

## DEMENTIA SCREENING

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### *IS IT A GOOD IDEA TO SCREEN PATIENTS FOR EARLY DEMENTIA?*

Prevailing opinions on the subject are mixed. Identification of the patient with presymptomatic dementia opens the possibility of therapeutic intervention before the pathology is advanced. Theoretically, early treatment would have disease-modifying effects, and this would be a *good thing*. The fact that there are no such treatments at the present time is not an argument against screening and early diagnosis. After all, no such treatment will ever be developed unless we are able to test it in people who have preclinical dementia; by the time the disease is overt, treatment may be too late.

The idea of screening and early diagnosis is current. The population is ageing in many countries, and the likelihood of developing dementia, if you live long enough, may be as high as 0.5. It has been natural, then, for the public eye to turn to the problem. People may appreciate that no cure is on the immediate horizon, but they are interested in prevention, early diagnosis and timely treatment. These strategies, after all, proved enormously successful in the recent “wars” against heart disease and cancer. Technologies for prevention, early diagnosis and treatment are not well developed with respect to dementia, but that has not assuaged public ardor for new advances.

The public and the medical community have been conditioned by the ubiquity of screening measures for cardiovascular disease and diabetes, hypertension, breast, colon and cervical cancer, and by their success. Less well understood, at least by the public, is that early diagnosis, at least for some conditions, is not necessarily a good thing. Certain cancers, notably prostate and lung, can be detected at a very early stage, but treating these cancers, or attempting to extirpate them, is likely to inflict greater morbidity and mortality than the tumors themselves would likely cause. That is because the most modern screening techniques detect cancers that are indolent, or slow-growing and with low likelihood of mortality. It is counter-intuitive, but in some cases early diagnosis may do more harm than good.

With respect to dementia, a good many physicians feel this way: if you knew that someone had early AD, what would you do about it? And wouldn't that knowledge have devastating emotional effects on the patient? The fact is that clinical trials of various drugs and supplements have not been successful in delaying the conversion of MCI to dementia. In this light, dementia screening is *not a good thing*.

In your author's opinion, the potential benefits of screening and early diagnosis outweigh the disadvantages. It is an embarrassment that, of all the major diseases, dementia is the only one for which early diagnosis strategies have *not* been emphasized. I am old enough to remember when the diagnosis of cancer was something to be ashamed of, and kept quiet. Perhaps the public attitude about cancer changed because of medical advances in the treatment of cancer; as I remember, though, attitudes changed, and that's what led to increased support for

medical research and cancer treatment. If we were able to identify preclinical dementia with confidence, we could test new treatments at a point when they were more likely to make a difference.

Diagnosis of preclinical dementia would be of inestimable value to families, for long-term planning; to employers and public safety officers, particularly with respect to driving; and especially to clinicians. It would give them a better handle on the neuropsychiatric disorders that develop during the prodromal phase of dementia, like depression, anxiety and personality change. Finally, when elderly people are asked if they would prefer to be screened, if a reliable test were available, the majority answer "yes".

Our premise, then, is that dementia screening is important. The next question is, is it possible? Wouldn't it be nice to have a simple test? The Holy Grail of dementia screening would be a short and inexpensive test that was (to psychologists) reliable and valid and (to physicians) sensitive and specific. Such a test would detect not only early dementia, but also presymptomatic dementia. The originator of such a test would be Galahad, indeed, to elderly patients and their physicians.

In fact, there are a number of tests in existence that are good for dementia screening. Since the essence of dementia is progressive cognitive impairment, the tests are computerized neurocognitive batteries. Administering a neuropsychological test on a computer is quick and inexpensive, and such tests are remarkably sensitive to very small decrements in cognitive performance. Because dementia usually has a gradual or "insidious" onset, careful appraisal of a patient's cognitive state can demonstrate an early or preclinical phase of the condition.

Would that it were so easy. Having developed one such computerized battery, CNS Vital Signs, I can assure the reader that no Galahad is wielding this pen. In fact, computerized testing generates as many questions as it does answers. During the development phase of our test battery, for example, when we were collecting data from a large number of normal people, it was not uncommon to discover individuals who did poorly on tests of memory, processing speed or executive function, and who happened to have one or more clinical risk factors for dementia, like a positive family history or incipient cardiovascular disease. Sometimes, these patients were in their forties or early fifties. Technically, they might qualify for the "diagnosis" of mild cognitive impairment (MCI). But they were normal volunteers; they weren't even *patients*. What to do in such an event? We have every reason to believe that, were computerized neurocognitive tests routinely administered to middle-aged people, enormous numbers would be discovered to have mild cognitive dysfunction. And it would take 10, 20 or 30 years to discover if that appraisal were meaningful.

We have encountered people in our clinic who did poorly on tests of memory, processing speed or executive function, and who happened to have one or more clinical risk factors for dementia, like a positive family history or incipient cardiovascular disease. Sometimes, these patients were in their forties or early fifties. Because they were patients, we could make the diagnosis of MCI and do something appropriate. We treated them symptomatically, e.g., for depression, or anxiety, and then followed-up. Years later, we expected to see further signs of cognitive decline, and sometimes we did. More often, however, their performance on neuropsychological tests was stable, or it actually improved. I don't think our estimable treatment necessarily delayed the clinical expression of an underlying dementia. I think that some of those patients had a form of MCI that was not "pre-dementia" and that others had an indolent or relatively benign form of the condition.

Screening for preclinical dementia is going to create numerous difficulties, but we continue to believe that it is an important thing to do. The potential benefits more than outweigh

the disadvantages. We also believe that dementia screening is an available technology, and that computerized neurocognitive testing is the best way to do it on a mass scale. But we also know that dementia screening is nothing like screening for cervical cancer or breast cancer or high blood pressure. Dementia is a much more complex condition than cancer or cardiovascular disease. Cognition is a much more complex variable than cellular pathology, radiographic images or blood chemistries. Simply identifying a person who performs poorly on a cognitive test does not comprise dementia screening.

Dementia screening and early diagnosis is not a matter of finding the right test. Cognitive testing for dementia screening is necessary but not sufficient. In fact, cognitive testing can indicate impairment in people who are never going to develop dementia. Testing can be quite normal, as we shall see, in patients who have prodromes of dementia like personality change. What is essential for effective screening is not a test, but a systematic approach.

In this chapter, we shall present a systematic approach to dementia screening. The method addresses three questions:

1. What are we looking for?
2. How do we find it?
3. Whom should we screen?

In the following chapters, we shall address the most important question, what are you going to do about it?

## WHAT ARE WE LOOKING FOR?

### *EARLY COGNITIVE SIGNS OF DEMENTIA*

We know that the preclinical phase of dementia usually precedes clinical diagnosis by many years. AD neuropathology begins during the third and fourth decades of life. There are four ways to detect it, potentially: gene studies, functional brain imaging, biomarkers and cognitive testing. At this point in time, only cognitive testing is appropriate for widespread clinical application, and numerous studies have shown early signs of neurocognitive impairment, not only in people who are bound to develop AD, but all of the dementias.

#### *Cortical Dementia*

The most common cortical dementias are AD and fronto-temporal dementia (FTD), and are typified by symptoms of cortical impairment: classically, amnesia, aphasia, agnosia and apraxia. The early signs of cortical dementia, however, are subtle.

Studies of people who are vulnerable to Familial Alzheimer's disease (FAD) by virtue of presenilin mutations indicate early signs of neuropathology and cognitive weakness. When carriers of that mutation are examined, years before dementia symptoms arise, they are found to have hippocampal loss, temporal lobe atrophy, memory impairment and deficits in perceptual and spatial skills. In the case of one 20 year old carrier who did relatively well on a memory test, functional imaging demonstrated a much wider area of cerebral activation during performance of the task than one would normally expect to see. This, presumably, represented a compensatory mechanism to deal with "preclinical neural dysfunction. (This may be why some people with preclinical dementia do not decline, as expected, on serial tests. They are trying hard to convince themselves that nothing is wrong, and they try harder on the tests. This sounds silly, but I am convinced that it happens.)

It has long been believed that the most common early deficit in patients with AD is in recent or episodic memory – that is, memory for personal experience in one’s recent past. Examples are remembering what you had for dinner yesterday, what you went to the grocery store to buy, or how to find your way back to the hotel after you go for a downtown stroll. The memory deficit may be verbal (the grocery list) or visuo-spatial (the way back to the hotel).

Selective impairment of episodic memory is not only the first sign of AD, it is a preclinical marker for AD as well. There is convergent data to this effect from studies of people who are genetically predisposed, from longitudinal studies of patients with MCI, and from epidemiological studies of incident AD cases. Presymptomatic memory deficits are most readily apparent in tests of learning new material, both verbal and visuospatial and have been described, in prospective studies, as many as eight years before AD was diagnosed. There is relative sparing of immediate memory (working memory, e.g., Digit Span), but the rate of forgetting is rapid within the first several minutes after exposure to a verbal or figural stimulus. In one study, patients who later developed AD showed presymptomatic deficits on a computerized test of verbal memory (Paired Associate Learning).

Memory impairment is not the only early sign of AD, however. Attention is also affected in the early stages. Measures of complex attention (e.g., divided attention, selective attention, set-shifting, response selection) are particularly sensitive while measures of sustained attention (e.g., vigilance, continuous performance) are relatively preserved.

Complex attention is, in fact, a component of the executive control system, and tests like Trails, the Stroop, Halstead Categories and the Wisconsin Card Sort are among the “most sensitive and useful” indicators of early AD. Fronto-temporal dementia, a familial condition caused by a mutation on chromosome 17, is typified by executive dysfunction, but not memory deficit. Executive control deficits were apparent in some of the youngest mutation carriers, who were evaluated many decades prior to the expected onset of dementia.

Cognitive slowing is another early sign of AD. Even before “slowing” is subjectively apparent to the patient or the patient’s family, it can be demonstrated in the latency of evoked potentials, or in psychological tests that measure reaction times, especially choice or complex reaction times. (Slowed reaction times and delayed EP latencies can be demonstrated in HIV-infected individuals long before there is clinical evidence of cerebral deterioration.

Historically, deficits in attention and information processing speed have been identified with the subcortical dementias. As new technologies are applied, like computerized tests that can generate results with millisecond accuracy (something that can’t be done with a paper-and-pencil test), it is possible that we shall understand the commonalities of the various dementias. The point to emphasize, though, is that AD, even in its earliest stages, is not just a disease of memory. Long before any clinical signs are apparent, before even a skilled neurologist or neuropsychologist can detect the condition, there are signs of cognitive weakness in various cognitive areas. Supportive evidence continues to accrue, for example, from PET studies of people with a genetic predisposition, who show evidence of reduced glucose metabolism in the temporal lobes, and from longitudinal studies, like the “Nun Study.” The earliest “detectable cognitive deficits” are not only tests of verbal and visual memory but also measures of complex attention, executive control and reaction time/information processing speed.

#### *subcortical dementia*

In the so-called subcortical dementias, the primary pathology is in the basal ganglia or subcortical white matter. Examples are Lewy Body dementia (DLB), Huntington’s disease (HD), Parkinson’s disease (PD), Wilson’s disease (WD), progressive supranuclear palsy, and vascular

dementia (CVD), or multi-infarct dementia or leuko-araiosis. Theoretically, the subcortical dementias are characterized by a different complex of cognitive symptoms: low arousal, deficits in vigilance, complex problem solving and psychomotor speed. The neuropsychological tests that are most sensitive to subcortical degeneration are time-dependent tests.

Subcortical dementias that affect the basal ganglia are also associated with impairment in functions that are usually associated with the prefrontal cortex (attention tests, executive function tests). That is because the basal ganglia participate in virtually all of the complex function systems that reside in the frontal lobes, a relationship that is reflective of the evolution of the frontal lobes, phylogenetically and developmentally.

Ultimately, the neurocognitive deficits of patients with cortical and subcortical dementias converge. As cortical disease advances, it inevitably involves subcortical tissues, and as subcortical disease advances, it inevitably compromises cortical function. But early in the course of both disorders, their neurocognitive profiles are differentiated. A neurocognitive battery that is sensitive to early manifestations of cortical dementia should emphasize memory, selective attention and cognitive flexibility. A subcortical dementia battery should include measures of reaction time and information processing speed, motor speed, working memory, and sustained attention.

Parkinson's Disease (PD) is almost always associated with at least a degree of cognitive impairment; a substantial number, but not all PD patients, become demented. Two types of dementia can occur in patients with PD. One has the characteristics of a subcortical dementia, and another shares the typical characteristics of AD. Cognitive impairments have been described, early in the course of PD, include sustained or shifting attention, memory, visuospatial ability, reaction time and processing speed.

Another type of dementia associated with mild or moderate parkinsonism is dementia with Lewy bodies (DLB). Lewy bodies are spherical intraneuronal inclusions that are found, in PD, mainly in the substantia nigra. In DLB, they are also found in the brain stem and the neocortex. The severity of dementia is correlated with the density of Lewy bodies.

DLB is not an uncommon dementing disease and accounts for 12-36% of dementia cases; less common than AD but almost as prevalent as vascular dementia. The wide range of prevalence data probably reflects the difficulty even dementia specialists have in distinguishing among DLB, AD and PD dementia, and the validity of the diagnostic criteria have been questioned. The overt characteristics of the condition, however, are striking, and belie the contention that it is just one more neuropathological oddity: they include marked fluctuations of alertness and cognitive performance, moderate parkinsonism, visual hallucinations, unexplained falls and syncopes, delirium, and adverse, sometimes severe reactions when the patients are treated with antipsychotic drugs. Mean age of onset is between 60 and 68 years. In contrast to AD, males are more commonly afflicted.

The neuropsychological profile of DLB is only gradually coming into focus, but it seems to have a subcortical profile. Compared to AD patients, DLB patients are more likely to have problems with attention, reaction time, working memory and visuo-perceptual ability.

The first symptoms of Huntington's Disease (HD) are typically choreic movements or behavioral aberrations, and cognitive decline only becomes obvious later on. Sometimes, though, memory problems are the first overt symptoms of the disease. Patients with mild or early HD have been found to have prominent deficits in memory, visuospatial ability and cognitive flexibility (e.g., Stroop test).

Although overt dementia is a relatively late symptom of HD, the gradual erosion of intellectual abilities begins long before clinical signs (i.e., choreic movements) become evident. This has been established by studies of asymptomatic carriers of the HD gene on chromosome 4. The identification of excessive trinucleotide repeats (CAG) is central to the genetic defect. But even before the HD gene was identified, it was clear that it did not simply “turn on” at the time involuntary movements begin to appear; subtle neurocognitive impairments can be demonstrated many years earlier.

Neuropsychological deficits in presymptomatic carriers of the HD gene have been noted in several areas, consistent with fronto-striatal pathology: memory and verbal learning, visuospatial abilities, especially visuospatial memory, executive abilities (e.g., the Wisconsin Card Sort test), attentional set shifting and verbal fluency, attention, learning and planning and information processing speed.

Patients with untreated Wilson’s Disease (WD) ultimately develop diffuse cognitive impairments, including intelligence, memory, perceptual speed, word fluency, rule finding and mental rotation. Overt neurocognitive deficits do not usually arise in WD until after neurological or psychiatric problems are manifest. As a result, patients’ performance on neuropsychological tests is complicated by the co-occurrence of motor impairment, which can compromise the speed and accuracy of responding. However, cognitive impairment is not necessarily correlated with neurological signs, and if one controls for motor impairment, subtle deficits in perceptual speed can be detected even in patients who are asymptomatic.

Although few multiple sclerosis (MS) patients are actually demented, cognitive dysfunction occurs in at least half of patients. General intelligence and language tend to be preserved in MS, but neurocognitive deficits are discovered in memory, attention, information processing speed, executive functions and visuospatial perception. In MS patients, the extent of lesions on MRI is correlated with deficits in memory, information processing speed, abstract reasoning, naming/verbal fluency and visuo-perceptual organization.

Patients with mild MS usually perform well on standard neuropsychological tests, apart from mildly reduced performance on tests of long-term memory. It has been suggested, however, that deficits in working memory are the earliest neurocognitive manifestation of the disorder.

Cerebrovascular dementia (CVD) is the second commonest form of dementia, after AD. The diagnosis is based on: evidence of cognitive loss, most often subcortical; vascular brain lesions demonstrated by imaging; and exclusion of other forms of dementia, such as AD.

Cerebral small vessel disease is a very common condition. Its onset is insidious and mild cognitive dysfunction may be the first clue to its presence. Indeed, the diagnosis is often serendipitous – multiple small white matter lesions are identified on an MRI that is undertaken for some other reason. The clinical presentation may be pre-syndromal: a middle-aged patient has a mild concussion, but complains of persistent, vague cognitive impairment; and so, an MRI is ordered. White matter lesions are demonstrated; not the result of trauma, but of pre-existing small vessel disease. In such cases, the only overt consequence of small vessel disease is a reduction in the patient’s “cerebral reserve.” In this example, it is the patient’s capacity to recover quickly from a minor brain insult.

White matter disease is an MRI diagnosis. The typical finding is white matter lesions (WML) or lacunes in the basal ganglia, thalamus and periventricular regions. They may also be noted in the frontal lobes. WML’s are so common in the MRI’s of elderly people that the film may be read as “normal for age.” A few such lesions may, indeed, be a correlate of normal ageing, but the number and extent of WML’s is correlated with cardiovascular risk factors, cognitive impairment and disability. But even healthy elderly subjects with WML’s have subtle disturbances in basic

attention and selected frontal lobe functions, including digit span, divided attention (multitasking), sorting (categories) but not IQ, memory, language, visuospatial ability or information processing speed.

One does not need an MRI to suspect the diagnosis of small vessel disease. A middle-aged patient with significant cardiovascular risk factors is likely to have the disorder, to some degree or another. Fundoscopic examination of the retinal vessels can indicate vascular pathology; the retinal arterioles are as vulnerable to vasculopathy as the arterioles of the brain.

Subtle signs of subcortical dementia occur in patients who are at risk for CVD by virtue of cardiovascular risk factors. Hypertensive patients, for example, have significant deficits in attention and verbal memory, even when the effects of ageing are controlled. Primary systemic hypertension is correlated with cognitive impairment in executive functioning, constructional- and memory-recall, but not in memory recognition or language. Elevated midlife BP, and the resulting increase in white matter hyperintensities, increase the risk for MCI in older men to at least the same degree as the ApoE4 genotype. Elderly patients with hypertension, but without dementia or stroke, have deficits in tests of reaction time, visual and verbal memory and attention, when compared to matched controls. Patients with hypertension are also at high risk to develop severe cognitive impairments following cardiac surgery.

In a large, multi-center longitudinal investigation of individuals with cardiovascular risk factors, followed from middle-age, hypertension and diabetes mellitus were found to be positively related with cognitive decline. The coding test (processing speed) was particularly sensitive.

The performance of patients with Type-2 diabetes on a battery of neurocognitive tests, compared to controls, is somewhat complex. In one study, performance on measures of visual memory, attention, executive function, general mental functioning and information processing was not impaired, but verbal memory was. The impairment in verbal memory was correlated with duration of the condition but not with indicators of recent glycemic control (e.g., HbA1c).

**Table X.01. Cognitive Impairment in Early Dementia**

		Memory	Attention	Executive Function	Language	Visuospatial	Personality	Behavior	Insight
CORTICAL DEMENTIAS	FAMILIAL ALZHEIMER'S	X							X
	ALZHEIMER'S DISEASE (AD)	X	X		X	X		X	
	PARKINSON'S DISEASE cum AD	X	X	X	X			X	X
SUBCORTICAL DEMENTIAS	PD LEWY BODY DEMENTIA			X	X		X		X
	HUNTINGTON'S DISEASE	X			X	X		X	X
	WILSON'S DISEASE						X	X	
	MULTIPLE SCLEROSIS	X					X		
	WHITE MATTER DISEASE			X	X	X	X		
	SYSTEMIC HYPERTENSION	X	X	X	X	X			
	DIABETES MELLITUS	X		X	X	X		X	

In all of the dementias, and in conditions that predispose to dementia, it is possible to detect signs of cognitive impairment early in the course of the disorder, before overt neurological or functional deficits are apparent. The theoretical differentiation between cortical and subcortical dementias is supported, to a degree.

It is possible, therefore, to screen for preclinical dementia using cognitive tests. The diversity of the dementias, however, indicates that no one domain is selectively afflicted, even in AD, and, therefore, no one test is sufficient for screening purposes. Screening should rely on a battery that contains, at the least, tests of memory, reaction time, processing speed, sustained and complex attention, executive function and visual-perceptual skills.

## HOW DO WE FIND IT?

### *QUICK, OFFICE-BASED TESTS*

Physicians use the **Mini-Mental State Examination (MMSE)** more than any other instrument to evaluate patients with cognitive disorders. It is quick and easy to administer, and is particularly useful for tracking demented patients over time. Although it covers several cognitive domains, it generates a single score: a number from 30 (best) to 0 (worst). It does that, however, in the most superficial way. It has a “ceiling effect”; that is, it is not at all sensitive to patients with mild degrees of cognitive impairment. It is not hard to score 29 or 30 on the MMSE, especially if you are a well-educated person. The insensitivity of the MMSE to relatively mild states of cognitive impairment is well established. Patients who do perfectly well on the MMSE may still be impaired when they are administered a more sophisticated cognitive battery.

In two independent longitudinal cohorts, two simple tests were as sensitive and specific for dementia screening as the MMSE: the recall of a five-item name and address, “John Brown 42 Market Street Chicago” and verbal fluency for animals (“Name as many animals as you can in one minute”). Combining these two tests generated better sensitivity and specificity than the MMSE.

On the MMSE, a score of 21-24 has been suggested as “the cutoff point for suggesting the presence of dementia.” By the time the patient has declined to this level, though, the condition is already well-established. The MMSE is certainly useful for diagnosing the condition when it is symptomatic, and it is good for tracking the course of dementia as the disease progresses. But it is not appropriate for picking up early or presyndromal signs.

Even though the MMSE is a crude instrument compared to neuropsychological testing, it is far more likely to detect cognitive impairment in elderly patients than routine clinical assessment by a medical practitioner. In one study of 446 elderly patients, for example, general practitioners diagnosed cognitive impairment in only 5%; the MMSE, 21%.

Researchers have tried to refine the process of medical screening for early dementia. Since memory impairment is an early sign of dementia, they have focused on short but reliable tests of episodic memory, for example, the Memory Impairment Screen and the Hopkins Verbal Learning Test. Such tests are quick and easy to administer and have high sensitivity and specificity (for dementia, though, not for pre-symptomatic dementia).

There are also abbreviated batteries of tests for dementia screening. The Seven Minute Screen (which actually takes 7 minutes and 42 seconds) includes tests of memory, orientation, clock drawing and verbal fluency. Another battery employs the Boston Naming Test, the Selective Reminding Test and the similarities subtest from the WAIS-R, but it probably takes a lot longer than 7 minutes and 42 seconds. There are many other screening tests used by neurologists and psychiatrists: the Clock Drawing Test, the Time and Change Test, the Blessed Information-Memory-Concentration Test, the Kokmen Short Test of Mental Status, DemTect and others. These are all worthwhile tests, but they share the disadvantages of the MMSE. They are quick and easy to administer, but they are not sufficiently sensitive to pick up very early cases of cognitive decline.

### *DEMENTIA RATING SCALES*

Rather than test a patient for cognitive impairment, some physicians prefer just to inquire about the problem. Ask the patient, or ask someone who lives with him. This is, in fact, what is

done, for example, in clinical trials of potential dementia drugs; the inquiries, though, are systematic, and in the form of rating scales.

Several dementia rating scales have been developed. They are reliable, and they tend to correlate well with the results of neuropsychological tests. In fact tests like the MMSE are neither more sensitive nor specific than informant questionnaires.

Dementia rating scales in common use include the ADAS (Alzheimer Disease Assessment Scale), the SADAS (Standardized Alzheimer Disease Assessment Scale), the IADLS (Instrumental Activities of Daily Living Scale) the PSMS (Physical Self-Maintenance Scale), the CPS (Cognitive Performance Scale), the DRS (Dementia Rating Scale), the SIDAM (Structured Interview for the Diagnosis of Dementia). There are many others. In fact, a post-hoc assessment rating can be derived from the Minimum Data Set, a comprehensive assessment of the patient's functional status that all US nursing homes are required to complete (by Medicare) when patients are admitted.

The course of a dementing illness can be tracked by administering a questionnaire to the patient's caregiver. The Short Memory Questionnaire, for example, inquires after problems observed by the caregiver in various situations.

Rating scales, then, are probably as good as the MMSE for tracking the course of a dementing condition, but they are not suitable for screening or early diagnosis. A questionnaire will only record data that the patient, or caretaker, observes. It cannot identify the presymptomatic patient.

*FORMAL NEUROPSYCHOLOGICAL TESTING*

Formal neuropsychological testing has always been considered the "gold standard" for dementia diagnosis. In Table 2, we list the cognitive tests that are most likely to express the earliest cognitive signs of cortical and subcortical dementia. If these tests were given together, they would be sufficiently sensitive to pick up the earliest signs of dementia, whatever the cause. (The list in Table 2 does not include all of the cognitive deficits that occur during the course of a dementing illness. It is just a list of the deficits that are known to occur during the pre-symptomatic stage.)

**Table X.02. An Appropriate Dementia Screening Battery**

Psychomotor speed (e.g., Coding)
Verbal Memory (word list learning, prose learning)
Visual memory (faces, geometric figures)
Prose memory (sentences, stories)
Executive function (e.g., Stroop, Categories, Card Sort)
Selective attention (Set shifting, multitasking)
Simple and Complex Reaction Time
Information Processing Speed (Trails, Coding)
Sustained Attention (Continuous Performance Test)

The tests in Table 2 are components of standard neuropsychological assessment. (Formal testing also includes an IQ test and Psycho-educational tests that address the patient's premorbid cognitive status, and personality tests, like the MMPI, to screen for psychopathology.)

Neuropsychological testing may be the “gold standard” for dementia diagnosis, but a full battery takes 4-8 hours and may cost \$1000-3000. For this reason alone, it is not appropriate for routine annual screening, even for patients at special risk.

Dementia researchers have struggled with this problem, and have tried to develop a shorter neuropsychological battery. One widely used battery is known as the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) and includes the verbal fluency test, the Boston naming test, word list memory, recall and recognition, constructional praxis and recall of constructional praxis. The CERAD is described as “highly accurate” in differentiating independent samples of normal controls and patients with depression, MCI, mild and moderate AD. Others suggest that CERAD may not be sufficiently sensitive to detect MCI and relying on the test battery “might result in false negatives.”

### *COMPUTERIZED SCREENING TESTS*

The dementia screening battery in Table 2 is formidable, even to specialists in psychiatry and neurology, let alone to internists and family practitioners. But if the battery were computerized, it would be feasible to administer it in a physician's office. Patients could take the test without supervision by medical personnel. A low-cost screening battery could be administered on an annual basis to patients at risk. As it happens, almost all of the cognitive functions and tests listed in Table 2 as signs of early dementia have been computerized.

The CANTAB (Cambridge Neuropsychological Test Automated Battery) is said to have been used “quite extensively” in the testing of patients with dementia, Parkinson's disease, Korsakoff's syndrome and depression. The entire battery takes about 90 minutes to administer, but a single test from the CANTAB battery (paired associate learning) is said to “provide firm evidence of risk at least 18 months before formal AD diagnosis...(and) distinguishes individual mild AD patients from depressed and control subjects with high accuracy.” PAL combined with the Graded Naming Test (not part of the battery) was even better.

A subtest of the CogState battery (continuous learning task) was reported to be more sensitive than conventional neuropsychological measures to memory decline in patients with amnesic MCI over a period of 12 months. The CogState battery was also sensitive to the earliest signs of AIDS dementia complex.

The Neurotrax battery (or “Mindsteams”) was successful in discriminating normal controls from patients with MCI and normals from MCI and mild dementia patients, even in the face of comorbid depression.

CNS Vital Signs, the author's contribution, has discriminant validity in studies of MCI and mild dementia and is sensitive to different subtypes of MCI.

The literature cited in this section was generated by the test developers themselves, or their close associates; since CANTAB, CogState, NeuroTrax and CNS Vital Signs are commercial products, one awaits confirmatory data from disinterested sources. In one such study, a computerized battery, CDR (Cognitive Drug Research Computerized Assessment System) was found to “have little added value in the diagnostic work-up of dementia in general practice.” This might possibly be a function of the test battery itself; in another study, CDR was not sensitive to cognitive decline in elderly people over a six-year period. Studies of noncommercial batteries, like the NES2 and ANAM have yielded results largely in agreement with the commercial batteries.

When computerized neurocognitive testing is compared, head-to-head, to conventional neuropsychological batteries, the results are comparable. Similar tests yield similar results. Each method has advantages and disadvantages. Examination by a neuropsychologist is more

flexible, more comprehensive, and more sensitive to subjective issues, like the patient's mood, his level of motivation, and the possibility of exaggerated or invalid responding. Computerized testing is quicker and less expensive. Computerized tests are probably more sensitive to mild cognitive dysfunction than conventional tests, because they are timed, and usually in milliseconds. This kind of precision renders a test more sensitive to subtle neurocognitive abnormalities, and lowers the false negative rate. As we shall see in the next chapter, it also raises the false positive rate.

## WHOM SHOULD WE SCREEN?

Older people are at risk to develop a dementing condition if they have a positive family history, especially of early onset dementia; if they have had a brain injury or a history of toxic exposure; if they have the  $\epsilon 4$  allele; if their educational attainment is low; if they have cardiovascular risk factors; and if they are depressed, or have a history of depression. Administering a sensitive neurocognitive test battery to such people will usually demonstrate some measure of cognitive impairment. Administering the battery on successive occasions, say, at six-month intervals, will indicate progressive deterioration in some, but not all. If the rate of decline exceeds the normal rate of ageing-related cognitive decline, the patient may be said to have "Mild Cognitive Impairment." At some later point, the trajectory of cognitive decline of some, but not all, will transect the threshold of disability. At that point, the patient can be said to have dementia.

The first step in an approach to dementia screening is to be alive to the various factors that can contribute to its development. However, of all the risk factors that contribute to dementia the most important is ageing. For that reason, it is arguable that everyone should be screened for early signs of dementia, beginning at age 40 or 50. If that were infeasible, then at least we should screen people who were at risk by virtue of one or more of the conditions described above.

Physicians refer elderly patients for formal neuropsychological testing because they suspect dementia. Usually, the patient is exhibiting symptoms, and has scored poorly on an office-based test, like the MMSE. Testing is used, therefore, to *confirm* the diagnosis. As we know, by this time the patient probably has a well-developed dementing condition. Standard testing will usually reveal deficits in several cognitive domains. The pattern of deficits is typical of one form of dementia or another. The diagnosis is thus affirmed.

With computerized testing, however, the process is turned around. Because computerized testing is quick and efficient, and requires no professional time whatever, it can be done routinely, for example, as part of an annual medical examination. The purpose of testing, therefore, would be not only to identify cases of MCI; if one were to begin screening patients at a young age, perhaps during their forties, a baseline would be generated to which later test performance could be compared.

## PRACTICAL PROBLEMS IN DEMENTIA SCREENING

When we developed CNS VS, we were confident that primary care physicians would embrace the technology, because computerized neurocognitive testing provided objective data for physicians to respond to a number of clinical questions: the diagnosis of ADHD, concussion management, neurocognitive drug effects, fitness to drive or to return to work, and, of course, early dementia. We were disappointed. Physicians are trained to interpret EKG's, laboratory tests, radiographs and other clinical data of inordinate complexity, but they are not accustomed to

interpreting the results of neuropsychological tests. What is one to make of the isolated finding of slow processing speed in a fifty-year old patient who is otherwise healthy, when all the other tests on the battery are within normal limits? If a patient does poorly on a test of figural memory but verbal memory is intact, does that mean the patient ought to have a dementia work-up? Suppose the patient says, "My memory has always been terrible" or "Maybe that's why I did so poorly in geometry when I was in high school." Or, "I always get so nervous when I take tests like that."

The literature indicates that many dementia patients seen in primary care clinics are undiagnosed, and is supportive of screening for cognitive impairment as a goal of high-quality geriatric medical care. The introduction of a cognitive screening test by medical assistants was not disruptive to workflow, in at least one study. Screening was associated with increased dementia diagnosis, specialist referrals, and prescribing cognitive enhancing medications. However, new physician action relevant to dementia was likely to occur only when impairment was severe. The authors concluded that primary care physicians needed to deal with information suggesting milder states of cognitive impairment. In another study, almost half of the patients in a primary care setting declined further assessment, when screening results indicated MCI. They tended to be older patients, and patients with very mild levels of impairment.

Dementia screening is something that ought to be universal, and if so, it should be available to patients at primary care sites. But even when primary care physicians are willing to learn the technology, they discover that third party carriers are unwilling to reimburse for testing that is not done by a specialist.

Psychiatrists, psychologists and neurologists are more likely to use computerized neurocognitive tests in their practice. We have had discussions with neurologists around the country, some at academic centers, who have tried CNS Vital Signs. Many have commented that their patients "were too impaired to take it." This is a revealing event. The neurologists are clearly not seeing patients where preclinical dementia is at issue. The Vital Signs test can be taken by a nine-year old, unassisted. It can be taken by elderly patients, attended only by a family member, whose MMSE score is as low as 20 (the patient, not the family member).

It is true that computerized tests generate massive amounts of precise data that can be misinterpreted or misused by poorly trained clinicians. In our communications with psychiatrists and neurologists who have used the test in their practices, we have not always been impressed by their facility at judging exactly what the test means and what to do next. The widespread use of computerized testing by unqualified professionals would be cause for concern. What happens when patients are identified with cognitive impairments that most physicians are ill-equipped to understand or to deal with?

If one gives an MMSE and the patient scores 24, one can feel pretty sure that the patient is cognitive impaired, and may well have early dementia. But relatively small deficits on a highly sensitive computerized battery may or may not be meaningful at all. The deficits may not have any more significance than a few white matter hyperintensities on an MRI scan. They may simply represent normal inter-individual variation in the ageing brain. Or, they may be the earliest signs of dementia.

The fact that computerized neurocognitive testing is so sensitive leads to the problem of potential false positives. Dementia screening, therefore, is not simply the administration of a test. It has to be accompanied by a systematic approach. What computerized tests reveal are signs of mild cognitive impairment – in some cases, a state of preclinical dementia, and in others, something else. From this perspective, mild cognitive impairment, or MCI, is not a diagnosis in its own right. It is the occasion for a differential diagnosis, and that will be the topic of the next chapter.