EBOOK

Transforming dementia-related symptoms into a tangible diagnosis with AI and sophisticated MRI biomarkers

Combinostics

Increased need for accurate dementia diagnoses

More than 55 million people worldwide have been diagnosed with dementia, with approximately 10 million new cases annually,[1] which is likely to increase as the population ages. Of the three dementias of focus in this white paper, Alzheimer's disease (AD), is the most common cause, followed by frontotemporal dementia (FTD) and vascular dementia (VaD).[2,3] In the larger population, people with these dementias can experience considerable delays in receiving a diagnosis, are misdiagnosed, or remain undiagnosed.[4,5]

Multiple factors contribute to under- and misdiagnosis, including heterogeneous clinical presentations, similarities in symptoms between dementias as well as psychiatric or movement disorders, evolving clinical criteria, and imprecise diagnostic tools. Together, these can result in a lack of confidence in making a differential diagnosis in the clinical setting. However, an early and precise dementia diagnosis is essential to providing the best possible care for the underlying pathology,[6,7] managing symptoms with existing treatments, and advancing therapeutic research. The development of disease-modifying drugs is also driving the need for more accurate diagnoses.

To support clinicians with a confident diagnosis of dementias, artificial intelligence (AI) and machine learning (ML) technologies applied to brain MRIs have the potential to provide accurate probabilities of the most likely diagnosis, especially when the system incorporates imaging biomarkers that help identify the underlying disease etiology. The principles underlying this process and its application to specific case studies are discussed in this white paper.

The role of MRI in dementia diagnosis

The diagnosis of dementias has been transformed over the last 20 years, moving from complete reliance on clinical assessment based on relatively subjective criteria to the use of biomarkers, including imaging and molecular biomarkers. Neuroimaging, such as MRI and PET, allow visualization of atrophy and vascular pathology as well as a greater understanding of genetic and molecular etiology. This shift to more objective measures has helped overcome the low sensitivity and specificity of clinical diagnostic criteria, which are only able to reliably detect the presence of cognitive impairment.[8] These clinical assessments are typically not able to accurately diagnose the underlying cause of poor cognition, contributing to under- and misdiagnosis.[5]

Visual rating scales, used extensively in some regions, add a semi-quantitative element to dementia diagnosis. These include the Fazekas scale to assess white matter hyperintensities (WMHs),[9] Pasquier scale or global cortical atrophy (GCA) scale,[10] Koedam scale to assess posterior cortical atrophy,[11] and Scheltens' scale to assess medial temporal lobe atrophy (MTA score).[12] However, although these visual scales can help reduce inter-rater variability,[13] they still have a subjective qualitative element, rely on prior experience of the reader, lack specificity,[14] and can have ceiling effects.[15] Using a combination of rating scales can improve diagnostic accuracy,[13] especially when there is a need to distinguish between dementia subtypes that have the same brain regions impacted, but is of limited practical use given that completion of rating scales is already considered too time-intensive for many institutes.[16]

Imaging biomarkers from MRI provide valuable information for differential diagnosis of dementias. As we understand more about how disease-related mechanisms manifest as volumetric differences in key brain structures (e.g., hippocampus, ventricles) and lesions, image analyses to detect and quantify these differences have become increasingly important.[13] With MRI, radiologists and clinicians can detect the distinguishing patterns of neurodegeneration such as mediotemporal (including the hippocampus) atrophy in typical AD, atrophy focused in the frontal and temporal lobes in FTD, and WMHs in VaD. Visual methods of imaging quantification were initially used to only exclude easily identifiable causes of cognitive impairment, such as tumors or hemorrhages. Today, imaging quantification is increasingly being used to analyze atrophy and lesion patterns, with the aim of identifying the underlying pathology.

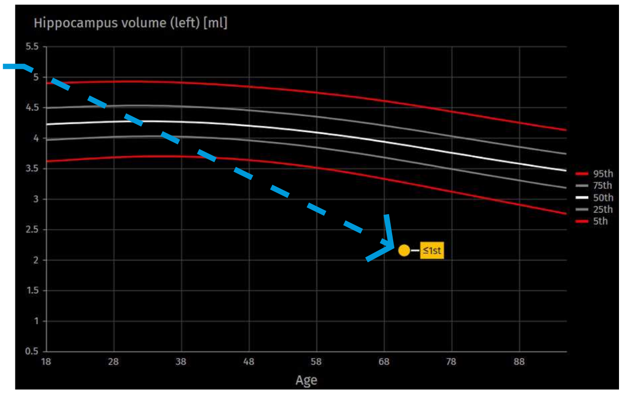
Automated MRI quantification for greater objectivity

Automated imaging quantification using AI technology can improve the objectivity and consistency of image interpretation, including analysis of atrophy patterns, even for less-experienced readers. These methods are based on automated segmentations, or divisions, of the brain to provide region-specific measurements that can be compared with normative populations using AI algorithms to place the volumes in context: are the volumes normal or abnormal for the person's age, gender, and head size/intracranial volume?

In addition to volumes, AI algorithms can characterize images in many other ways, automatically computing visual rating scores, adding objectivity to an otherwise subjective process. Compared with manual visual reads, automated quantification has resulted in earlier detection of abnormalities[15] and greater differentiation.[18]

Although image quantification results are typically compared with values from healthy controls, clinicians are interested in the underlying disease. Only comparing with a cognitively normal data set limits the accuracy of differential diagnoses and enables only the identification of a deviation from normal cognition.

For example, this patient's left hippocampal volume (the yellow dot) falls below the 1st percentile, when compared with people of the same age with normal cognition. Although it is clear that the patient's value is atypical, hippocampal atrophy can be present in several conditions including AD and FTD, making a diagnosis challenging. This is even more challenging because the percentile curves are for normal cognition, not for AD or FTD, and it is unknown if the patient's value corresponds with the typical values for AD or FTD. Therefore, a clinician would be challenged to determine a confident diagnosis, and additional information is needed.



Taking automated MRI quantification one step further

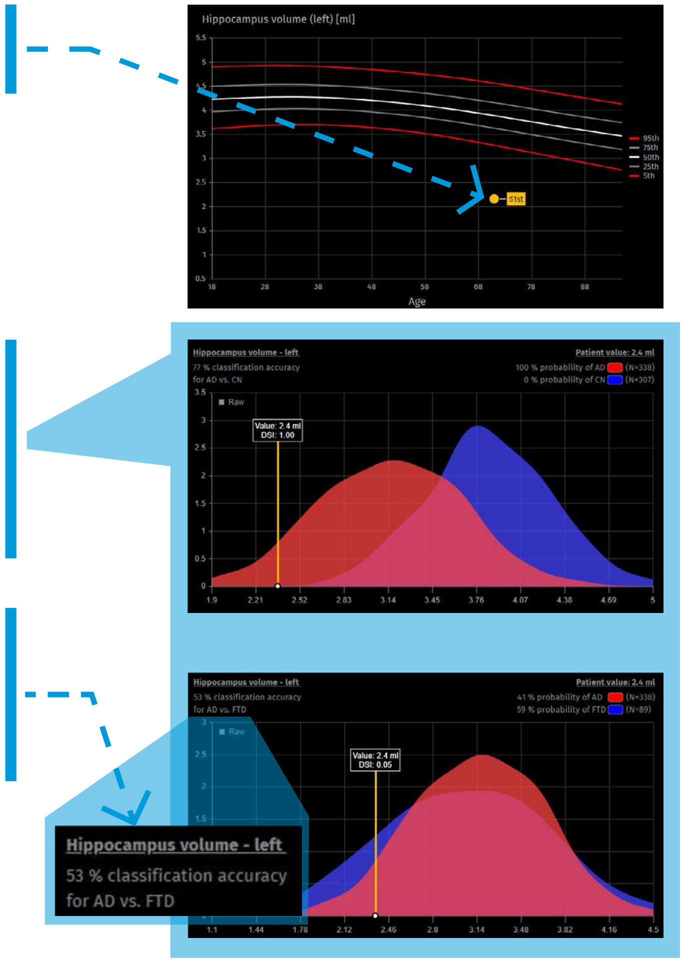
To distinguish between dementias based on MRI, it is necessary to compare a patient's MRI quantitative values against those of patients previously diagnosed with a specific dementia, such as AD, FTD, or VaD, as well as against people with normal cognition.

Using AI technology on a data set of previously diagnosed patients, disease-specific imaging biomarkers can be derived and used to create a unique imaging signature for each disease (AD, FTD, VaD, normal cognition). Imaging from new patients is compared against that signature.

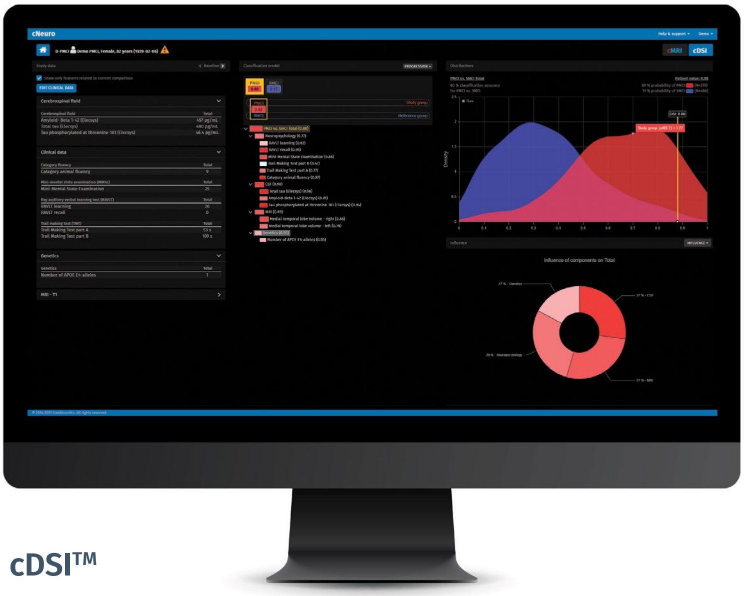
For example, the Combinostics cMRI™ application automatically computes the aforementioned visual rating scales, resulting in the following imaging biomarkers:

- **Hippocampal atrophy/MTA score:** captures the pattern of atrophy in the temporal lobe
- **Cortical atrophy/GCA score:** measures the global distribution of gray matter
- **Anterior vs posterior score:** compares atrophy patterns between the anterior and posterior regions of the brain, which is useful to differentiate FTD from AD
- **WMH volume/Fazekas score**

For the patient with a left hippocampal volume less than the 1st percentile, more information was needed to make a diagnosis. The Combinostics cDSI™ application uses a proprietary machine-learning method to compare all the patient's values with those from different diagnostic groups. The application provides easy-to-understand visualizations of these comparisons, making it easy to see the level of similarity with specific diagnoses.



The application also provides an estimate of how accurate the classification is for that patient and can indicate whether additional information is needed for diagnosis. For this patient, although effective for AD vs normal cognition, left hippocampal volume is not a good differentiator between FTD and AD. Therefore, more information, specifically additional imaging biomarkers, is still needed to confidently diagnose this patient.

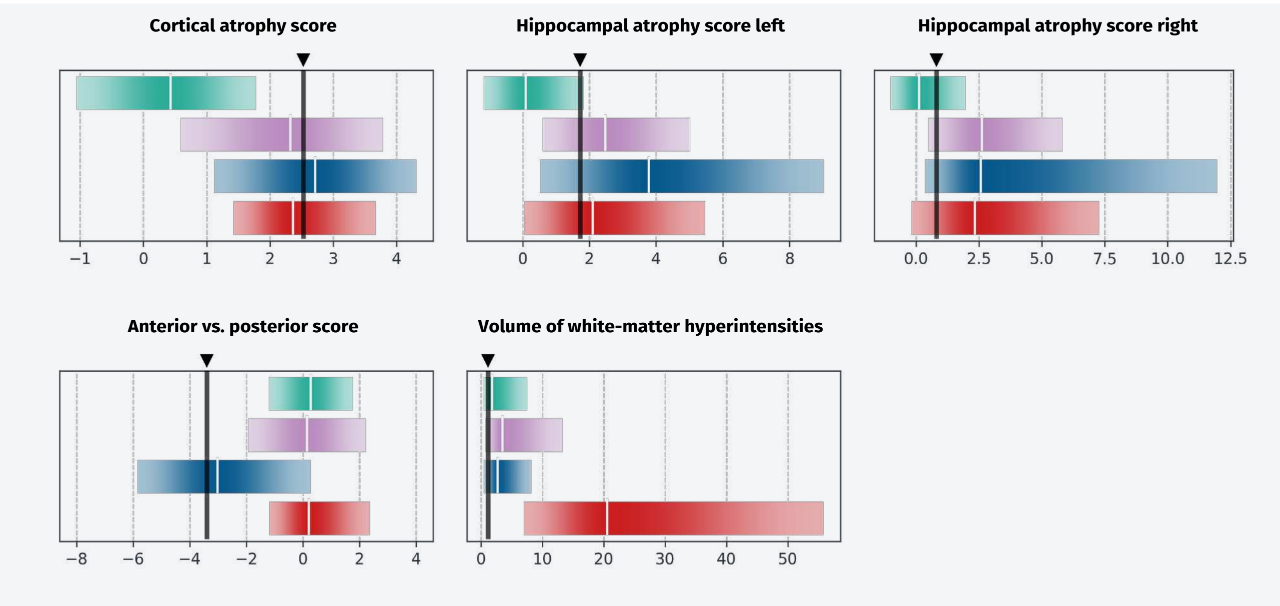


cDSI™

For a further step, the cDSI application aggregates all the imaging biomarkers and and systematically combines them using an ML method. The ML method compares the similarities of the patient's values with the four diagnostic groups and takes into account the age-dependent prevalence of each diagnosis group to determine the probability of each diagnosis for that specific patient.

Using this information, cDSI generates a report that provides these probabilities for each diagnosis. With this report, clinicians can easily visualize where the patient falls within each distribution of atrophy and has a quick reference for the most likely diagnosis.

For example, the colored bars for each diagnostic group represent 80% of the patients, and the white line in the middle of each box shows the median value. The vertical black line shows the patient's value.



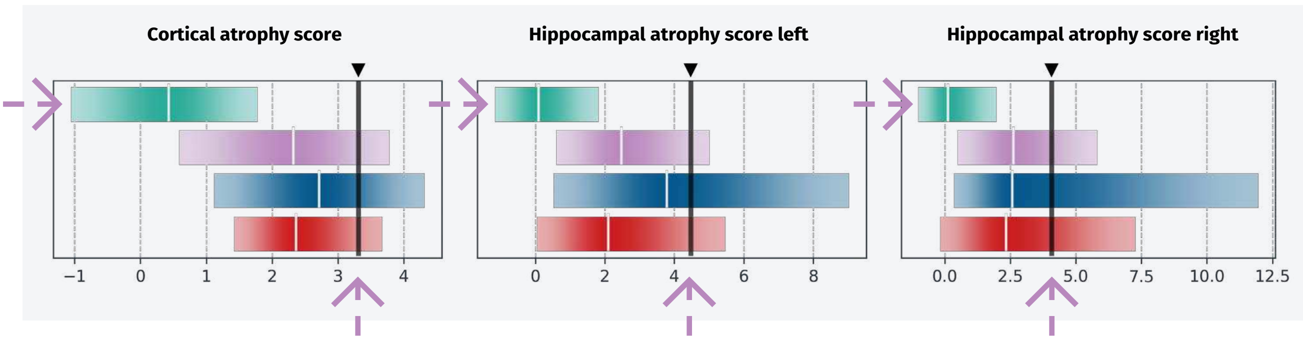
Case studies: the report's true diagnostic value

These four case studies demonstrate how the imaging biomarkers, compared against the reference database in our cDSI application, provide the probability for each of the potential four diagnoses (AD, FTD, VaD, or normal cognition) for each patient, helping to improve the accuracy of the dementia diagnosis. When presented in the visual report format, this information also increases clinician confidence in the diagnosis.

Case 1: 70-year-old male memory clinic patient

A 70-year-old man with a 4-year history of repetitiveness and memory loss was referred to a memory clinic. Neurocognitive assessment revealed a Mini Mental State Examination (MMSE) score of 23 and Rey Auditory Verbal Learning Test (RAVLT; which assesses verbal learning and memory) scores of 21 for word learning and 0 for delayed recall.

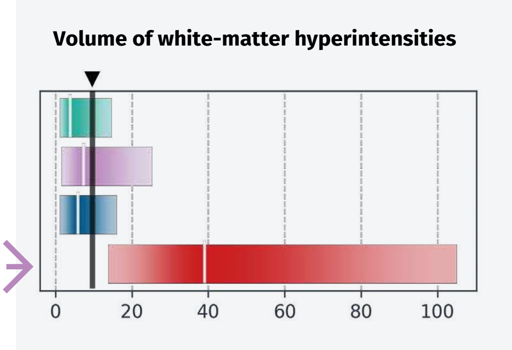
Upon evaluation of the MRI biomarker patterns on the report, the patient's values for cortical atrophy and both left and right hippocampal atrophy deviated from normal.



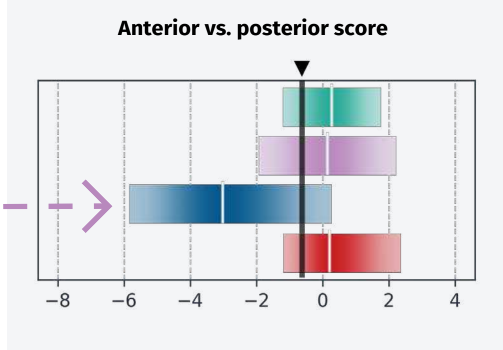
The cMRI analysis revealed generalized cortical atrophy with a cortical atrophy score of 3.3 as well as clear evidence of elevated bilateral hippocampal atrophy with a hippocampal atrophy score (L/R) of 4.5/4.1.

Cognitively normal (CN) Alzheimer's disease (AD) Frontotemporal dementia (FTD) Vascular dementia (VaD) ▼ Patient's value

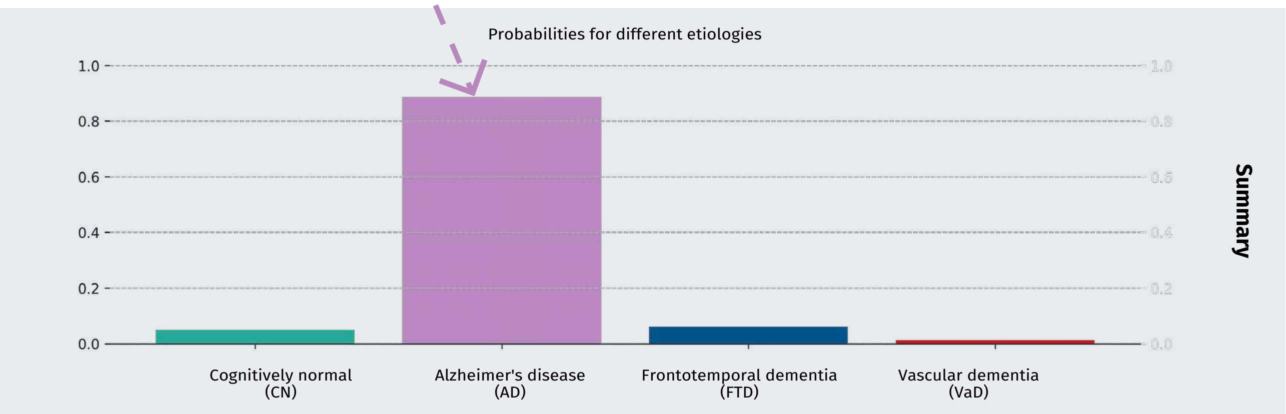
Although WMH was present, the volumes fell within the normal range for the patient's age, supporting a diagnosis of AD. The WMH volume also indicated that VaD is not a suitable diagnosis because his value did not intersect with the reference range.



FTD was excluded based on the patient's anterior vs. posterior score: the more negative the anterior vs. posterior score, the stronger the frontotemporal atrophy pattern. This patient's score was closer to zero, making FTD unlikely and further supporting AD as the cause.



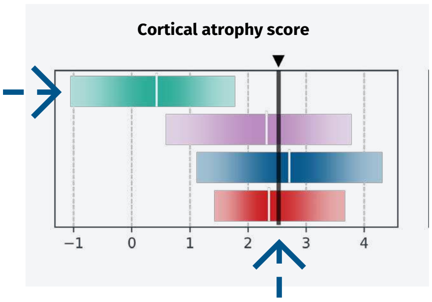
The most probable diagnosis of AD indicated by the application was also later confirmed with CSF.



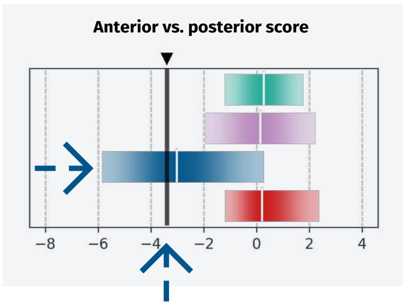
Cognitively normal (CN) Alzheimer's disease (AD) Frontotemporal dementia (FTD) Vascular dementia (VaD) ▼ Patient's value

Case 2: 64-year-old female memory clinic patient

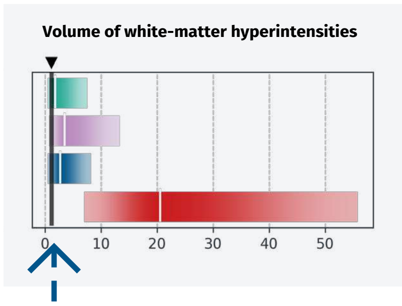
A 64-year-old woman was referred to a memory clinic with some neuropsychiatric issues and minor memory loss. Although she was initially diagnosed with AD, she was later found to be amyloid-negative. Upon presentation, she had an MMSE score of 24 and RAVLT scores of 26 for word learning and 4 for delayed recall.



Some degree of cortical atrophy was present (cortical atrophy score = 2.52).

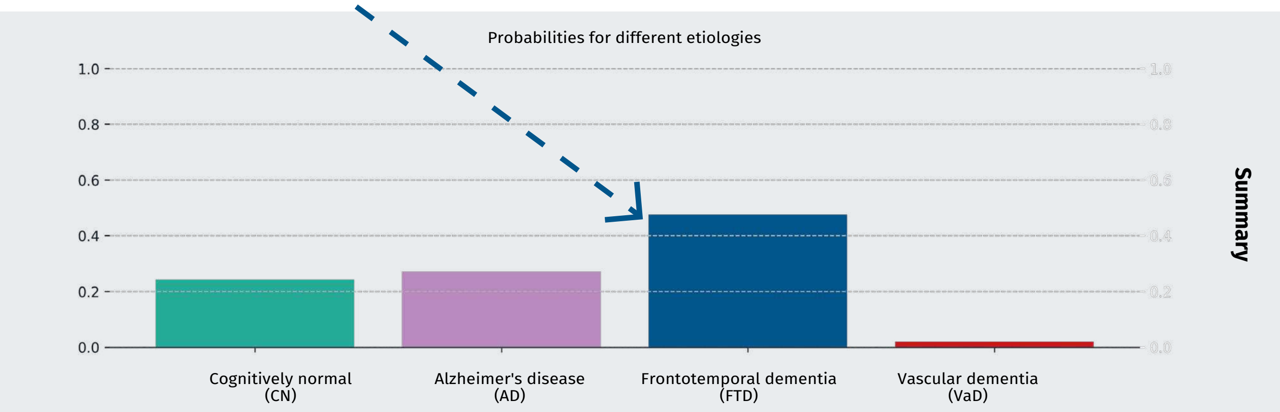


The anterior vs posterior score (-3.4) indicated a frontotemporal atrophy pattern.



There were very few WMHs.

Considering the patient's age and other clinical findings, combined with MRI, a diagnosis of FTD was supported.

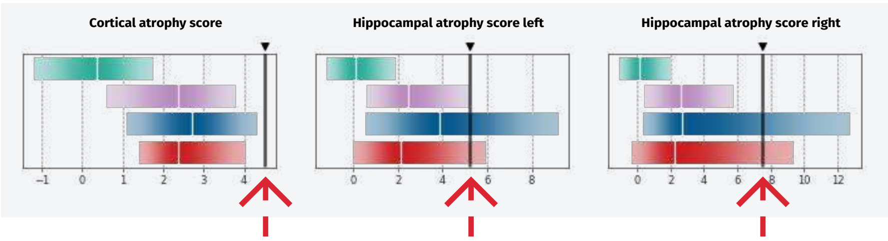


Cognitively normal (CN) Alzheimer's disease (AD) Frontotemporal dementia (FTD) Vascular dementia (VaD) ▼ Patient's value

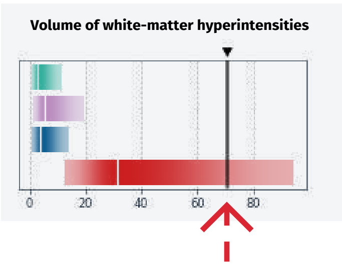
Case 3:
68-year-old male memory clinic patient

A 68-year-old male patient presented to a memory clinic with gradual and progressive cognitive impairment involving cognitive domains of memory, executive function, and mood. His MMSE score was 24, and his RAVLT scores for word learning and delayed recall were 10 and 1, respectively.

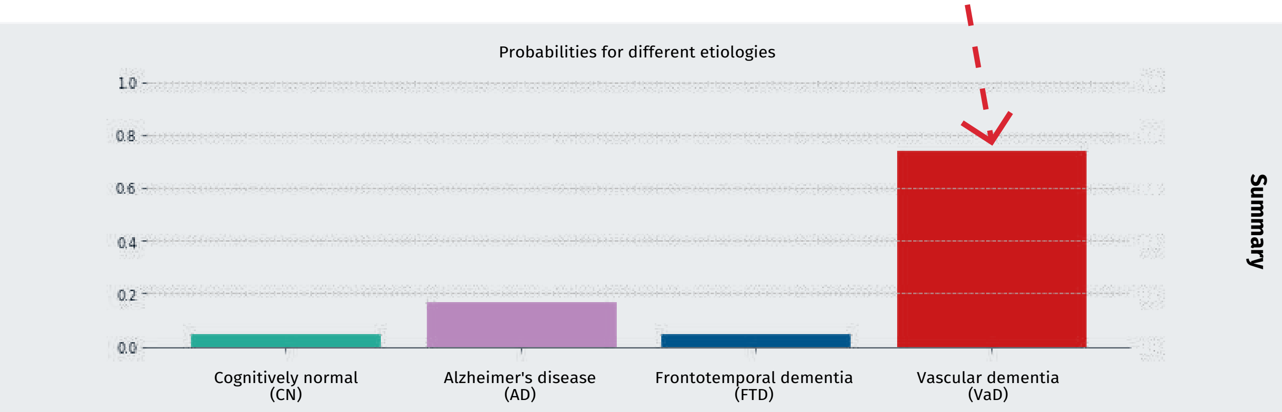
The MRI biomarker patterns showed increased atrophy in the cortical regions as well as both left and right hippocampi.



The increased WMH volume is suggestive of VaD.



The biomarker patterns for this case indicated a diagnosis of VaD.

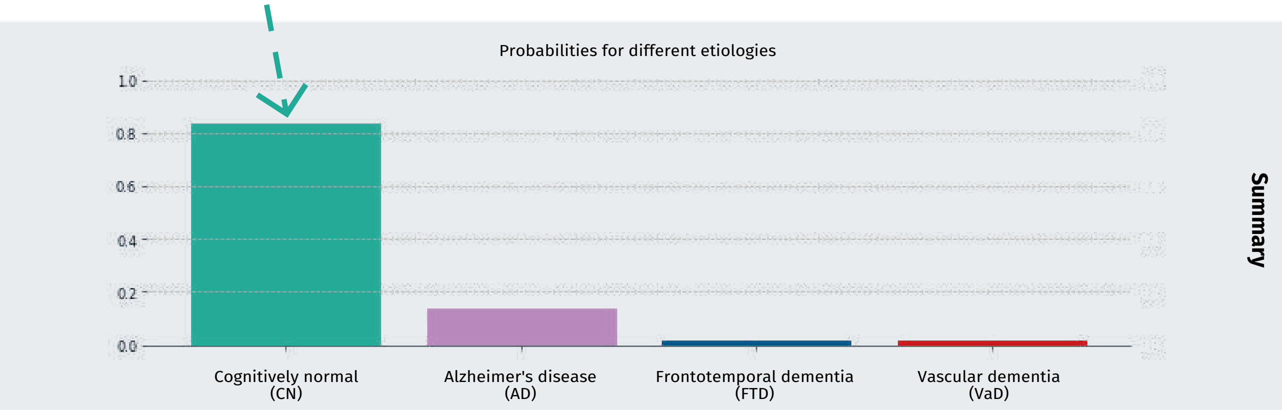


Cognitively normal (CN) Alzheimer's disease (AD) Frontotemporal dementia (FTD) Vascular dementia (VaD) Patient's value

Case 4:
82-year-old woman with memory concerns

Finally, an 82-year-old woman presented with some memory concerns. She scored 29 on the MMSE and underwent an MRI for further evaluation.

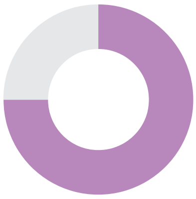
Using the imaging biomarkers, the probability of normal cognition for this woman was high.



Cognitively normal (CN) Alzheimer’s disease (AD) Frontotemporal dementia (FTD) Vascular dementia (VaD) ▼ Patient’s value

Highly accurate diagnoses based on MRI alone

The diagnoses and report from the cDSI application are based solely on MRI data from the Combinostics cMRI application, achieving 74% (US)/76% (EU) accuracy in separating AD, FTD, VaD, and normal cognition in approximately 770 patients,[19] which is much higher than that achieved with other methods. The remaining 24% of cases comprised mixed dementia diagnoses and pre-clinical disease, among others. For the 50% of patients with the highest probability of a correct diagnosis, the accuracy increased to 88% (US)/90% (EU).



74% (US)
76% (EU)

MRI only achieved 74% (US) and 76% (EU) accuracy in separating AD, FTD, VaD, and normal cognition.

Achieving greater accuracy with more patient data

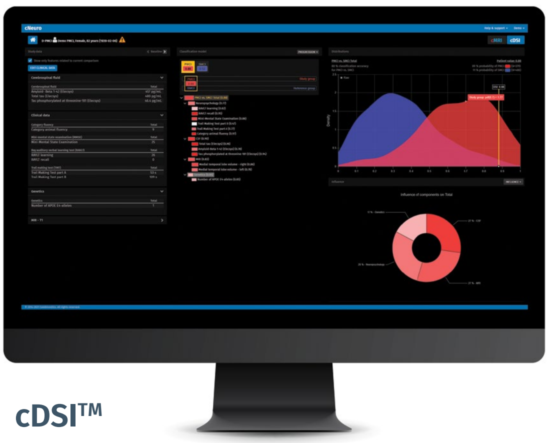
Advances in disease understanding obtained from cognitive, genetic, and other biomarkers have broadened the ability to pinpoint underlying abnormalities and provide a more comprehensive view of a patient's condition. In the Combinostics cDSI application, key patient data such as demographics and cognitive, neuropsychological, CSF, and genetic test results are combined with the imaging biomarkers to further differentiate between dementias, resulting in greater accuracy. Using the same memory clinic cohort as in the previous section, the diagnostic accuracy increased to 87% for all patients and 97% (US)/96% (EU) for the 50% of patients with the highest probability of a correct diagnosis.[19]

87%

Diagnostic accuracy increased to 87% for all patients.

97% (US)
96% (EU)

Diagnostic accuracy increased to 97% (US) and 96% (EU) for the 50% of patients with the highest probability.



cDSI™

Benefits for radiologists, clinicians, and patients

The importance of an accurate diagnosis is coming to the forefront with the development of disease-modifying drugs, and radiologists, clinicians, and patients alike benefit from the ability to use AI technology on MRI alone to generate disease-specific imaging biomarkers, thereby supporting a confident diagnosis. Radiologists have the opportunity to provide consistent, reproducible MRI quantifications to their referring clinicians, who are supported with accurate information that aids in decision-making about the best management pathway for their patients. For patients, MRI is less invasive than lumbar puncture for CSF testing, for example. For some patients, basic cognitive tests in addition to MRI biomarkers provide high diagnostic confidence, eliminating the need for additional testing. For other patients, the MRI biomarker assessment could guide the need for additional testing, for example by indicating that CSF biomarkers would be useful for diagnosis. In the end, getting patients access to effective treatments, faster, is the ultimate goal, and AI-derived MRI biomarkers can help achieve this end.

Combinostics

Combinostics' AI-powered cNeuro suite of products helps clinicians make a difference in the lives of patients with neurological disorders. By quantifying brain images and integrating patient data from multiple sources with insights from previous patients, the company's unique software tools provide radiologists and clinicians the support they need for confident, evidence-based diagnostic and management decisions. The company was founded in 2014 and is headquartered in Tampere, Finland. For more information, please visit combinostics.com.

References

1. Dementia. World Health Organization. Available at: https://www.who.int/news-room/fact-sheets/detail/dementia. Accessed on June 8, 2022.

2. van der Flier WM, Scheltens P. Amsterdam Dementia Cohort: Performing Research to Optimize Care. Journal of Alzheimer's Disease 2018;62(3):1091-1111.

3. Wolters FJ, Ikram MA. Epidemiology of Vascular Dementia: Nosology in a Time of Epiomics. Arteriosclerosis, Thrombosis, and Vascular Biology 2019;39:1542-1549. https://doi.org/10.1161/ATVBAHA.119.311908.

4. Leroy M, Bertoux M, Skrobala E, et al. Characteristics and progression of patients with frontotemporal dementia in a regional memory clinic network. Alz Res Therapy 2021;13:19. https://doi.org/10.1186/s13195-020-00753-9.

5. James BD, Power MC, Gianattasio KZ, et al. Characterizing clinical misdiagnosis of dementia using Medicare claims records linked to Rush Alzheimer's Disease Center (RADC) cohort study data. Alzheimer's & Dementia 2020;16(S10). https://doi.org/10.1002/alz.044880.

6. Boxer AL, Boeve BF. Frontotemporal dementia treatment: current symptomatic therapies and implications of recent genetic, biochemical, and neuroimaging studies. Alzheimer Dis Assoc Disord. 2007;13(4):S79–S87

7. Kerchner GA, Tartaglia MC, Boxer A. Abhorring the vacuum: use of Alzheimer's disease medications in frontotemporal dementia. Expert Rev Neurother. 2011;13(5):709–717. doi: 10.1586/ern.11.6.

8. Phung TK, Andersen BB, Kessing LV, et al. Diagnostic evaluation of dementia in the secondary health care sector. Dement Geriatr Cogn Disord 2009;27:534-542.

9. F Fazekas, JB Chawluk, A Alavi, et al. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. American Journal of Roentgenology 1987;149(2):351-356.

10. Pasquier F, Leys D, Weerts J, et al. Inter-and Intraobserver Reproducibility of Cerebral Atrophy Assessment on MRI Scans with Hemispheric Infarcts. Eur Neurol 1996;36:268-272. https://doi.org/10.1159/000117270.

11. Koedam EL, Lehmann M, van der Flier WM, et al. Visual assessment of posterior atrophy development of a MRI rating scale. Eur Radiol. 2011;21(12):2618-25. https://doi.org/10.1007/s00330-011-2205-4.

12. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry. 1992;55(10):967-972. doi: https://doi.org/10.1136/jnnp.55.10.967.

13. Harper L, Fumagalli GG, Barkhof F, et al. MRI visual rating scales in the diagnosis of dementia: evaluation in 184 post-mortem confirmed cases. Brain 2016;139(4):1211-1225. https://doi.org/10.1093/brain/aww005.

14. Barkhof F, Polvikoski TM, van Straaten ECW, et al. The significance of medial temporal lobe atrophy: A postmortem MRI study in the very old. Neurology 2007;69(15):1521-1527. https://doi.org/10.1212/01.wnl.0000277459.83543.99.

15. van Straaten EC, Fazekas F, Rostrup E, et al. Impact of white matter hyperintensities scoring method on correlations with clinical data: the LADIS study. Stroke 2006;37(3):836-840. https://doi.org/10.1161/01.STR.0000202585.26325.74.

16. Vernooij MW, Pizzini FB, Schmidt R, et al. Dementia imaging in clinical practice: a European-wide survey of 193 centres and conclusions by the ESNR working group. Neuroradiology 2019;61:633-642. https://doi.org/10.1007/s00234-019-02188-y.

17. Clerx L, van Rossum IA, Burns L, et al. Measurements of medial temporal lobe atrophy for prediction of Alzheimer's disease in subjects with mild cognitive impairment. Neurobiol Aging 2013;34(8):2003-13. https://doi.org/10.1016/j.neurobiolaging.

18. Koikkalainen JR, Rhodius-Meester HFM, Frederiksen KS, et al. Automatically computed rating scales from MRI for patients with cognitive disorders. Eur Radiol 2019;29:4937-4947. https://doi.org/10.1007/s00330-019-06067-1.

19. Koikkalainen J, Rhodius-Meester H, Tolonen A, et al. Differential diagnosis of neurodegenerative diseases using structural MRI data. Neuroimage Clin 2016;11:435-449. https://doi.org/10.1016/j.nicl.2016.02.019.

combinostics.com | contact@combinostics.com | +46 730 699 057
Combinostics Oy | Hatanpään valtatie 24 | 33100 Tampere, Finland |