

# Brain imaging and Biomarkers

Read about DDRC's research projects on brain imaging and biomarkers.

## Development and evaluation of data-driven diagnostic approaches (PredictND)

PredictND is an international multicenter study performed in the period 2014 to 2018. The aim was to increase the diagnostic accuracy following dementia evaluation in patients with cognitive dysfunction.

The project developed and evaluated a diagnostic software tool that could help clinicians evaluating all available data in the diagnostic process. The PredictND project has since continued as a research collaboration between the four European memory clinics involved and data experts from Finland.

The project was financed by the European 7th Framework Program and included VTT Technical Research Centre of Finland, GE Healthcare, Imperial College London, The University of Eastern Finland, Danish Dementia Research Center, Rigshospitalet, Amsterdam University Medical Centers, The University of Perugia, Alzheimer Europe.

### Contact

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### Publications

[Gjerum L, Frederiksen KS, Henriksen OM et al. Evaluating 2-\[\(18\)F\]FDG-PET in differential diagnosis of dementia using a data-driven decision model. \*NeuroImage Clinical\*. 2020;27:102267.](#)

[Rhodius-Meester HFM, van Maurik IS, Koikkalainen J et al. Selection of memory clinic patients for CSF biomarker assessment can be restricted to a quarter of cases by using computerized decision support, without compromising diagnostic accuracy. \*PLoS one\* 2020;15\(1\):e0226784.](#)

[Bruun M, Frederiksen KS, Rhodius-Meester HFM, et al. Impact of a Clinical Decision Support Tool on Dementia Diagnostics in Memory Clinics: The PredictND Validation Study. \*Current Alzheimer research\*. 2019;16\(2\):91-101.](#)

[Bruun M, Koikkalainen J, Rhodius-Meester HFM, et al. Detecting frontotemporal dementia syndromes using MRI biomarkers. \*NeuroImage Clinical\*. 2019;22:101711.](#)

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[Koikkalainen JR, Rhodius-Meester HFM, Frederiksen KS et al. Automatically computed rating scales from MRI for patients with cognitive disorders. \*European radiology\*. 2019;29\(9\):4937-4947.](#)

[Bruun M, Rhodius-Meester HFM, Koikkalainen J, et al. Evaluating combinations of diagnostic tests to discriminate different dementia types. \*Alzheimer's & dementia \(Amsterdam, Netherlands\)\*. 2018;10: 509-518.](#)

[Tolonen A, Rhodius-Meester HFM, Bruun M et al. Data-Driven Differential Diagnosis of Dementia Using Multiclass Disease State Index Classifier. \*Frontiers in aging neuroscience\* 2018;10:111.](#)

[Oliveira F, Leuzvy A, Castelhamo J et al. Data driven diagnostic classification in Alzheimer's disease based on different reference regions for normalization of PIB-PET images and correlation with CSF concentrations of A \$\beta\$  species. \*NeuroImage Clinical\* 2018;20:603-610.](#)

[Tong T, Ledig C, Guerrero R et al. Five-class differential diagnostics of neurodegenerative diseases using random undersampling boosting. \*NeuroImage Clinical\* 2017;15:613-624.](#)

## Diagnosis and prognosis in Normal Pressure Hydrocephalus (NPH)

In NPH, decreased flow and absorption of brain fluid leads to cognitive dysfunction, gait and balance problems and urinary incontinence. All patients referred on suspicion of NPH are evaluated by a standardized program and patients that are operated with ventriculo-peritoneal shunting are followed up in collaboration with the Neurosurgical department. New imaging tools, supplementary investigations and biomarkers are investigated for their ability to increase diagnostic and prognostic accuracy.

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#### Publications

[Thorlacius-Ussing G, Frederiksen KS, Holst AV, et al. \[Diagnosis and treatment of normal pressure hydrocephalus\]. Ugeskr Laeger. 2020;182\(19\):V12190710.](#)

[Manniche C, Simonsen AH, Hasselbalch SG et al. Cerebrospinal Fluid Biomarkers to Differentiate Idiopathic Normal Pressure Hydrocephalus from Subcortical Ischemic Vascular Disease. J Alzheimers Dis. 2020;75\(3\):937-947.](#)

[Manniche C, Hejl AM, Hasselbalch SG, Simonsen AH. Cerebrospinal Fluid Biomarkers in Idiopathic Normal Pressure Hydrocephalus versus Alzheimer's Disease and Subcortical Ischemic Vascular Disease: A Systematic Review. J Alzheimers Dis. 2019;68\(1\):267-279. doi: 10.3233/JAD-180816. PMID: 30741681.](#)

## BIOMARKAPD

The aim of the BIOMARKAPD project was to standardize all aspects of the measurement of AD and PD biomarkers across Europe. I. e. how to collect samples, how to perform the measurements and how to interpret the results.

The project also created a virtual biobank with samples from well characterised AD and PD patients, including patients in very early disease stages, as well as neurologically healthy controls. These samples could then be used to develop new and better assays and to test new and better biomarker candidates.

Furthermore, the project partners also developed certified reference materials that can be used to harmonise assays that are used to measure the different biomarkers.

The project was financed through the EU JPND (EU Joint Programme – Neurodegenerative Disease Research) and Innovation Fund Denmark. BIOMARKAPD was a collaboration between fifteen EU member countries together with Turkey, Switzerland and Canada.

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#### Publications

[Oliveira F, Leuzy A, Castelhano J, et al. Data driven diagnostic classification in Alzheimer's disease based on different reference regions for normalization of PIB-PET images and correlation with CSF concentrations of A \$\beta\$  species. Neuroimage Clin. 2018;19\(20\):603-610.](#)

[Leuzy A, Chiotis K, Hasselbalch SG et al. Pittsburgh compound B imaging and cerebrospinal fluid amyloid- \$\beta\$  in a multicentre European memory clinic study. Brain. 2016;139\(Pt 9\):2540-53.](#)

[Zwan MD, Rinne JO, Hasselbalch SG et al. Use of amyloid-PET to determine cutpoints for CSF markers: A multicenter study. Neurology. 2016;86\(1\):50-8.](#)

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[Simonsen AH, Herukka SK, Andreasen N et al. Recommendations for CSF AD biomarkers in the diagnostic evaluation of dementia. Alzheimers Dement. 2017;13\(3\):274-84.](#)

[Herukka SK, Simonsen AH, Andreasen N et al. Recommendations for cerebrospinal fluid Alzheimer's disease biomarkers in the diagnostic evaluation of mild cognitive impairment. Alzheimers Dement. 2017;13\(3\):285-95.](#)

[Travassos M, Santana J, Baldeiras I et al. Does Caffeine Consumption Modify Cerebrospinal Fluid Amyloid-beta Levels in Patients with Alzheimer's Disease? J Alzheimers Dis. 2015;47\(4\):1069-78.](#)

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[del Campo M, Mollenhauer B, Bertolotto A et al. Recommendations to standardize preanalytical confounding factors in Alzheimer's and Parkinson's disease cerebrospinal fluid biomarkers: an update. Biomark Med. 2012;6\(4\):419-30.](#)

## Mitochondrial health in AD (MITO-AD)

Throughout life, the brain is exposed to significant stress, among these are aging processes, decreasing brain metabolism, and oxidative stress. This project will investigate the importance of aging processes for the development of Alzheimer's disease with a focus on the reduced energy metabolism in the brain.

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## Biomarkers for Alzheimer's Disease and other Neurodegenerative Diseases in Saliva

There is a need for an early, inexpensive and noninvasive diagnostic biomarker for AD. A saliva sample could be a valid alternative to cerebrospinal fluid or blood, and a valid and reproducible saliva biomarker would therefore be preferable over other present biomarkers.

The project was coordinated by Helena Sophia Gleeurup, Anja Hviid Simonsen and Steen Gregers Hasselbalch at the DDRC, and its primary partners are the Regional Dementia Research Centre, Zealand University Hospital, Denmark and the Sahlgrenska Academy at the University of Gothenburg. The collaboration is still ongoing and continues to publish papers from the project.

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#### Publications

[Gleeurup HS, Hasselbalch SG, Simonsen AH. Biomarkers for Alzheimer's Disease in Saliva: A Systematic Review. Dis Markers. 2019;2019:4761054.](#)

[Gleeurup HS, Jensen CS, Høgh P, Hasselbalch SG, Simonsen AH. Lactoferrin in cerebrospinal fluid and saliva is not a diagnostic biomarker for Alzheimer's disease in a mixed memory clinic population. 2021;67:103361.](#)

[Gleeurup HS, Sanna F, Høgh P, Simrén J, Blennow K, Zetterberg H, Hasselbalch SG, Ashton NJ, Simonsen AH. Saliva Neurofilament Light Chain Is Not a Diagnostic Biomarker for Neurodegeneration in a Mixed Memory Clinic Population. 2021;13:659898.](#)

## Biomarkers for idiopathic normal pressure hydrocephalus

Idiopathic normal pressure hydrocephalus (iNPH) is one of the few potentially reversible causes of dementia. However, the diagnostic workup can be challenging.

The purpose of this study is to investigate the molecular profile of patients with iNPH. The aim is three-fold: First, to find biomarkers that can aid in the diagnosis of iNPH, second, to find biomarkers that can aid in predicting whether a patient will benefit from a drainage operation, and third, to identify possible pharmacological targets for the treatment of hydrocephalus.

This project is done in collaboration with the department of Neurosurgery, Rigshospitalet and the department of Neuroscience, University of Copenhagen.

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#### Publications

[Manniche C, Hejl AM, Hasselbalch SG, Simonsen AH. Cerebrospinal Fluid Biomarkers in Idiopathic Normal Pressure Hydrocephalus versus Alzheimer's Disease and Subcortical Ischemic Vascular Disease: A Systematic Review. J Alzheimers Dis. 2019;68\(1\):267-79.](#)

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[Oembo EK, Steffensen AB, Gredal H, Poulsen HH, Rostgaard N, Rasmussen CH, Møller-Nissen M, Simonsen AH, Hasselbalch SG, Juhler M, MacAulay N. Fluids Barriers CNS. 2022 Jun 27;19\(1\):52. doi: 10.1186/s12987-022-00349-5. PMID: 35761330.](#)

[Oembo EK, Steffensen AB, Razzaghi Khamesi P, Toft-Bertelsen TL, Barbuskaite D, Vilhardt F, Gerkau NJ, Tritsaris K, Simonsen AH, Lolansen SD, Andreassen SN, Hasselbalch SG, Zeuthen T, Rose CR, Kurtcuoglu V, MacAulay N. Fluids Barriers CNS. 2022 Aug 29;19\(1\):65. doi: 10.1186/s12987-022-00358-4. PMID: 36038945.](#)

[Lolansen SD, Rostgaard N, Andreassen SN, Simonsen AH, Juhler M, Hasselbalch SG, MacAulay N. Fluids Barriers CNS. 2021 Dec 4;18\(1\):54. doi: 10.1186/s12987-021-00289-6. PMID: 34863228.](#)

## Biomarkers for Bipolar Disease, a longitudinal study

The aim of this ongoing study is to investigate state-specific changes in cerebrospinal fluid markers in outpatients diagnosed with Bipolar Disease compared to healthy individuals during a one-year prospective, longitudinal follow-up study.

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#### Publications

[Knorr U, Simonsen AH, Zetterberg H, et al. Biomarkers in cerebrospinal fluid of patients with bipolar disorder versus healthy individuals: A systematic review. Eur Neuropsychopharmacol. 2018;28\(7\):783-794.](#)

[Knorr U, Simonsen AH, Roos P, et al. Cerebrospinal fluid oxidative stress metabolites in patients with bipolar disorder and healthy controls: a longitudinal case-control study. Transl Psychiatry. 2019;9\(1\):325.](#)

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[Knorr U, Blom RA, Simonsen AH, Poulsen HE, Akhøj M, Forman J, Hasselbalch SG, Kessing LV. Nord J Psychiatry. 2021 Oct;75\(7\):532-537. doi: 10.1080/08039488.2021.1901987. Epub 2021 Mar 29. PMID: 33781161.](#)

[Miskowiak KW, Simonsen AH, Meyer M, Poulsen HE, Wilkan M, Forman J, Hasselbalch SG, Kessing LV, Knorr U. J Psychiatr Res. 2023 Jul;163:240-246. doi: 10.1016/j.jpsychires.2023.05.045. Epub 2023 May 17. PMID: 37244061.](#)

## Neuroimaging

Neuroimaging of brain structure is essential in dementia evaluation, and functional imaging can increase the diagnostic accuracy. Imaging of glucose metabolism using Fluoro-deoxyglucose positron emission tomography (FDG-PET) is widely used, and the added diagnostic and prognostic value of FDG-PET is evaluated.

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#### Publications

[Gramkow MH, Gjerum L, Koikkalainen J, et al. Prognostic value of complementary biomarkers of neurodegeneration in a mixed memory clinic cohort. PeerJ. 2020; \(9\):e9498.](#)

[Gjerum L, Frederiksen KS, Henriksen OM, et al. A visual rating scale for cingulate island sign on 18F-FDG-PET to differentiate dementia with Lewy bodies and Alzheimer's disease. J Neurol Sci. 2020;410:116645.](#)

[Kaltoft NS, Mamer L, Larsen VA, et al. Hybrid FDG PET/MRI vs. FDG PET and CT in patients with suspected dementia – A comparison of diagnostic yield and propagated influence on clinical diagnosis and patient management. PLoS One. 2019;14\(5\):e0216409.](#)

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