THE MCI SCREEN

A Pragmatic Clinical Tool for Assessing Memory Concerns in a Primary Care Setting

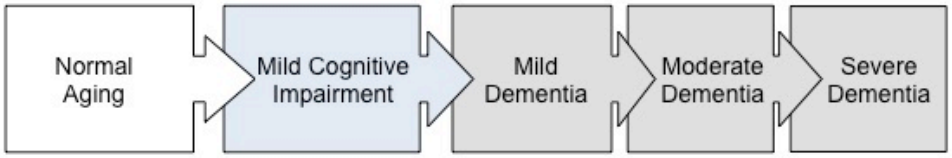
Timely detection of emerging cognitive difficulties is vital for patients' well being and for the state of the healthcare industry. People suffering from cognitive impairment experience reduced quality of life as they struggle to manage chronic conditions and to participate in cognitively demanding hobbies or activities of daily living. As the population ages, the prevalence of cognitive impairment will continue to increase, the quality of life for a large segment of the population will decline, and associated healthcare costs will rise significantly. This unfolding scenario argues for prompt and appropriate clinical intervention against emerging cognitive deficits, which requires pragmatic tools for detecting the earliest signs of cognitive decline in primary care settings. **The MCI Screen is part of a well-validated, pragmatic approach to reducing the burden of cognitive impairment across a rapidly aging population.**

COGNITIVE HEALTH CONTINUUM

Cognitive health exists along a continuum from normal aging through mild cognitive impairment to dementia (**Figure 1**).

Normal aging refers to a healthy brain, with cognitive abilities remaining fairly stable throughout life. Although most people are subjectively aware of subtle cognitive changes after age 40, such changes do not affect functional abilities and do not result in the loss of one's most complex functional abilities. In the absence of any known medical conditions that impair cognition, these subtle changes are attributable to "normal aging".

Figure 1: Cognitive Health Continuum



Mild cognitive impairment (**MCI**) refers to a small but measurable degree of cognitive decline caused by a medical condition. It has the prevalence as high as 42% in population-based studies of primary care practices [Pedersen et al. 2014]. MCI is not usually detectable by casual conversation or observation, and approximately 60% of persons with MCI are unaware they have a memory problem [Purser et al. 2006]. Persons with MCI perform well-learned skills normally, such as cooking, shopping, paying bills, managing finances or driving, but have trouble incorporating and applying new knowledge. Indicators of MCI are difficulty remembering recent conversations or events, keeping track of schedule and appointments, or using new guidelines to manage a business. Distinguishing MCI from normal aging is a difficult task, even for the most conscientious primary care physicians, yet doing so is the key to timely intervention and optimal treatment outcomes.

Common causes of MCI include poorly controlled chronic conditions (e.g., hypertension, high cholesterol, heart disease, and diabetes), depression, medications, thyroid disorders, and early stage Alzheimer's disease (see **Appendix A** for a more complete list of common causes and achievable treatment outcomes). It is important to note, although not widely appreciated, that about 50% of cases of MCI are highly treatable conditions not related to Alzheimer's disease (**AD**) [Montine et al. 2012].

Dementia is much more severe than MCI. The term, "mild dementia", refers to loss of the ability to carry out activities of daily life, including shopping, cooking, paying bills, managing a household, managing financial affairs, driving, and doing well learned hobbies or pastimes. By the time "mild dementia" has begun, there is extensive damage throughout the brain, which results in loss of connections between brain areas that are hard to re-establish. In terms of functional decline, "mild dementia" is not mild.

While most cases of MCI are not caused by AD, the majority of dementia cases can be attributed, at least in part, to AD. Left untreated, MCI due to AD progresses to dementia at a rate of 15% per year [Reisberg et al. 2010]. However, even conditions that can be cured or arrested, such as B12 deficiency, hypothyroidism, or cerebrovascular disease, can ultimately cause dementia if left untreated. Furthermore, reversal of cognitive impairment in such treatable conditions, especially once the impairment has progressed to the dementia stage, is much harder, more costly, and less certain than preventing it through early detection and effective management.

There are **two key benefits** of precise memory assessment The first is to reassure healthy individuals, who are aging normally, that any perceived memory changes are benign. The second is to detect mild cognitive impairment due to an emerging medical condition at its earliest and most treatable stage. Doing so maximizes public health and facilitates efficient use of healthcare resources.

MCI SCREEN BACKGROUND

The MCI Screen (**MCIS**) is based on a 10-word recall test that is common to both the National Institute of Aging's Consortium to Establish a Registry for Alzheimer's Disease (**CERAD**) and the Alzheimer's Disease Assessment Scale – Cognitive Subscale (**ADAS-Cog**). The 10-word recall test is well-validated and has been found to be the most sensitive test for discriminating between normal aging and MCI (amnestic or non-amnestic) [Fleisher et al. 2008], and was therefore selected as the basis for the MCIS.

This well-validated 10-word recall test from the public domain was enhanced in several ways to create the MCIS:

- The word presentation order during the list learning tasks was held constant across trials to reduce the unexplained variance in recall trials [Shankle et al. 2005].
- Sixteen equivalent word lists with low item-associability were scientifically developed and incorporated into a user-specific rotation to eliminate learning effects.
- Correspondence analysis was applied to the pattern of responses to precisely quantify and discriminate normal recall patterns from those affected by a medical condition.
- A short judgment task, recognition task, and associative memory tasks were appended to the recall task to gain more insight about the health of the brain.

- The test was enabled with an electronic user-interface, computerized scoring, and automatic report generation to enable a pragmatic, reimbursable approach to managing cognitive health for busy practitioners in a clinical setting.

The MCIS achieves its high discrimination accuracy by using advanced scoring methods based on correspondence analysis of the subject's recall pattern. It also quantifies cognitive performance onto a 0 to 100 scale (below normal: <50) called the Memory Performance Index (**MPI**) [Shankle et al. 2009]. All scores are adjusted for age, gender, race, and level of education.

Administration of the MCIS is guided by an intuitive online interface, requires no professional credentials, and is supported by training built into the online delivery system. One practice test is sufficient to achieve a test-retest and inter-rater reliability of 0.83 [Trenkle et al. 2007].

ACCURACY

The MCIS consistently has shown high accuracy, sensitivity and specificity in the difficult but important task of discriminating normal aging from MCI, across a broad range of patient populations. These patient populations were classified using well-accepted criteria for MCI (Clinical Dementia Rating [**CDR**] score of 0.5 and Functional Assessment Staging Test [**FAST**] score of 3). The MCIS has also shown high accuracy in discriminating normal aging from pre-MCI subjects (FAST stage 2) in primary care practice (bottom row, Table 1). The MCIS has been validated in four separate populations including normal aging, MCI, and/or mild dementia subjects, drawn from two university Alzheimer's centers in the USA [Shankle et al. 2005], a Japanese university memory center [Cho et al. 2008], a community dementia program [Shankle et al. 2005], and a primary care practice [Trenkle et al. 2007]. **Table 1** summarizes the MCIS classification performance across these studies.

Table 1: Summary of MCIS Classification Performance Across 3 Validation Studies

Study Comparisons	ROC Accuracy	Sensitivity	Specificity
Normal vs. MCI*[1-3]	96-97%	94-96%	88-100%
Normal vs. MCI Due To AD[1]	99%	98%	92%
Normal vs. MCI Due To Non-AD[1]	96%	91%	88%
Normal vs. Mild Dementia[1]	99%	96%	99%
Normal vs. Pre-MCI** (Primary Care)[2]	93%	86%	99%

*MCI criteria were either CDR = 0.5 or FAST stage = 3. **Pre-MCI criteria were FAST stage 2 with clinical diagnosis confirmation of ADRD etiology. [1]Shankle et al. 2005. [2]Trenkle et al. 2007. [3]Cho et al. 2008.

RELIABILITY

The electronically guided format of the MCIS was designed to improve test-retest and inter-rater reliability over a wide variety of medical office personnel. When comparing a neuropsychologist to a medical office assistant that had one MCIS practice session (electronically guided), the MCIS was administered to the same 30 subjects over a 3-month period, with the administrator order randomized. The combined test-retest and inter-rater reliability of the MCIS was 0.83 [Trenkle et al. 2007].

COGNITIVE DOMAINS ASSESSED

The MCIS is a 10-minute test of memory, judgment, language and executive function (**Table 2**). It consists of five primary tasks drawn from the public domain, an electronic user-interface that ensures reliability and reproducibility, and optimal scoring of the item responses.

Table 2: Cognitive Domains Assessed by the MCIS

MCI Screen Components	Cognitive Domain	Primary Brain Localization
Three immediate recall trials of 10-word list	Attention, working memory, comprehension	Prefrontal cortex
Judgment of short-term recall	Insight, awareness of cognitive abilities	Ventromedial prefrontal, right inferior frontal, right fronto-polar cortex
Triadic comparison of animals	Working memory, judgment, semantic memory, comprehension	Left inferior prefrontal cortex
Delayed free recall of 10-word list	Short-term memory	Para-hippocampus, hippocampus
Delayed cued recognition of 10-word list items	Recognition (information storage), source memory, comprehension, response bias	Hippocampus
Delayed free recall of items from triadic comparison	Associative memory	Association cortex, entorhinal cortex

COMPARISON TO OTHER COGNITIVE ASSESSMENT INSTRUMENTS

Comparison to the MMSE and Clock Drawing Test in Primary Care Practice

The MCIS, Clock Drawing test, and the MMSE were administered to all patients (N=254) over 65 years old in a primary care practice. All subjects classified as impaired by any of the tests were diagnostically evaluated for AD or a related disorder (**ADRD**) using a standardized assessment. ADRD etiologies included 43% AD, 36% cerebrovascular disease, 9% alcohol, 4% traumatic brain injury, 3% depressive pseudo-dementia, 1% Parkinson's disease, and 1% other causes. **Table 3** shows that the MCIS substantially outperformed the MMSE and Clock Drawing Tests in classifying clinically diagnosed patients with MCI due to ADRD vs. normal aging patients [Trenkle et al. 2007].

Table 3: Classification performance of the MCIS, MMSE, and Clock Drawing tests for normal aging vs. clinically diagnosed and confirmed MCI patients in primary care practice.

Test	N	Acc.	Sn.	Sp.	PPV	NPV	Validity
MCIS	121	91-100%	94%	97%	86%	99%	91%
MMSE	121	51-72%	71%	36%	17%	87%	0.7%
Clock Draw	121	43-64%	59%	39%	16%	83%	0.0%

Comparison to the MMSE, Quantitative Volumetrics, and Brain Activity

The Japanese MCIS (**JMCIS**) was compared to the Mini-Mental State Exam (**MMSE**), quantitative MRI volumetrics and quantitative HMPAO SPECT brain activity measures in a sample of 63 normal or MCI outpatients of the Fukuoka University Hospital clinic [Cho et al.

2008]. The Japanese MCIS was more accurate, sensitive and specific than these other tests, as is shown in **Table 4**.

Table 4: Test Performance in Classifying Normal (CDR = 0) and MCI (CDR = 0.5) Groups.

Method	N	Accuracy	Sn	Sp	PPV	NPV	Kappa
JMCIS	56	.964	.958	1.000	0.813	1.000	0.868
MMSE	56	.768	.792	.625	0.420	0.897	0.305
qSPECT	36	.722	.688	1.000	0.296	1.000	0.328
qMRI	45	.733	.700	1.000	0.308	1.000	0.342
qSPECT+qMRI	25	.840	.833	1.000	0.487	1.000	0.553

CDR: Clinical Dementia Rating Scale: CDR of 0 and 0.5 correspond to normal aging and MCI. **Sn**: sensitivity for MCI. **Sp**: specificity for normal. **PPV**: Positive Predictive Value. **NPV**: Negative Predictive Value. **Kappa**: Kappa validity statistic after removing chance effects. **JMCIS**: Japanese MCI Screen. **qSPECT**: quantitative HMPAO SPECT post cingulate and precuneus activity classified normal vs. MCI. **qMRI**: cortical and hippocampal volumes were used to classify patients as normal or MCI.

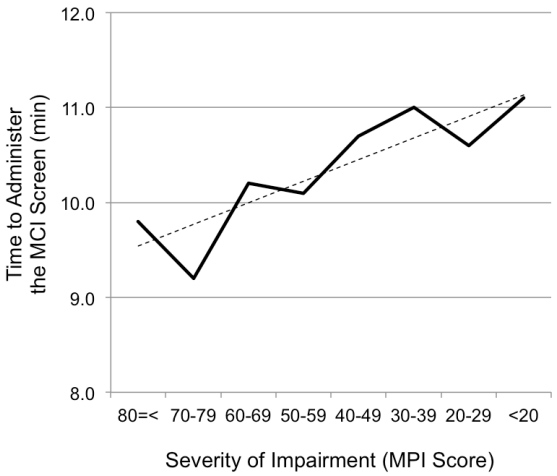
Comparison to AD Cooperative Study Neuropsychologic Test Battery

The UC San Diego AD Center evaluated the MCIS against the full neuropsychologic test battery, which consists of 16 tasks, and is used by all AD Cooperative Study members in the USA. 86 outpatients from the VA clinic (12 with amnestic MCI, 49 with mild AD dementia, and 25 healthy elderly) were assessed with both instruments. The MCIS provided the same level of discrimination as the full ADCS test battery, and gave a classification accuracy of 86%, sensitivity of 92% and specificity of 72% [Rafii et al. 2011].

TIME TO ADMINISTER

Based on analysis of 10,000 MCI Screens administered across approximately 200 administrators in US-based primary care clinics, the average time to administer the MCIS is 9 to 11 minutes, depending upon the subject's cognitive status (**Figure 2**). Normally aging patients usually complete the assessment in less than 10 minutes while demented patients may take several minutes longer. The test administrator needs no professional credentials, only an ability to effectively interact with patients in a busy, clinical setting.

Figure 2: Assessment Time vs. MPI Score



EFFECT OF DELIVERY METHOD (PHONE VS. IN-PERSON)

The effect of the mode of administration has also been measured in a sample of 121,481 long-term care insurance applicants, ages 18 to 106 years old, who were either administered the MCIS over the telephone or in person. The variability in performance due to mode of administration was measured as the *effect size*, which is expressed in terms of standard deviations of the MPI score. Mode of administration negligibly influences a given subject's MPI score by 5/100 of a standard deviation [Shankle et al. 2009].

EQUIVALENT WORD LISTS

To eliminate learning effects across repeat assessments with the MCI Screen, 16 wordlists of 10 words each were developed from an initial sample of 1 million common nouns [Shankle et al. 2013b]. The word lists are managed and presented in random order by the MCI Screen's electronic user interface. The eligibility criteria used to create the 16 linguistically equivalent wordlists with low inter-item associability within each list include:

- 1-2 syllables
- Common noun
- No homonyms, antonyms, synonyms
- High frequency usage
- Low word-word associability
- Distractor and target lists linguistically balanced

The effect of each wordlist on the MPI score was measured in a study of 121,481 long-term care insurance applicants, ages 18 to 106 years old. The largest effect size of any wordlist on the MPI score was 9/1000 of a standard deviation, which is a negligible effect. The MCIS user-interface manages the wordlist rotation to ensure that any given subject must be assessed nine times before being tested twice with the same wordlist.

SUMMARY

With the aging of the world's population and the increased healthcare costs driven by cognitive impairment, it is becoming crucially important to detect, diagnose, and treat medical conditions that affect memory, judgment, and executive function. Primary care physicians, especially those in Accountable Care Organizations, are ideally positioned in the US healthcare system to proactively intervene and optimize the cognitive health of their patient populations, but doing so requires a pragmatic approach that fits within the constraints of a busy clinical setting. The MCI Screen offers precise assessment capabilities within these constraints, as it requires minimal training to administer, attractive reimbursement by Medicare and other payers, and automatic results interpretation and report generation. It is highly accurate in distinguishing between signs of normal aging and symptoms of emerging medical conditions, which facilitates timely intervention, improved outcomes, and lower overall costs. With extensive, published validation and fast growing adoption, the MCI Screen is ideally designed to play a key role in managing the cognitive health of aging patients all over the world.

REFERENCES

- Cho A, Sugimura M, Nakano S, et al. The Japanese MCI Screen for Early Detection of Alzheimer's Disease and Related Disorders. Am J Alzheimers Dis Other Demen. 2008;23:162-6.
- Cohen MA. Improved Mental Screening Can Cut Claim Costs: A new look at dementia claims by screened policyholders. National Underwriter. 11/2/2009: 1-2.
- Fleisher AS, Sun S, Taylor C, et al. Volumetric MRI vs clinical predictors of Alzheimer disease in mild cognitive impairment. Neurology. 2008;70(3):191-9.
- Guo H, Tabara Y, Igase M, et al. Abnormal nocturnal blood pressure profile is associated with mild cognitive impairment in the elderly: the J-SHIPP study. Hypertension Research. 2009:1–5.
- Kamogawa K, Kohara K, Tabara Y, et al. Abdominal Fat, Adipose-Derived Hormones and Mild Cognitive Impairment: The J-SHIPP Study. Dement Geriatr Cogn Disord. 2010;30:432–439
- Kido T, Tabara Y, Igase M, et al. Postural Instability Is Associated with Brain Atrophy and Cognitive Impairment in the Elderly: The J-SHIPP Study. Dement Geriatr Cogn Disord 2010;29:379–387.
- Montine TJ, Sonnen JA, Montine KS, et al. Adult Changes in Thought study: dementia is an individually varying convergent syndrome with prevalent clinically silent diseases that may be modified by some commonly used therapeutics. Curr Alzheimer Res. 2012;9(6):718-23.
- Pedersen MM, Holt NE, Grande L, et al. Mild Cognitive Impairment Status and Mobility Performance: An Analysis From the Boston RISE Study. J Gerontol A Biol Sci Med Sci. 2014;69(12):1511-8.
- Purser JL, Fillenbaum GG, Wallace RB. Memory complaint is not necessary for diagnosis of mild cognitive impairment and does not predict 10-year trajectories of functional disability, word recall, or short portable mental status questionnaire limitations. J Am Geriatr Soc. 2006;54:335–8.
- Rafii M, Taylor C, Coutinho A, et al. Comparison of the memory performance index with standard neuropsychological measures of cognition. Am J Alzheimers Dis Other Demen. 2011;26:235-9.
- Reisberg B, Franssen EH, Souren LEM, et al. Medical Aspects of Disability. Springer Publishing. 2010. Eds. Flanagan SR, Zaretsky H, Moroz A.
- Shankle WR, Romney AK, Hara J, et al. Method to improve the detection of mild cognitive impairment. PNAS. 2005;102(13):4919-24.
- Shankle WR, Mangrola T, Chan T, et al. Development and validation of the Memory Performance Index: Reducing measurement error in recall tests. Alzheimer’s & Dementia. 2009;5:295–306.
- Shankle WR, Hara J, Mangrola T, et al. Hierarchical Bayesian cognitive processing models to analyze clinical trial data. Alzheimers Dement. 2013a;9(4):422-428.
- Shankle WR, Pooley JP, Steyvers M, et al. Relating Memory to Functional Performance in Normal Aging to Dementia Using Hierarchical Bayesian Cognitive Processing Models. Alzheimer Dis Assoc Disord. 2013b;27(1):16-22.
- Trenkle D, Shankle WR, Azen SP. Detecting Cognitive Impairment in Primary Care: Performance Assessment of Three Screening Instruments. Journal of Alzheimer's Disease. 2007;11(3):323-35.

APPENDIX A

WHY ASSESS MEMORY CONCERNS IN A PRIMARY CARE SETTING?

Answer: For early detection of all these conditions

Condition or Disease that causes short-term memory loss	**Treatment** for condition or disease	**Result** of treatment on memory loss
Anxiety	Anxiolytic agents	Memory usually restored
ADHD	Psycho stimulants	Memory usually restored
Depression	Anti-depressants	Memory usually restored
Thyroid gland disease	Thyroid hormone	Memory usually restored
Diabetes	Anti-diabetics	Memory usually restored
Metabolic encephalopathy	Diagnose etiology and treat	Memory usually restored
Vitamin B-12 deficiency	B-12 vitamin therapy	Memory usually restored
Infections- meningitis and encephalitis	IV antibiotics	Memory usually restored
Medications (both prescription and over-the-counter)	Manage interactions and adverse effects	Memory usually restored
Alzheimer's disease	Cholinesterase inhibitor and glutamate modulation	Reduced rate of memory decline
Parkinson's disease	Dopaminergic stimulation	Reduced rate of memory decline and sometimes improvement
Frontal lobe dementia	Cognitive Therapy	Reduced rate of memory decline and sometimes improvement
Head injury	Cognitive therapy and medication	Frequent memory improvement
Cerebro-vascular disease	Anti-platelet therapy, manage risk factors, cognitive medication	Reduced rate of memory decline and sometimes improvement
Normal pressure hydrocephalus	Reduce pressure fluctuations with dynamic pressure shunt	Reduced rate of memory decline and sometimes improvement
Seizure disorders/Epilepsy	Anti-epileptic medications	Reduced rate of memory decline and sometimes improvement

Another important benefit of memory screening is that the MCI Screen accurately identifies memory loss due to Normal Aging. Undue stress and anxiety over perceived memory loss is harmful to one's health but can be easily relieved with an accurate verification of normal memory function.