**Request for Information**

Clinical Care Screening Solution

**Dear Roche Diagnostics Team:**

Cogstate is pleased to respond to a Request for Information regarding solutions for clinical care screening in Alzheimer’s Disease. In the following document, we describe how our team can support your needs via well-validated and extensively leveraged screening options.

Cogstate has a proven track record as leaders in cognitive measurement across clinical trials and healthcare. In Alzheimer’s Disease alone, we have supported 125+ industry-sponsored trials (across all phases), 100+ academic studies, and numerous registries and trial ready cohort initiatives (ADNI, AIBL, A4, AHEAD 3-45, DIAN, ATRI, etc.). Healthcare professionals worldwide have leveraged our digital tests as simple and scientifically valid measures to aid with rapid assessment of cognition with 77,000 unique patients having completed 144,000 assessments in total.

Cogstate tests have been validated extensively, demonstrating both scalability and validity across diverse populations, in both clinical and remote settings. Results from our tests demonstrate high sensitivity for detecting cognitive impairment associated with MCI and AD dementia versus healthy controls.

**Regarding this request for clinical care screening, we propose the following two-step solution for consideration:**

* Initial screening via the Cogstate Cognigram™, FDA Class II Exempt Digital Medical Device. To keep the screening as short as possible, we propose to use the 2 tests that assess memory, bundled as the Cognigram Memory Assessment which comprises the Cogstate One Card Learning (OCL) and One Back (ONB) tests.
* Participants who screen positive for impairment during the Cognigram testing would then receive confirmatory testing for memory impairment using the Cogstate International Shopping List Test.

Cogstate Cognigram Memory Assessment™ (OCL and ONB tests) is the commercially available product that we have provided detailed answers for in the below RFI. Supplemental materials have been provided to support the use of the ISLT.

**Cogstate and Eisai Co. Ltd. Work in Healthcare**

In August 2019, Cogstate and pharmaceutical company Eisai Co. Ltd. (Eisai) entered an exclusive license enabling Eisai to distribute Cogstate digital cognitive assessment technologies in healthcare markets in Japan – the “Japan Agreement”.

In October 2020, Cogstate and Eisai entered into a second exclusive licensing agreement enabling Eisai to distribute Cogstate digital cognitive assessment technologies in Healthcare markets in all other geographies, excepting Japan – the “Global Agreement”.

In April 2024, Cogstate and Eisai agreed to amend the Global Agreement, whereby Cogstate reacquired global rights to technology that had been previously licensed to Eisai. Under the amended Global Agreement, Eisai was granted a non-exclusive license to distribute commercials products (all based on the Cogstate Brief Battery) in certain distinct geographies.

Today, Eisai holds the following licenses:

* Exclusive license of Cogstate digital cognitive testing technologies in Japan, excluding use in clinical trials;
* Non-exclusive license to distribute Cognigram in the USA; and
* Non-exclusive license to distribute CogMate (a direct-to-consumer product based on the Cogstate Brief Battery) in the following geographies: Taiwan, South Korea, Thailand, India, Malaysia, Philippines, and Vietnam

The amended agreement allows Cogstate greater freedom to market directly, or via other partners, Cogstate technology for use in community and healthcare environments. The Eisai non-exclusive licenses apply only to the defined products (Cognigram in the USA and CogMate in the Asian territories) and does not apply to other digital assessments (such as the smartphone-based memory assessment application, Lila, and the test on which Lila is based, the International Shopping List Test).

Through this collaboration, Cogstate tests (including those recommended below) have been leveraged by healthcare professionals to screen for cognitive impairment in patients exhibiting memory related challenges.

We thank you for your consideration and look forward to answering additional questions.

The Cogstate Team

1. **Name of the Product**

**Cognigram™** is a simple and scientifically valid digital test system intended to aid healthcare professionals with rapid assessment of cognition in individuals aged 6 – 99 years old. Cognigram is a HIPAA compliant U.S. FDA Class II Exempt Digital Medical Device, which has received marketing authorization in multiple additional regulatory jurisdictions around the world (Australia, Canada, New Zealand, United Kingdom).

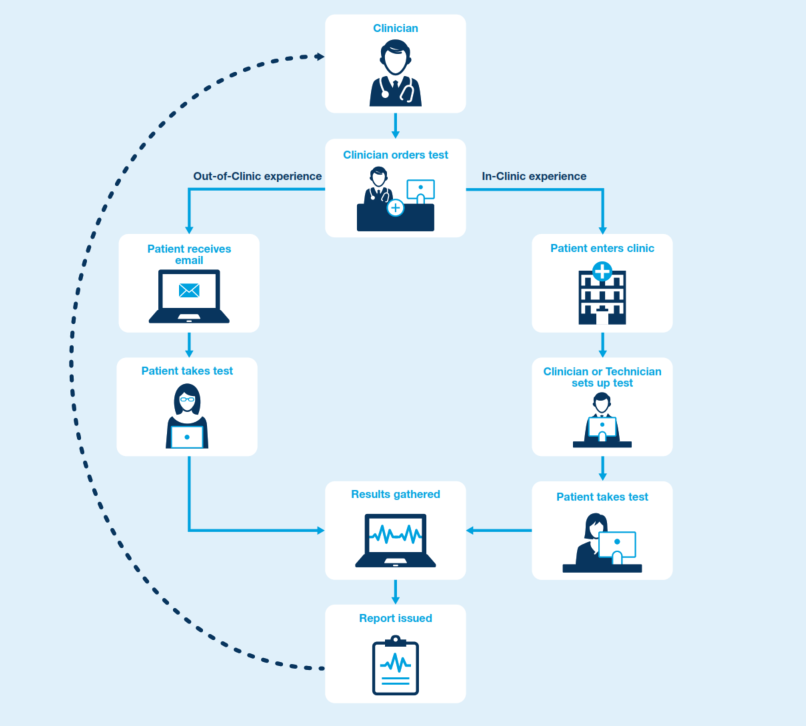
Cognigram has been used across various indications and in diverse healthcare settings (hospitals, clinics, out-of-clinic, etc.) with users noting favorable experiences with the system ([Adler et al., 2019](https://alz-journals.onlinelibrary.wiley.com/doi/10.1016/j.jalz.2019.07.004)).

Cognigram was selected by the Davos Alzheimer's Collaborative to be implemented as a digital cognitive screening tool in their Early Detection Flagship Program involving healthcare systems from six countries. The goal of the program was to increase early detection of cognitive impairment in non-specialty settings by implementing a digital cognitive assessment and a blood-based biomarker test. Cognigram was deployed in a primary care setting in Brazil and the US, and in a specialty care setting in Japan. Results of the program are not yet published.

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AI-generated content may be incorrect.The Cognigram system is powered by tests from the Cogstate Brief Battery. Specifically for this proposal, we recommend utilizing the **Cognigram Memory Assessment**, which is comprised of two tests: the Cogstate One Card Learning (OCL) and One Back (ONB) tests. As shown in the data below, OCL and ONB have been extensively leveraged via their inclusion in Cognigram, as well as in academic, registry, and industry clinical trials.

**For use in a healthcare setting, the process has been as follows:**



* 1. **Cognitive Domains the tests measure**
     1. **One Card Learning** measures learning based on accuracy of selection. Participants are shown a playing card stimulus and then asked “yes” or “no” whether they have seen the card before in that testing session.
     2. **One Back** measures working memory. Participants are shown a playing card stimulus and asked to answer “yes” or “no” if the card is the same as the previous card.
     3. **Learning/Working Memory (LWM)** composite score is derived from performance scores on the OCL and ONB tests at each assessment.
  2. **Platform e.g. smartphone / tablet / web in what combination**
     1. The Cognigram system is compatible with desktop, laptop, and tablet devices (i.e. iPad) and has minimal operating requirements. The ONB and OCL tests are available for smartphone use, but the smartphone versions of the tests have not yet been integrated into the Cognigram system.
     2. Supporting the validity of use of the Cognigram tests across platforms, a large (n>35,000) Bring Your Own Device (BYOD) validation study demonstrated that the accuracy of performance on OCL and ONB was equivalent across non-touch PC, touch smartphone, and touch tablet devices (Cohen’s d effect sizes < 0.3), with no clear influences of device, brand, or browser ([Edgar et al., 2023](https://alz-journals.onlinelibrary.wiley.com/doi/abs/10.1002/alz.078218)).
  3. **Provisioned/BYOD Setup Time for Testing (in mins)**
     1. The two tests in the Cognigram Memory Assessment each take an average of 5 minutes to complete. This includes brief interactive training immediately prior to each test to familiarize patients with the test requirements and response format, followed by a brief practice session, and then the actual test.

1. **Intended Use of the Product**
   1. **Device classification and FDA # (if relevant)**

FDA: Class II exempt Registration number: 3014109815

* 1. **Clinical use environment - unsupervised remote or supervised in-clinic**

Testing can be completed either in-clinic (supervised) or out-of-clinic (unsupervised). Published papers showcasing the unsupervised use of Cogstate tests including the ONB and OCL include the following: ([Banh et al., 2022](https://link.springer.com/article/10.14283/jpad.2021.68)), ([Mackin et al., 2018](https://www.sciencedirect.com/science/article/pii/S2352872918300307)), ([Maruff et al., 2017](https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1016/j.jalz.2017.07.236?casa_token=614yLbmn9BEAAAAA%3ACdg6MnZ9wwWYkSLooSUgW6rMftpY5Fbgtqv-1YauVR89kyzd9i0-YV74JBgbHP1e36la8m3f4MAGCWw)), ([Perin et al., 2020](https://pubmed.ncbi.nlm.nih.gov/32607409/))

* 1. **Total patients tested since the product launch**

Since its launch in 2017, Cognigram has assessed 77,012 patients worldwide.

* 1. **Task completion rates (% in both unsupervised and supervised/oversight environments)**

Of 164,797 Cognigram assessments ordered, 144,257 have been completed. The in-clinic completion rate is 95.7% (78,503 assessments completed) and the out-of-clinic completion rate is 79.4% (65,754 assessments completed).

* 1. **Participant demographics**
     1. **Age ranges**

The Cognigram system is intended to aid healthcare professionals with an objective measurement of cognition for use in individuals aged 6 - 99 years old.

* + 1. **Symptomatic vs asymptomatic**
       1. This information is not captured via Cognigram, but could be added to the build (self-report question) for Roche if desired.
       2. The OCL and ONB have been extensively used in both symptomatic and asymptomatic people. The tests are valid and reliable for use across both symptomatic and asymptomatic disease stages, in clinic and unsupervised ([Harrington et al., 2017](https://pubmed.ncbi.nlm.nih.gov/28761926/); [Lim et al., 2013](https://pubmed.ncbi.nlm.nih.gov/23552802/); [Lim et al., 2014](https://pubmed.ncbi.nlm.nih.gov/24176981/); [Mackin et al., 2018](https://pubmed.ncbi.nlm.nih.gov/30406176/); [Maruff et al., 2013](https://pubmed.ncbi.nlm.nih.gov/25566378/); Thai et al., 2015; [White et al., 2021](https://pubmed.ncbi.nlm.nih.gov/34881380/)).
    2. **Disease severity**

Disease severity is not captured within Cognigram, however, the OCL and ONB tests have been validated for use with preclinical AD, MCI, and dementia disease stages ([Maruff et al., 2013](https://pubmed.ncbi.nlm.nih.gov/25566378/); [Lim et al., 2014](https://pubmed.ncbi.nlm.nih.gov/24176981/); [Lim et al., 2013](https://pubmed.ncbi.nlm.nih.gov/23552802/); [Mackin et al., 2018](https://pubmed.ncbi.nlm.nih.gov/30406176/); [White et al., 2021](https://pubmed.ncbi.nlm.nih.gov/34881380/))

* + 1. **Gold standard diagnosis**

Performance on the OCL and ONB tests has been evaluated against gold standard clinical diagnosis by clinical review panel ([Maruff et al., 2013](https://pubmed.ncbi.nlm.nih.gov/25566378/)) according to internationally agreed criteria for MCI ([Winblad et al., 2004](https://pubmed.ncbi.nlm.nih.gov/15324367/)), and NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association) criteria for dementia ([McKhann et al., 1984](https://pubmed.ncbi.nlm.nih.gov/6610841/)). With more recent availability of Alzheimer’s disease biomarkers, performance has also been evaluated against clinically and biologically defined diagnoses such as amyloid negative cognitive normal, pre-clinical Alzheimer’s disease (amyloid positive cognitive normal), MCI due to AD, and dementia due to AD.

* + 1. **Urban vs Rural (Education levels & socioeconomic status)**
       1. This information is not captured in Cognigram, however, performance on the OCL and ONB tests is not related to demographic characteristics such as gender, educational background, language or culture. Data collected across different geographic regions around the world (Australia, the USA, Finland, Japan, China, and Uganda) have provided evidence to suggest that there is sound cross-cultural equivalence of performance on tests within the battery ([Lim et al, 2012](https://pubmed.ncbi.nlm.nih.gov/22248010/); [Kataja et al, 2017](https://pubmed.ncbi.nlm.nih.gov/28365750/); [Yoshida et al., 2011](https://pubmed.ncbi.nlm.nih.gov/21637776/); [Dingwall et al., 2009](https://www.tandfonline.com/doi/abs/10.1080/00050060903136839); [Hammers et al., 2011](https://pubmed.ncbi.nlm.nih.gov/21636581/); [Rentz et al., 2016](https://pubmed.ncbi.nlm.nih.gov/26998469/)).
       2. The processes for creation of test versions for different languages and cultures is controlled by Cogstate Standard Operating Procedures (SOPs). The test stimuli are language free and use ‘playing card’ images and so do not require translation/adaptation. Translation of test instructions is controlled by SOP ADM 013 Procedure for Handling Translation related to Cogstate Computerized Tests. Multinational clinical trials have collected data from participants in >90 languages and the commercial product Cognigram has test instructions available in 58 languages.

1. **Clinical Validity of the Product**
   1. **Clinical association evidence**
      1. **The Learning/Working Memory (LWM) composite score, the score derived from the OCL and ONB tests, is highly sensitive for cognitive impairment, including impairment consistent with MCI and dementia due to AD**. In a recent study with older adults whose medical and cognitive status had been defined using the rigorous inclusion/exclusion criteria required for AD clinical trials, accuracy of performance on the OCL and ONB tests showed strong ability to discriminate cognitively normal from MCI (e.g., CDR= 0.5) and dementia (e.g., CDR >0.5) participant groups ([White et al., 2023](https://pubmed.ncbi.nlm.nih.gov/38007647/)). These recent findings are consistent with results from the AIBL study, which also found accuracy measures from these tests, either alone or combined into a learning and working memory composite score, to be the most sensitive to cognitive impairment ([Maruff et al., 2013](https://pubmed.ncbi.nlm.nih.gov/25566378/); [Lim et al., 2013](https://pubmed.ncbi.nlm.nih.gov/23552802/); [Harrington et al., 2017](https://pubmed.ncbi.nlm.nih.gov/28761926/)).
      2. **The magnitude of impairment for individuals with MCI and mild/moderate AD on the learning/working memory (LWM) composite and the ONB and OCL tests individually is linked to the severity of cognitive impairment** and has been explored extensively. Results from the AIBL study indicate that the magnitude of impairment MCI individuals is large for OCL (d = -0.93), and very large for ONB (d = -1.55) and theLWM composite (the score derived from the OCL and ONB tests) (g = -2.15) relative to healthy controls ([Lim et al., 2012](https://pubmed.ncbi.nlm.nih.gov/22248010/); [Maruff et al., 2013](https://pubmed.ncbi.nlm.nih.gov/25566378/)). For individuals with AD dementia that magnitude of impairment is consistently larger than for MCI, with very large magnitude of impairment evident on the OCL (d = -1.70), ONB (d = -2.89), and learning/working memory composite (g = -3.18).

Please see sections 3d-f for more details relevant to clinical associations.

* 1. **Usability scores from real-world participants (if any)**

In a study conducted by [Adler et al., 2019,](https://alz-journals.onlinelibrary.wiley.com/doi/10.1016/j.jalz.2019.07.004) responses were collected as part of a pilot of Cognigram in the Emergency Department, Family Medicine, and Geriatric Psychiatry clinics in Brooklyn, NY from 58 adults (23 men, 35 women, mean age 67.9 ± 9.8 years [range 43–91]). Patients in this setting (rich in diversity and with low socio-economic status) took all 4 Cognigram tests, taking about 20-minutes to complete. 95% of patients thought test instructions were easy to understand, 91% liked completing the test while they were waiting, 97% said they would complete the tests again in 6 months or one year.

* 1. **Test-retest reliability of screening scores**

The LWM composite from the ONB and OCL has high test-retest reliability. In a subset of participants enrolled in the AIBL study, testing with the Cogstate brief battery was given monthly for 4 months to assess test-retest reliability. Cognitive classification was per the clinical gold standard described above in 2.e.iv., separated into healthy controls, mild cognitive impairment and Alzheimer’s dementia. For all groups, the test-retest reliability was high (r > 0.70) and equivalent across groups. See Table below ([Maruff et al., 2013](https://pubmed.ncbi.nlm.nih.gov/25566378/)). In addition, the OCL and ONB tests individually also have strong test-retest reliability, even with repeated administrations on the same day, with coefficients of stability p <0.01 on ONB in MCI and AD samples and on OCL in the AD sample ([Hammers et al., 2011](https://pubmed.ncbi.nlm.nih.gov/21636581/)).

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* 1. **Correlation with standard screening assessments, i.e., MMSE, MoCA, PACC**
     1. The performance scores from the Cognigram assessments have been demonstrated against the MMSE and the ADAS-Cog in a large sample of older adults (Healthy Control = 4021, biomarker defined Preclinical AD = 773, MCI due to AD = 420, AD dementia = 414, Unclassified = 3250) drawn from studies of Alzheimer’s disease and aging ([Barbone et al., 2023](https://alz-journals.onlinelibrary.wiley.com/doi/abs/10.1002/alz.077060)). The figure below shows the relationship between performance on Cognigram tests (proportion correct) and ADAS-cog scores, demonstrating that lower accuracy on the OCL, ONB, and LWM correspond with greater impairment on the ADAS-cog. For example, a score of 93% correct on ONB corresponds to an ADAS-cog score of 10 and a score of 72% correct corresponds to 20 on the ADAS-cog.

We would like to call out that this figure shows a floor effect of the OCL test (50% accuracy is chance for this test). The test has since been revised, made easier (paradoxically), resulting in greater range of scores, better discrimination between healthy controls and impaired persons, and resolution of the floor effect ([White et al., 2021](https://pubmed.ncbi.nlm.nih.gov/34881380/))

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* + 1. In AIBL, older adults diagnosed with MCI or dementia due to AD based on clinical criteria (MCI n = 107; AD n = 51), we showed a statistically significant linear relationship observed between CDR sum of boxes scores and the learning/working memory composite ([Maruff et al., 2013).](https://pubmed.ncbi.nlm.nih.gov/25566378/)

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**Relationship between LWM composite score and CDR sum of boxes score in MCI/AD dementia (n= 158).**

The diamond markers on each figure represent the mean composite score for each group of individuals with the same score on the CDR-SOB.

* + 1. Additionally, in a sample (n= 76) of cognitively unimpaired older adults from the Healthy Brain Project (healthybrainproject.org.au), the LWM composite obtained from unsupervised remote testing moderately correlated (ß = 0.38, p = 0.006) with an in-clinic PACC score that was derived from the MMSE, International Shopping List, Logical Memory, and Digit Symbol Substitution tests ([Maruff et al., 2023](https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/alz.079309)). The LWM score has also been shown to correspond with screening measures in a healthcare context, with a strong correlation (r = .65, p<0.005) with MoCA scores for patients in a tertiary neurological care center that had presented with acute ischaemic stroke 3-months prior ([Gagnon and Laforce, 2016](https://pmc.ncbi.nlm.nih.gov/articles/PMC5482710/)).
  1. **Correlation with biomarkers, i.e., MRI, PET, pTau181, pTau217**
     1. The OCL and ONB tests, as well as the LWM composite, have been shown to be sensitive to cognitive decline in in both preclinical (Aβ+ cognitively normal) and prodromal (Aβ+ MCI) AD, over study periods ranging from 6-months to 6-years ([Lim et al., 2013](https://pubmed.ncbi.nlm.nih.gov/23001710/); [Lim et al., 2015](https://link.springer.com/article/10.1007/s12031-016-0822-8); [Harrington et al., 2017](https://pubmed.ncbi.nlm.nih.gov/28761926/) ). Results consistently show that individuals with evidence of elevated Aβ on PET scan show accelerated cognitive decline on one or both tests, relative to Aβ- controls (Cohen’s d for difference in rate of change = -0.15 to -1.38). Change in the LWM composite has also been shown to coincide with decline in hippocampal volume on MRI in both preclinical and prodromal AD ([Lim et al., 2014](https://academic.oup.com/acn/article-abstract/30/1/49/2726842?redirectedFrom=fulltext)).
     2. Evidence for cross-sectional associations between performance on the OCL and ONB tests and AD biomarkers is weaker. Among cognitively normal participants (clinically assessed with standard neuropsychological tests and clinician interview) from a population-based sample (n = 464; Mage (SD) 62.7 (5.40); 48% female), poorer accuracy on OCL was associated with smaller hippocampal volume by MRI (p = 0.02), but not with amyloid SUVR measured with PiB PET. \ That said, standard pencil and paper tests from a common Alzheimer’s disease test battery were also not associated with amyloid SUVR in this sample ([Mielke et al., 2016](https://www.sciencedirect.com/science/article/abs/pii/S1552526014028210)). In the Wisconsin Registry for AD (WRAP), poorer OCL test performance was associated with higher levels of CSF phosphorylated-tau/Aβ42 ([Racine et al., 2016](https://pubmed.ncbi.nlm.nih.gov/27589532/)).
  2. **Classification performance, i.e., sensitivity, specificity, NPV, PPV**
     1. When applied in populations selected for clinically diagnosed and/or biologically confirmed Alzheimer’s disease pathology, the LWM composite score, the score derived from the OCL and ONB tests, is highly sensitive and specific for discriminating those with disease (MCI or dementia) from those deemed cognitively normal. In one of the early studies of the clinical utility of the Cogstate Brief Battery (CBB) in identifying cognitive impairment associated with MCI and dementia, participants in the AIBL study were assessed with the CBB as well as traditional neuropsychological tests and were diagnosed as cognitively normal (n = 659), MCI (n = 107), or Alzheimer’s dementia (n = 51) by the clinical gold standards at that time. To increase the reliability of classification, all individuals classified with MCI and AD were required to meet the criteria for these clinical classifications on two consecutive assessments. In this study, Maruff et al. showed that the LWM composite had 80% sensitivity and 85% specificity for discriminating between MCI and cognitively normalusing a cut-point of 1SD below normative means. Sensitivity and specificity for AD (vs cognitively normal) at the same cut-point (-1SD) was 100% and 85% respectively. The ROC curves are shown below. (Maruff et al., 2013). It should also be noted that, as expected, the psychomotor speed and attention composite (derived from the Detection and Identification tests from the CBB) was much less sensitive for discriminating MCI and dementia likely due to AD from cognitively normal.

A graph of a patient's performance

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Similarly, in a more recent study of the sensitivity of the CBB to cognitive impairment in AD, 5,001 cognitively unimpaired older adults who screened for the A4 study and 194 people with early Alzheimer’s disease (CDR 0.5 or 1; confirmed medial temporal lobe atrophy or presence of CSF AD biomarker signature) randomized in the ADAMANT, accuracy of performance on the OCL and ONB tests, as well as the LWM composite, showed strong ability to discriminate between cognitively normal participants and those with early AD at either CDR 0.5 or CDR >0.5 (White et al., 2023), see Table below.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **CN** | **CDR 0.5\*** | | | **CDR >0.5^** | | |
| **Measure** | **Mean (SD)** | **Mean (SD)** | **Sens** | **Spec** | **Mean (SC)** | **Sens** | **Spec** |
| ONB accuracy | 1.38 (0.16) | 1.06 (0.22) | 74% | 87% | 0.95 (.017) | 90% | 87% |
| OCL accuracy | 1.05 (0.13) | 0.91 (0.12) | 55% | 85% | 0.86 (0.08) | 77% | 85% |
| LWM | 1.21 (0.11) | 0.98 (0.13) | 79% | 84% | 0.90 (0.10) | 96% | 84% |

\* Sensitivity and specificity vs cognitively normal (CN) using -1SD as the threshold. Sensitivity and specificity are slightly higher using Youden’s J as the threshold. ^ Sensitivity and specificity vs CN using -1SD as the threshold. Sensitivity and specificity are slightly higher using Youden’s J as the threshold.

Other potential composites were also examined. Integration of performance speed measures into learning and working memory composites did not improve the discrimination between cognitively normal and AD-related cognitive impairment. These recent findings are consistent with other results from the AIBL study, which also found accuracy measures from these tests, either alone or combined into a LWM composite score, to be the most sensitive to cognitive impairment (Maruff et al., 2013; Lim et al., 2013; Harrington et al., 2017).

* + 1. The excellent sensitivity and specificity of the LWM composite score, when applied in carefully selected populations enriched for impairment of the AD type, may not be replicated in more general populations. Where the etiology of MCI is unclear, or is likely to reflect other non-AD processes, sensitivity of the LWM composite to MCI-related cognitive impairment has not been as high ([Alden et al., 2021](https://pubmed.ncbi.nlm.nih.gov/33650308/)). However, the CBB tests were designed and optimized initially for measuring change over time, not with the intent of using them cross-sectionally to classify cognitive impairment. None-the-less, the need for digital screening tools has emerged and use cases have evolved. Consequently, Cogstate has carefully considered data from studies which have applied the CBB to identify cognitive impairment in individuals suspected of having AD and used this to continually improve and optimize the test battery for use in clinical contexts. The revision of the OCL test ([White et al., 2021)](https://pubmed.ncbi.nlm.nih.gov/34881380/) is one example of this improvement process, where it was shown that simplification of the OCL improved its sensitivity by providing a greater range of values that reflected impaired performance. The resultant analyses published in White et al., 2023 and described above in 3.f.i. incorporate those changes as well as improvements. Other improvements to the CBB tests are detailed in the study by Perin et al (2020) where it was shown that addition of an interactive and self-directed “Learn” module prior to each test improved the acceptability of the CBB when it was given in a remote unsupervised context. While it is now important to determine how this optimized CBB performs with respect to sensitivity and specificity in different health care contexts, where individuals do not have well- characterized disease, data from application of the CBB in remote and unsupervised contexts, including the demonstration of relationships to disease relevant characteristics such as carriage of an Apoe4 allele ([Lim et al., 2021](https://pubmed.ncbi.nlm.nih.gov/33492293/)), level of Tau determined from CSF sampling ([Lim et al., 2023](https://www.sciencedirect.com/science/article/abs/pii/S019745802300101X)), presence of cerebral vascular risk ([Bransby et al., 2023](https://pubmed.ncbi.nlm.nih.gov/36931817/); [Yassi et al., 2022](https://pubmed.ncbi.nlm.nih.gov/35147538/)) all suggest strongly that the psychometric characteristics of the CBB tests will remain acceptable in these new contexts of use.
  1. **Availability of age and education adjusted normative data**
     1. The Cogstate normative dataset was last updated on October 17, 2024, and includes over 50,000 people, with 5,477 ³65 years old. This normative sample represents data from a healthy population of children, adolescents and adults aged between 4 and 89 years. The normative sample for subjects aged 18 to 89 years is based on a healthy population of subjects enrolled in a series of clinical trials, research and academic studies. Whilst some of these studies incorporated a single assessment only, others included longitudinal research designs with practice, baseline and follow-up assessments. Irrespective of where the data was sourced, only baseline sessions were included in the normative database and only a single session was included for each subject. All subjects included in the normative database had completed at least one practice assessment prior to their baseline assessment. For the CBB (consisting of the Detection Test, Identification Test, One Card Learning Test, and One Back Test), data are co-normed for subjects aged 20-89, i.e. all subjects completed all four tests at the same assessment.
     2. The normative sample is aggregated data from many studies, and whilst data is collapsed across different modes of administration, data was captured predominantly on Windows and Mac-based desktop/laptop devices. Participants were recruited from countries in North and South America, Europe, Asia and Australia. The normative data is also collapsed across these geographic regions given the evidence to suggest that there is sound cross-cultural equivalence of performance on tests within the Cogstate battery ([Lim et al, 2012](https://pubmed.ncbi.nlm.nih.gov/22248010/); [Kataja et al, 2017](https://pubmed.ncbi.nlm.nih.gov/28365750/); [Yoshida et al., 2011](https://pubmed.ncbi.nlm.nih.gov/21637776/); [Dingwall et al., 2009](https://www.tandfonline.com/doi/abs/10.1080/00050060903136839); [Hammers et al., 2011](https://pubmed.ncbi.nlm.nih.gov/21636581/); [Rentz et al., 2016](https://pubmed.ncbi.nlm.nih.gov/26998469/)).
     3. Performance scores on the OCL and ONB do not need adjustment for education. In a recent study with 5001 cognitively normal older adults, there was no strong or systematic effect of education on test performance. Where a statistically significant relationship was observed, the magnitude of the effect was trivial; for example, the most amount of variance explained by education was 0.5% for OCL accuracy and 0.2% for ONB accuracy ([White et al. 2023](https://pubmed.ncbi.nlm.nih.gov/38007647/)).
  2. **Validity and reliability**
     1. The ONB and OCL tests have been identified to have optimal psychometric properties for measurement of cognitive change for cognitively normal older adults, including absence of floor/ceiling effects, normal data distributions, and high test-retest reliability (ICC = .75 for ONB and .74 for OCL over 18-month retest interval; [Harrington et al. 2017b](https://pubmed.ncbi.nlm.nih.gov/27932344/)). Similarly, the LWM composite has high test-retest reliability across 4-months for healthy controls (ICC = 0.78), as well as MCI (ICC = 0.86) and AD dementia (ICC = 0.91) groups ([Maruff et al., 2013](https://pubmed.ncbi.nlm.nih.gov/25566378/)). Furthermore, the tests can be repeated at brief intervals (e.g., 10-minute intervals) without practice effects, so alternate stimuli for repeated testing is not required (e.g., [Falleti et al., 2006](https://pubmed.ncbi.nlm.nih.gov/16840238/)).
     2. Construct validity of the OCL and ONB tests has been determined in a sample of 215 healthy adults (aged 35 – 50 years). OCL and ONB showed strong correlations with conventional neuropsychological measures of learning and working memory respectively (r’s = .79 to .83 for OCL, .71 to .81 for ONB; [Maruff et al., 2009](https://pubmed.ncbi.nlm.nih.gov/19395350/)). Criterion validity for each of these tests has been determined by examining patterns of performance in groups of individuals with MCI, AD dementia (Lim et al., 2013a; [Maruff et al., 2013](https://pubmed.ncbi.nlm.nih.gov/25566378/)), as well as mild head injury, schizophrenia, and AIDS dementia complex ([Maruff et al., 2009](https://pubmed.ncbi.nlm.nih.gov/19395350/)).
     3. In unsupervised settings usability of the OCL and ONB tests remains high. In a sample of 1594 middle and older aged adults with a self-reported a family history of dementia and no personal dementia diagnosis: 95% of OCL and ONB assessments passed pre-specified validity criteria – indicating that even in the remote unsupervised setting participants were able to comprehend the test requirements and provide valid performance data ([Perin et al, 2020](https://pmc.ncbi.nlm.nih.gov/articles/PMC7317647/)).

1. **Product Reliability**
   1. Net promoter scores (NPS) from clinicians and patients
      1. NPS is not collected for Cognigram. Data from [Adler et al., 2019](https://alz-journals.onlinelibrary.wiley.com/doi/10.1016/j.jalz.2019.07.004) show that 91% of Cognigram participants enjoyed taking the test in a waiting room setting and 97% said that they would do the test again at the clinic every 6 months or once a year.
   2. Uptime and MTTR (mean time to repair)
      1. Cogstate uses commercially reasonable efforts to make the Services available twenty-four hours a day, seven days a week, except for planned downtime, which may include but is not limited to software updates and hardware maintenance.
      2. Cogstate enters SLAs per customer contract.
   3. Any corrective action and preventive actions (CAPA) that were raised and closed?
      1. Total of 3 Cognigram related CAPA’s were raised since 2023 and all have been closed. More details can be provided if contract is pursued.
2. **Market Growth (at least 3 years data)**
   1. **Customer growth** i.e. number of sites / customer or number of users / customer
      1. Commercialization efforts for Cogstate products in healthcare including Cognigram have been primarily led by Eisai Co. Ltd, therefore specific details regarding users/customers cannot be shared outside of what is available publicly:
         1. Cogstate technology marketed in Japan as a pre-installed application on a smartphone used widely by the senior population  
             [https://www.eisai.com/news/2022/pdf/enews202249pdf.pdf](https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.eisai.com%2Fnews%2F2022%2Fpdf%2Fenews202249pdf.pdf&data=05%7C02%7Ctmartin%40cogstate.com%7C52662947e1754938a5bd08dd372e593b%7Cbd387433a5db4219badaac99d865360a%7C0%7C0%7C638727394387869277%7CUnknown%7CTWFpbGZsb3d8eyJFbXB0eU1hcGkiOnRydWUsIlYiOiIwLjAuMDAwMCIsIlAiOiJXaW4zMiIsIkFOIjoiTWFpbCIsIldUIjoyfQ%3D%3D%7C0%7C%7C%7C&sdata=J9HJTqmjIVgsV1VBwM0V9Fg5%2Fcs2%2FrZl0%2Fj0ucTeHKU%3D&reserved=0)
         2. Cogstate technology marketed in Japan through E. Design Insurance Co., Ltd. to promote Safe Driving in an aging society   
             <https://www.cogstate.com/wp-content/uploads/2022/07/enews202251pdf.pdf>
      2. Additional evidence of market interest in the product:
         1. Cogstate technology selected for Davos Alzheimer’s Collaborative Innovative Early Detection Effort: Seven Flagship Pilot Sites Aim to Measurably Increase Timely, Accurate Diagnosis of Alzheimer’s  
            [https://www.davosalzheimerscollaborative.org/news-press/https/wwwdavosalzheimerscollaborativeorg/news-and-press/davos-alzheimers-collaborative-launches-innovative-early-detection-effort?rq=early%20detection](https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.davosalzheimerscollaborative.org%2Fnews-press%2Fhttps%2Fwwwdavosalzheimerscollaborativeorg%2Fnews-and-press%2Fdavos-alzheimers-collaborative-launches-innovative-early-detection-effort%3Frq%3Dearly%2520detection&data=05%7C02%7Ctmartin%40cogstate.com%7C52662947e1754938a5bd08dd372e593b%7Cbd387433a5db4219badaac99d865360a%7C0%7C0%7C638727394387889253%7CUnknown%7CTWFpbGZsb3d8eyJFbXB0eU1hcGkiOnRydWUsIlYiOiIwLjAuMDAwMCIsIlAiOiJXaW4zMiIsIkFOIjoiTWFpbCIsIldUIjoyfQ%3D%3D%7C0%7C%7C%7C&sdata=Rebw3yr0kaictYVzxWDGYiwigyakg%2FdhEnjN9vNu09I%3D&reserved=0)
         2. AdventHealth is one of two U.S. sites participating in groundbreaking Alzheimer’s disease research <https://www.adventhealth.com/medical/adventhealthmd/news/adventhealth-one-two-us-sites-participating-groundbreaking-alzheimers-disease-research>
   2. Revenue growth - share if possible absolute $ and % growth yoy (year over year)
      1. Cogstate revenue contribution from healthcare segment as shared in annual reports (USD):
         1. FY24: $2,874,603
         2. FY23: $3,115,097
         3. FY22: $3,242,434
         4. FY21: $2,958,919
         5. FY20: $1,320,780
   3. Customer profile - any reference sites of IHN (Integrated health networks)?
      1. Commercialization efforts for Cogstate products in healthcare including Cognigram have been primarily led by Eisai Co. Ltd, therefore specific details regarding users/customers cannot be shared outside of what is available publicly (see list above).