in Plexiglas boxes at room temperature (24-26°C) with a 12:12 hour light/dark cycle and had access to food and water. Brain slices containing the striatum were incubated at RT and bubbled (95% O_2-5% CO_2) in saline in the presence of bicuculline; then the slices were exposed to (a) BDNF (50 ng/mL), (b) BDNF (50 ng/mL) NT-4/5 (50 ng/mL), (c) NT-4/5 (50 ng/mL) or (d) NT-4/5 (50 ng/mL) BDNF (50 ng/mL) for 10 or 30 minutes. The COS-7 cell line obtained from the ATCC was grown in DMEM; glucose (1/1) supplemented with 10% fetal bovine serum; 2 mmol/L L-glutamine; 100 U/mL penicillin; and 100 µg/mL streptomycin, and the cells were maintained under a humidified atmosphere (5% CO_2, 37°C). When the cells reached 50%-60% confluence, the medium was changed to a FBS-free Optimem specialized medium (GIBCO) and the cells were transiently cotransfected with 1 µg of DNA from the TrkB constructs (plasmid pGFP-N1-TrkB and pRc/CMV HA-TrkB). After cell transfection and neurotrophin treatment, cell cultures were washed twice with PBS, scraped, lysed in radioimmunoprecipitation assay (RIPA) buffer containing a cocktail of protease inhibitors, and centrifuged (12,000 g × 10 minutes). The supernatant was collected, and protein content determined by the mini-Bradford assay. A total of 30 µg of the protein was mixed in 5× sample buffer (TRIS-HCL 250 mmol/L pH 6.8, sodium dodecyl sulfate (SDS) 10%, bromophenol blue 0.5%, β-mercaptoethanol 12.5%, and glycerol 50%) and boiled (95°C, 5 minutes). The proteins were separated by electrophoresis on a 10% SDS-polyacrylamide gel (SDS-PAGE) and transferred onto a nitrocellulose membrane for immunoblotting analysis. Membranes were blocked in 10% nonfat dried milk in PBS or TBS-0.1% Tween 20 (PBS-tw or TBS-tw) overnight at 4°C and incubated for 12 hours in primary antibodies diluted in PBS-tw or TBS-tw. After washing, incubation with the corresponding HRP-conjugated secondary antibodies to either mouse or rabbit was carried out for 1-2 hours (RT).	With a stable recording, either BDNF or NT-4/5 was applied to the recording bath. Figures 1A and B show that BDNF increased spike amplitude in response to S1 compared to the control, as we previously reported. However, when NT-4/5 was administered in the presence of BDNF, the spike amplitude significantly decreased. This implies that NT-4/5 antagonizes the effect of BDNF on corticostriatal transmission. PPR analysis (S2/S1) did not show significant differences, suggesting that both neurotrophins modulate corticostriatal transmission via postsynaptic mechanisms.

36	The multiplex model of the genetics of Alzheimer's disease	Rebecca Sims, Matthew Hill, Julie Williams	2020	UK	Predictive study	Analysis of published data on the multiplex model as a new perspective for understanding AD.	Over 50 loci are now implicated for AD, suggesting that AD is a disease with multiple components, as supported by pathway analyses (immunity, endocytosis, cholesterol transport, ubiquitination, amyloid-[beta], and tau processing). Over 50% of late-onset AD heritability has been captured, allowing researchers to calculate the accumulation of AD genetic risk through polygenic risk scores. A polygenic risk score predicts disease with up to 90% accuracy and is an exciting tool in our research armory that could allow selection of those with high polygenic risk scores for clinical trials and precision medicine.
37	Apolipoprotein E and Alzheimer's disease	Benjamin R Troutwine, Laylan Hamid, Colton R Lysaker, Taylor A Strope, Heather M Wilkins	2022	USA	Predictive study	Analysis of published data on the association of APOE with AD and the specific effects of the APOE isoform in the brain and in the periphery.	APOE polymorphisms modulate the risk of vascular disease and AD. There are likely other unidentified associations of APOE isoforms with diseases across lifespan. It's also important to note that some APOE isoforms confer advantages early in life but are a disadvantage in aging. The role of APOE in the brain has largely focused on the effects of APOE ε4. While APOE is mostly expressed in glial cells (astrocytes and microglia), its effects are observed on other cell types, including neurons. APOE ε4 influences pathologies observed in AD. APOE ε4 is associated with increased Aβ burden likely through reducing its clearance and degradation. Tau hyperphosphorylation and NFTs are increased in the presence of APOE ε4. Not surprisingly, APOE ε4 modulates neuroinflammation and this role directly impacts its effects on Aβ and tau pathologies. Mitochondrial function and metabolism are altered by the expression of APOE ε4, and these effects are observed in the periphery as well as the brain. Overall, the effects of APOE ε4 on AD associated pathologies are clear.
38	APOE and Alzheimer's Disease: From Lipid Transport to Physiopathology and Therapeutics	Mohammed Amir Husain, Benoit Laurent, and Mélanie Plourde	2021	USA	Predictive study	38,537 people from six population cohorts. **Method:** analysis of the effect of APOE on lipid metabolism and various CNS functions.	Carrying APOE4 is the major genetic risk factor for developing late-onset Alzheimer's disease, although not everyone carrying APOE4 develops the disease. APOE not only affects lipid metabolism but various CNS functions in an isoform-dependent manner. In addition to controlling blood cholesterol levels, APOE4 proteins also regulate Aβ deposition, aggregation and clearance. However, the exact molecular mechanisms behind Aβ regulation observed in human and animal models remain to be elucidated. It is still unclear whether APOE4 allele affects LOAD pathogenesis by a gain of toxic functions or a loss of defensive functions (or a combination of both).
39	Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing	Brian W Kunkle, Benjamin Grenier-Boley, Rebecca Sims, et al	2019	USA, France, UK, Belgium, Iceland, Spain, Finland, Germany, Switzerland, Ireland, Italy, Canada, Australia	Predictive study	Determination of clinically significant genetic markers for the diagnosis of the late onset Alzheimer's disease (94,437 subjects).	Human leukocyte (HLA) genetic mapping confirms the neurological and immune-mediated disease haplotype HLA-DR15 as a risk factor for AD. Pathway analysis implicates immunity, lipid metabolism, tau binding proteins, and amyloid precursor protein (APP) metabolism, showing that genetic variants affecting APP and Aβ processing are associated not only with early-onset autosomal dominant Alzheimer's disease but also with late onset Alzheimer's disease. Analyses of risk genes and pathways show enrichment for rare variants ($P = 1.32 \times 10^{-7}$), indicating that additional rare variants remain to be identified.

40	Assessment of the genetic variance of late-onset Alzheimer's disease	Perry G Ridge, Kaitlyn B Hoyt, Kevin Boehm, Shubhabrata Mukherjee, Paul K Crane, Jonathan L Haine, Richard Mayeux, Lindsay A Farrer, Margaret A Pericak-Vance, Gerard D Schellenberg, John S K Kauwe	2016	USA	Predictive study	SNP data set from the Alzheimer's Disease Genetics Consortium (ADGC). The final filtered dataset consisted of 9699 individuals and 8,712,879 SNPs. **Method:** Genome-wide Complex Trait Analysis to 1) estimate phenotypic variance explained by genetics; 2) calculate genetic variance explained by known AD single nucleotide polymorphisms (SNPs); and 3) identify the genomic locations of variation that explain the remaining unexplained genetic variance.	In total, 53.24% of phenotypic variance is explained by genetics, but known AD SNPs only explain 30.62% of the genetic variance. Of the unexplained genetic variance, approximately 41% is explained by unknown SNPs in regions adjacent to known AD SNPs, and the remaining unexplained genetic variance outside these regions.
41	Interpretation of risk loci from genome-wide association studies of Alzheimer's disease	Shea J Andrews, Brian Fulton-Howard, Alison Goate	2020	USA	Predictive study	Three new Alzheimer's GWAS published in 2018 and 2019. The first, an updated GWAS from IGAP, included 94,437 individuals and discovered 24 susceptibility loci. The other two studies used samples of 388,324 and 534,403 individuals. These two studies identified 27 and 29 susceptibility loci, respectively. **Method**: Genetic analysis of 40 loci that are associated with Alzheimer's disease.	APOE, CR1, BIN1, TREM2, CLU, SORL1, ADAM10, ABCA7, CD33, SPI1 and PILRA are important genes in the diagnosis of Alzheimer's disease.
42	Polygenic Risk Scores in Alzheimer's Disease Genetics: Methodology, Applications, Inclusion, and Diversity	Clark,Yuk Yee Leung, Wan-Ping Lee, Benjamin Voight, and Li-San Wanga	2022	USA	Predictive study	Analysis of PRS calculation methods and their applications in disease prediction.	PRS have been informative in many different disease contexts, with multiple software developed in the recent past to increase its accuracy. The goal of these new methods is to expand the benefit of PRS beyond a research tool, gaining value in both clinical settings and the lives of the general public. Despite this effort, PRS remain the most useful for subjects of European descent due to differences in genetic architecture between ethnic populations. While the clear solution is to increase the diversity of populations with calculated risk scores, this is only possible if the populations of the underlying large-scale GWAS are also diversified. Once this task is undertaken, PRS can grow to be applicable to people of all communities. This is especially true in the case of AD, where disease prevalence is much higher in people of African and Hispanic descent as compared to that of people of European or Asian descent. With continued effort to increase the predictive ability of PRS software and an investment into GWAS of non-European populations, it is very likely that PRS will be a common tool used by the medical community.
43	A cluster of cholesterol-related genes confers susceptibility for Alzheimer's disease	Andreas Papassotiropoulos 1, M Axel Wollmer, Magdalini Tsolaki, Fabienne Brunner, Dimitra Molyva, Dieter Lütjohann, Roger M Nitsch, Christoph Hock	2005	Switzerland	Predictive study	12 cholesterol-related single nucleotide polymorphisms and 48 control polymorphisms in 545 study participants (Alzheimer's disease group n=284; control group n=261). **Method:** Cluster analysis of polymorphisms in APOE, SOAT1, APOE 5'-untranslated region, OLR1, CYP46A1, LPL, LIPA, and APOA4 conferring significant (p=0.0002) susceptibility to Alzheimer's disease	We identified a cluster of polymorphisms in APOE, SOAT1, APOE 5'-untranslated region, OLR1, CYP46A1, LPL, LIPA, and APOA4 conferring significant (p=0.0002) susceptibility for Alzheimer's disease. This gene cluster reached a diagnostic accuracy of 74% and correlated significantly (p=0.018) with the levels of the brain cholesterol catabolite 24S-hydroxycholesterol in the cerebrospinal fluid.

44	Evaluation of a Genetic Risk Score to Improve Risk Prediction for Alzheimer's Disease	Vincent Chouraki, Christiane Reitz, Fleur Maury, Joshua C Bis, Celine Bellenguez, Lei Yu, Johanna Jakobsdottir, Shubhabrata Mukherjee, Hieab H Adams, Seung Hoan Choi, Eric B Larson, Annette Fitzpatrick, Andre G Uitterlinden, Philip L de Jager, Albert Hofman, Vilmundur Gudnason, Badri Vardarajan, Carla Ibrahim-Verbaas, Sven J van der Lee, Oscar Lopez, Jean-François Dartigues, Claudine Berr, Philippe Amouyel, David A Bennett, Cornelia van Duijn, Anita L DeStefano, Lenore J Launer, M Arfan Ikram, Paul K Cran, Jean-Charles Lambert, Richard Mayeux, Sudha Seshadri	2016	USA, Iceland, Netherlands	Predictive study	19,687 participants at risk, 2,782 of whom developed AD. **Method:** Genetic risk assessment (GRS) including common genetic variants associated with AD, assessing its association with AD disease, and assessing its ability to improve risk prediction over traditional models based on age, sex, education, and APOEε4.	The GRS was associated with a 17% increase in AD risk (pooled HR =1.17; 95% CI =[1.13-1.21] per standard deviation increase in GRS; p-value =2.86×10^{-16}). This association was stronger among persons with at least one APOEε4 allele (HRGRS =1.24; 95% CI = [1.15-1.34]) than in others (HRGRS =1.13; 95% CI =[1.08-1.18]; interaction =3.45×10^{-2}). Risk prediction after seven years of follow-up showed a small improvement when adding the GRS to age, sex, APOEε4, and education (Δ-Cindex =0.0043 [0.00190.0067]). Similar patterns were observed for IDI and NRI >0.
45	Polygenic risk scores in familial Alzheimer disease	Giuseppe Tosto, Thomas D. Bird, Debby Tsuang, David A. Bennett, Bradley F. Boeve, Carlos Cruchaga, Kelley Faber, Tatiana M. Foroud, Martin Farlow, Alison M. Goat, Sarah Bertlesen, Neill R. Graff-Radford, Martin Medrano, Rafael Lantigua, Jennifer Manly, Ruth Ottman, Roger Rosenberg, Daniel J. Schaid, Nicole Schupf, Yaakov Stern, Robert A. Sweet, and Richard Mayeux	2017	USA	Predictive study	Data from the National Institute on Aging Genetics Initiative for Late-Onset Alzheimer Disease. **Method:** The first association model obtained from the literature. Subsequent models were adjusted for the presence of the APOE ε4 allele and further the interaction between APOE ε4 and GRS was tested. Then we constructed a similar GRS in a cohort of Caribbean Hispanic families multiply affected by late-onset Alzheimer's disease by selecting the SNP with the strongest p value within the same regions.	In families with late-onset familial Alzheimer's disease, the GRS was significantly associated with late-onset Alzheimer's disease (odds ratio [OR] 1.29; 95% confidence interval 1.21–1.37). The results did not change after adjusting for APOE ε4. In Caribbean Hispanic families, the GRS also significantly predicted late-onset Alzheimer's disease (OR 1.73; 1.57–1.93). Higher scores were associated with lower age at onset in both cohorts.

46	Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score	Rahul S Desikan, Chun Chieh Fan, Yunpeng Wang, Andrew J Schork, Howard J Cabral, L Adrienne Cupples, Wesley K Thompson, Lilah Besser, Walter A Kukull, Dominic Holland, Chi-Hua Chen, James B Brewer, David S Karow, Karolina Kauppi, Aree Witoelar, Celeste M Karch, Luke W Bonham, Jennifer S Yokoyama, Howard J Rosen, Bruce L Miller, William P Dillon, David M Wilson, Christopher P Hess, Margaret Pericak-Vance, Jonathan L Haines, Lindsay A Farrer, Richard Mayeux, John Hardy, Alison M Goate, Bradley T Hyman, Gerard D Schellenberg, Linda K McEvoy, Ole A Andreassen, Anders M Dale	2021	USA, Norway, Denmark	Predictive study	Genotype data of 17,008 AD patients and 37,154 controls from the International Genomics of Alzheimer's Project (IGAP Stage 1). **Method:** analysis of SNP patterns associated with AD.	Within the ADGC Phase 1 cohort, individuals in the highest PHS quartile developed AD at a considerably lower age and had the highest yearly AD incidence rate. Among APOE ε3/3 individuals, the PHS modified expected age of AD onset by more than 10 years between the lowest and highest deciles (hazard ratio 3.34, 95% CI 2.62–4.24, $p=1.0 \times 10^{-22}$). In independent cohorts, the PHS strongly predicted empirical age of AD onset (ADGC Phase 2, $r=0.90$, $p=1.1 \times 10^{-26}$) and longitudinal progression from normal aging to AD (NIA ADC, Cochran–Armitage trend test, $p=1.5 \times 10^{-10}$), and was associated with neuropathology (NIA ADC, Braak stage of neurofibrillary tangles, $p=3.9 \times 10^{-6}$, and Consortium to Establish a Registry for Alzheimer's Disease score for neuritic plaques, $p=6.8 \times 10^{-6}$) and *in vivo* markers of AD neurodegeneration (ADNI, volume loss within the entorhinal cortex, $p=6.3 \times 10^{-6}$, and hippocampus, $p=7.9 \times 10^{-5}$).
47	Risk prediction of late-onset Alzheimer's disease implies an oligogenic architecture	Qian Zhang, Julia Sidorenko, Baptiste Couvy-Duchesne, Riccardo E Marioni, Margaret J Wright, Alison M Goate, Edoardo Marcora, Kuan-Lin Huang, Tenielle Porter, Simon M Laws, Perminder S Sachdev, Karen A Mather, Nicola J Armstrong, Anbupalam Thalamuthu, Henry Brodaty, Loic Yengo, Jian Yang, Naomi R Wray, Allan F McRae, Peter M Visscher	2020	Australia, UK, USA	Predictive study	Three independent data sets comprising 676 cases and 35,675 family history proxy cases. **Method:** analysis of SNP models associated with AD risk prediction.	The number of causal common SNPs for late-onset Alzheimer's disease may be less than 100, suggesting that late-onset Alzheimer's disease is more oligogenic than polygenic. The best GRS explains approximately 75% of SNP-heritability, and individuals in the top decile of GRS have ten-fold increased odds when compared to those in the bottom decile. In addition, 14 variants are identified that contribute to both late-onset Alzheimer's disease risk and age at onset of late-onset Alzheimer's disease.

48	Polygenic risk and hazard scores for Alzheimer's disease prediction	Ganna Leonenko, Rebecca Sims, Maryam Shoai, Aura Frizzati, Paola Bossù, Gianfranco Spalletta, Nick C Fox, Julie Williams, John Hardy, Valentina Escott-Price	2019	UK, Italy	Meta-analysis	9903 (2626 cases and 7277 controls) individuals from the Genetic and Environmental Risk in Alzheimer's Disease consortium (GERAD). **Method:** Quantifying individual differences in age-specific genetic risk for AD.	Polygenic Risk Score significantly predicted the risk associated with age at AD onset when SNPs were preselected for association to AD at $p \leq 0.001$. The strongest effect (B=0.28, SE=0.04, $p=2.5\times10^{-12}$) was observed for PRS based upon genome-wide significant SNPs ($p \leq 5\times10^{-8}$). The strength of association was weaker with less stringent SNP selection thresholds.
49	A comprehensive analysis of methods for assessing polygenic burden on Alzheimer's disease pathology and risk beyond APOE	Andre Altmann, Marzia A Scelsi, Maryam Shoai, Eric de Silva, Leon M Aksman, David M Cash, John Hardy, Jonathan M Schott	2019	UK	Diagnostic study	Single nucleotide polymorphism (SNP) genotyping data for n=1674 subjects from the ADNI database. **Method:** MMSE (IQR), PET with amyloid ligands data on CSF biomarkers associated with Alzheimer's disease, amyloid β protein fragment 1-42 (Aβ), total tau (tau), and tau phosphorylated at threonine 181 (p-tau), analysis of SNP models.	We found that polygenic scores were associated beyond APOE with clinical diagnosis, CSF-tau levels and, to a minor degree, with progressive atrophy. However, for many other tested traits such as clinical disease progression, CSF amyloid, cognitive decline and cortical amyloid load, the additional effects of polygenic burden beyond APOE were of minor nature. Overall, polygenic risk scores and the polygenic hazard score performed equally and given the ease with which polygenic risk scores can be derived; they constitute the more practical choice in comparison with polygenic hazard scores. Furthermore, our results demonstrate that incomplete adjustment for the APOE locus, i.e. only adjusting for APOE-ε4 carrier status, can lead to overestimated effects of polygenic scores due to APOE-ε4 homozygous participants. Lastly, on many of the tested traits, the major driving factor remained the APOE locus, with the exception of quantitative CSF-tau and p-tau measures.
50	Association of Alzheimer's Disease Genetic Risk Loci with Cognitive Performance and Decline: A Systematic Review	Shea J Andrews, G Peggy McFall, Andrew Booth, Roger A Dixon, Kaarin J Anstey	2019	USA, Canada, UK, Australia	Systematic review	Studies published between January 2009 and April 2018 were identified by searching the PubMed database using keywords and by scanning the literature lists. **Method:** Analysis of published data for the association of Alzheimer's disease genetic risk loci with cognitive performance and decline.	Fifteen percent of the associations between non-APOE LOAD risk loci and cognition were significant. However, these associations were not replicated across studies, and the majority were rendered non-significant when adjusting for multiple testing. One-third of the studies included genetic risk scores, and these were typically significant only when APOE was included. The findings of this systematic review do not support a consistent association between individual non-APOE LOAD risk and cognitive performance or decline.
51	Polygenic Score Models for Alzheimer's Disease: From Research to Clinical Applications	Xiaopu Zhou, Yolanda Y T Li, Amy K Y Fu, Nancy Y Ip	2021	China	Systematic review	Analysis of published data for the rationale and methods used to construct polygenic score models for studying AD.	Fifteen percent of the associations between non-APOE risk loci and cognition were significant. However, this has not been proven in all studies. The findings of this systematic review do not support a consistent association between individual non-APOE AD risk and cognitive performance or decline. However, evidence suggests that aggregate LOAD genetic risk exerts deleterious effects on decline in episodic memory and global cognition.
52	Volunteering, polygenic risk for Alzheimer's disease, and cognitive functioning among older adults	Sae Hwang Han, J Scott Roberts, Jan E Mutchler, Jeffrey A Burr	2020	USA	Predictive study	US retirees (n=9,697). **Method:** cognitive decline assessment by interview, Polygenic Risk Score for AD (PGS-AD).	Robust within-person associations between volunteering (assessed as volunteer status and time commitment) and cognitive functioning over time, such that volunteering was associated with higher levels of cognitive functioning and slower cognitive decline. The findings also provided evidence that the within-person associations for volunteering and cognitive decline were more pronounced for older adults at higher genetic risk for developing AD.
53	Polygenic risk scores for Alzheimer's disease, and academic achievement, cognitive and behavioural measures in children from the general population	Roxanna Korologou-Linden, Emma L Anderson, Hannah J Jones, George Davey Smith, Laura D Howe, Evie Stergiakouli	2019	UK	Predictive study	Avon Longitudinal Study of Parents and Children (ALSPAC) The study included 14,541 pregnant women who gave birth to 14,062 babies. **Method:** genotyping using the Illumina HumanHap550 quad chip genotyping platforms, polygenic risk assessments, sensitivity analysis.	We did not detect any evidence that the genome-wide significant PRS ($5x10^{-8}$) were associated with these outcomes. PRS at the highest P-value threshold examined ($p \leq 5x10^{-1}$) were associated with lower academic achievement in adolescents (key stage 3; β: -0.03; 95% confidence interval: -0.05, -0.003) but the effect was attenuated when single nucleotide polymorphisms (SNPs) associated with educational attainment were removed. These PRS were associated with lower IQ (β: -0.04; 95% CI: -0.07, -0.02) at age 8 years with the effect remaining after removing SNPs associated with educational attainment.

54	Effects of polygenic risk for Alzheimer's disease on rate of cognitive decline in normal aging	Karolina Kauppi, Michael Rönnlund, Annelie Nordin Adolfsson, Sara Pudas, Rolf Adolfsson	2020	Sweden	Predictive study	Participants who remained non-demented until the most recent dementia screening (13 years after the last test occasion) (n=1087). **Method:** Studying the APOE ε4 allele, a polygenic score for general cognitive ability (PGS-cog), and a polygenic risk score for late-onset AD.	PRS-LOAD predicted the rate of cognitive decline in a carefully selected sample of healthy older adults who remained non-demented at least within six years of the last assessment, in addition to the APOE ε4 allele.
55	An Alzheimer's Disease Genetic Risk Score Predicts Longitudinal Thinning of Hippocampal Complex Subregions in Healthy Older Adults	Theresa M. Harrison, Zanjbeel Mahmood, Edward P. Lau, Alexandra M. Karacozoff, Alison C. Burggren,Gary W. Small, Susan Y. Bookheimer	2016	USA	Диагности-ческое исследо-вание	The current study recruited 66 participants aged ≥48 years. For 45 of these subjects, longitudinal 2-year follow-up data were also available. There were no differences in sex composition (p=0.42), age (p=0.95), education (p=0.42), or MMSE score (p=0.31) between our larger baseline group and the subset with longitudinal data. **Method:** polygenic risk assessment, assessment of APOE (apolipoprotein E), CLU (clusterin), PICALM (phosphatidylinositol binding clathrin assembly protein), and family history of AD.	WRSs ranged from −0.09 to 1.15. There was a high correspondence between URS and WRS within subjects (r=0.72, p <0.0001). We found no significant relationship between behavior and URS (baseline: r=0.14, p=0.13; follow-up: r=−0.06, p=0.34) or WRS (baseline: r=−0.06, p=0.34; follow-up: r=0.05, p=0.37). The lack of an association between cognition and genetic risk score highlights the preclinical focus of this work, which is to identify biomarkers that are associated with genetic risk for AD in cognitively healthy older adults. There was no significant relationship between GRS and ICV-normalized thickness across the entire HC (URS: r=0.15, p=0.16; WRS: r=0.02, p=0.44 Fig. 4). Next, we examined ERC and SUB, two regions affected early in AD, and again found no association between GRS and ICV-normalized thickness (URS: r=0.14, p=0.13; WRS: r=0.05, p=0.35). We found a significant negative correlation between increasing GRS and more negative percentage change in cortical thickness across the entire HC (URS: r=−0.40, p=0.003; WRS: r=−0.25, p=0.048. In ERC, thickness correlated with both GRS types (URS: r=−0.35, p=0.009; WRS: r=−0.35, p=0.009; Fig. 6). In SUB, the association was significant but not as strong (URS: r=−0.31, p=0.01; WRS: r=−0.22, p=0.07). Partial correlation coefficients were still significant for whole HC cortical thickness and URS (URS: r=−0.34, p=0.028; WRS: r=−0.27 p=0.086), and for ERC thickness with both risk scores (URS: r=−0.32 p=0.038; WRS: r=−0.34 p=0.025). As exploratory analyses, we examined each remaining HC subfield and found additional significant relationships to URS with FUS (r=−0.35, p=0.009), PHC (r=−0.26, p=0.042), and CA1 (r=−0.25, p=0.009, p=0.048) thickness. The URS model overall was highly significant (p <0.001) and that URS was a significant predictor within the model (p=0.028), along with time between visits (p=0.002) and a trend for sex (p=0.059). In contrast, the APOE-alone overall model was significant (p=0.003), but APOE itself was not a significant predictor of thickness (p=0.15).
56	Combining Polygenic Hazard Score With Volumetric MRI and Cognitive Measures Improves Prediction of Progression From Mild Cognitive Impairment to Alzheimer's Disease	Karolina Kauppi, Chun Chieh Fan, Linda K. McEvoy, Dominic Holland, Chin Hong Tan, Chi-Hua Chen, Ole A. Andreassen, Rahul S. Desikan, Anders M. Dale	2018	USA, Norway, Italy	Predictive study	Control group of elderly healthy people (n=200), patients with Alzheimer's disease (n=200) and those with MCI (n=400), followed by annual follow-up for 36 months. **Method:** CDR-SB and MMSE data from ADNI 1, progression data to ADNI 2 and ADNI GO, MRI, polygenic hazard score (PHS), statistical analysis.	The PHS significantly predicted progression from MCI to AD over 120 months follow-up (p=1.07e-5), and PHS was a significantly stronger predictor of progression than APOE ε genotype (p=0.0152, for model comparison of APOE vs. APOE +PHS). When including atrophy score (McEvoy et al., 2009) in the model, PHS remained significant and the two-factor prediction model was significantly more predictive than either single-factor model (*p*'s =5.61e-11, and 0.0015 for comparison with single-factor models of PHS and atrophy score, respectively). Finally, we included cognitive functioning at baseline (MMSE) to a three-factor prediction model, which yielded a combined model p-value of 4.28e-17. Model comparisons showed that the three-factor model was significantly more predictive than the two-factor model (p <0.005). PHS significantly improved prediction of both MMSE ($\chi2$=26.7, df=1, p=2.34e-07) and CDR-SB ($\chi2$=21.57, df=1, p=3.41e-06) compared to the baseline variables. Further, the PHS performed significantly better than APOE ε4 status in prediction of both MMSE ($\chi2$=8.61, df=1, p=0.0033) and CDR-SB ($\chi2$=6.12, df=1, p=0.013). Again, PHS remained significant after adding atrophy score to the model. Compared to atrophy score alone, the combined model of PHS and atrophy score was significantly more predictive of change in both MMSE ($\chi2$=19.04, df=1, p=1.281e-05, [controlling for APOE ε4 alleles: χ^2=6.97, df=1, p=0.008]) as well as CDR_SB (χ^2=13.43, df=1, p=0.00025 [controlling for APOE ε4 alleles: $\chi2$=4.57, df=1, p=0.033]).

57	Polygenic risk of Alzheimer disease is associated with early- and late-life processes	Elizabeth C Mormino, Reisa A Sperling, Avram J Holmes, Randy L Buckner, Philip L De Jager, Jordan W Smoller, Mert R Sabuncu	2016	USA	Predictive study	Clinically normal (CN=1322) participants, patients with mild cognitive impairment (MCI=1031), and patients with AD dementia (AD=166). **Method:** PET, MRI, Illumina Human610-Quad Bead Chip genotyping data, statistical analysis.	In participants without dementia, elevated PGRS was associated with worse memory (p=0.002) and smaller hippocampus (p=0.002) at baseline, as well as greater longitudinal cognitive decline (memory: p=0.0005, executive function: p=0.01) and clinical progression (p <0.00001). High PGRS was associated with AD-like levels of β-amyloid burden as measured with florbetapir PET (p=0.03) but did not reach statistical significance for CSF β-amyloid (p=0.11). In the younger group, higher PGRS was associated with smaller hippocampus volume (p=0.05). This pattern was evident when examining a PGRS that included many loci below the genome-wide association study (GWAS)–level significance threshold (16,123 single nucleotide polymorphisms).
58	Genetic Risk as a Marker of Amyloid-β and Tau Burden in Cerebrospinal Fluid	Nicola Voyle, Hamel Patel, Amos Folarin, Stephen Newhouse, Caroline Johnston, Pieter Jelle Visser, Richard J.B. Dobson, Steven J. Kiddle	2017	UK, USA, Netherlands	Predictive study	This study uses data from ADNI 1 and the ADNI 2 and ADNI GO subgroups, henceforth referred to as ADNI 2. **Method:** genotyped on Illumina HumanOmniExpressExome-8v1.2 BeadChip, studying Aβ and tau markers in CSF, statistical analysis.	In EDAR and DESCRIPA test data, inclusion of a case/control PGRS was no more predictive of Aβ, and a combined Aβ and tau endpoint than the basic models (accuracies of 66.0%, and 73.3% respectively). The tau model showed a slight increase in accuracy compared to basic models (59.6%). ADNI 2 test data also showed a slight increase in accuracy for the Aβ model when compared to the basic models (61.4%).
59	Dissociable influences of APOE ε4 and polygenic risk of AD dementia on amyloid and cognition	Tian Ge, Mert R. Sabuncu, Jordan W. Smoller, MD, Reisa A. Sperling, Elizabeth C. Mormino	2018	USA	Predictive study	702 ADNI-GO/2 participants (221 CNs, 367 with mild cognitive impairment [MCI] and 114 with AD dementia. **Method:** Aβ imaging, neuropsychological assessments, structural MRI, genetic data processing, calculation of polygenic risk score, statistical analysis.	In general, PRS was greater in the Aβ+ compared to the Aβ− group (2-sample t-test p <0.05 across diagnosis and PRS thresholds). However, the associations between PRS and base-line Aβ were weak, regardless of whether Aβ is treated as a continuous variable or as a binary variable. For instance, the most significant relationship between PRS and continuous Aβ explained only 0.75% of the Aβ variation (p=0.013). As expected, APOE e4 was strongly associated with elevated continuous Aβ at baseline, explaining 17.94% of the variance.
60	Polygenic hazard score: an enrichment marker for Alzheimer's associated amyloid and tau deposition	Chin Hong Tan, Chun Chieh Fan, Elizabeth C Mormino, Leo P Sugrue, Iris J Broce, Christopher P Hess, William P Dillon, Luke W Bonham, Jennifer S Yokoyama, Celeste M Karch, James B Brewer, Gil D Rabinovici, Bruce L Miller, Gerard D Schellenberg, Karolina Kauppi, Howard A Feldman, Dominic Holland, Linda K McEvoy, Bradley T Hyman, David A Bennett, Ole A Andreassen, Anders M Dale, Rahul S Desikan	2018	USA	Predictive study	We restricted analyses to CN individuals (n=347, baseline age range=59.7–90.1) and patients diagnosed with MCI (n=599, baseline age range=54.4–91.4), who had both genetics and CSF or PET biomarkers (CSF Aβ1–42, CSF total tau, or PET ^{18}F-AV45) data at baseline. **Method:** polygenic hazard score (PHS), statistical analysis.	In CN and MCI individuals, we found that amyloid and total tau positivity systematically varies as a function of PHS. For individuals in greater than the 50th percentile PHS, the positive predictive value for amyloid approached 100%; for individuals in less than the 25th percentile PHS, the negative predictive value for total tau approached 85%. High PHS individuals with amyloid and tau pathology showed the steepest longitudinal cognitive and clinical decline, even among APOE ε4 noncarriers. Among the CN subgroup, we similarly found that PHS was strongly associated with amyloid positivity and the combination of PHS and biomarker status significantly predicted longitudinal clinical progression. In the ROSMAP cohort, higher PHS was associated with higher post-mortem amyloid load and neurofibrillary tangles, even in APOE ε4 noncarriers.

61	Machine learning approaches to mild cognitive impairment detection based on structural MRI data and morphometric features	Anna Y Morozova, Yana A Zorkina, Olga Abramova, Olga V Ukhova	2023	Russia	Systematic review	Analysis of published data on specific genetic markers of AD in plasma.	Plasma biomarkers, including neurotrophic factors, pro-inflammatory cytokines, and oxidative stress markers, are persistently elevated in a significant proportion of patients with cognitive dysfunction and thus may determine symptoms. In addition, these plasma markers certainly depend on the DNA sequences of genes and transcription mechanisms. Moreover, environmental factors such as lifestyle, diet, unhealthy habits, and stress levels regulate gene transcription via epigenetic mechanisms of DNA and histone methylation and acetylation. The genetic basis of mental disorders is complex and still poorly understood. There is limited data on neuroinflammatory processes in mental disorders associated with cognitive impairment and how they contribute to their development, progression, and persistence.