I. Dementia Prevalence
   A. Increases geometrically with age
      1. 5-10% of individuals > age 65
      2. 50% of those > age 85
   B. Alzheimer’s disease is by far the most common form of dementia, affecting about 9 out of every 10 patients.
   C. Distribution of pathology in Alzheimer’s disease:

   A. Structure of appointment:
      • With both patient & caregiver: brief hx per patient’s perspective, PMH, All, Meds, SHx including education & occupation, FHx (25-40% of AD patients have at least one other afflicted relative) (10 min)
• **Caregiver alone:** History per caregiver’s perspective. Key questions: (1) What was the **first symptom** suggesting impairment, and (2) **when** did it occur? (3) What was the **pace** of the decline? Was it gradual or stepwise? (4) What cognitive areas are **currently** impaired & (5) which are the **most prominent**? (15 min)

• **Patient alone:** Physical, Neurological & Cognitive exam. (20 min)

• **Both patient & caregiver:** Assessment, further work-up and/or treatment plan. (15 min)

• Do in two visits if necessary. (An extra 10 minutes each on the history and cognitive exam is worth at least as much diagnostically as a PET or SPECT scan, neuropsychological testing, expert referral, etc., and is much more cost effective.)

B. **History:** (Although classically in neurology exam tells where, and history tells what, history often tells where as well as what in dementia.)

****Need to talk with caregiver/child/spouse alone****

  **General:** Gradual and insidious onset over months to years, not stepwise (ask about when retired and why; keep checkbook; do taxes; continue community participation; etc.)

  **Hippocampal:** Inability to learn new information, with striking preservation of older memories initially (repeats self; needs to be told information multiple times; misses appointments).

  **Temporal:** Word finding difficulties. Disruption in the semantic storage and retrieval of linguistic information (anomia, not just for names of people; empty speech).

  **Parietal:** Visuo-spatial deficits (difficulty planning routes; gets lost; cannot draw intersecting pentagons).

  **Frontal:** (late) Dysexecutive syndrome (disinhibition; aggression; agitation; also much worse memory, attention and other cognitive functions).

C. **General Exam:** Check for cervical bruits; look for signs of systemic disease (COPD, liver failure, etc.)

D. **Neuro exam:**

*Inconsistent:* focal signs suggesting strokes, subdural fluid collections, tumors, etc.; signs suggesting Parkinson’s (rigidity, tremor, etc.), PSP (no downgaze) or other neurodegenerative disease. (Note: some patients have both PD and AD.)

*Supportive (early):* none

*Supportive (mid to late):* Brisk reflexes, extensor plantars, snout, grasp, palmomental reflexes. (These are, however, not sensitive or specific.)

E. **Cognitive exam:**

Use one simple global cognitive exam to evaluate cognitive function.

*Use the MMSE*—*but copyrights held by Psychological Assessments Resources.*

*Use the Montreal Cognitive Assessment (MoCA)*—*my new favorite—*test & instructions below.

*Using the Blessed Dementia Scale (BDS).* Useful for:

* Establishing the pattern of deficits
* Evaluation of drug effects (typical increases of 3-4 points are seen [2-3 on MMSE])
* Annual comparisons (typical yearly decline of 3-4 points/year [2-3 on MMSE]).
• Framework for history (caregiver side)

Section H (5 Minutes Recall) tests new learning which is always impaired in early AD.
Section E (Information) tests recent memory, which is generally impaired in early AD.
Section I (Concentration) tests both simple attention (1-20) which is always intact in early AD, and complex attention (20-1, months backward) which may be impaired in early AD.
Section G (Nonpersonal Memory) tests remote nonpersonal memory which is generally intact in early AD (but dates of WWI is an out of date question—don’t bother with it!) (Vice president is likely most sensitive measure of cognitive dysfunction).
Section F (Personal Memory) tests remote personal memory which is always preserved in early AD.

BDS Administration and Scoring Notes: 0 indicates normal performance or a correct response. Left side (A-D; Activities, Habits, Personality subtest) is for caregiver (ask tactfully). Some items have ; “coarsening of affect” is for you to judge. AD patients can have little or great impairment on this side. (Note: if only problems with B, C or D, this may suggest a non-AD dementia.) Right side (E-I; Information, Memory, Concentration subtest) is for patient. 0-3 is normal, 4 or > indicates impairment. Give name and address for H (5 minute recall) first (they should be able to at least repeat the whole name and address together), and it will be about 5 minutes when you get to it. (Better if timed.) Can be off by one on the “hour” and “Date.” “Recognition of persons” is people they came with. Check personal memory data with caregiver or previous testing. There is a correlation between the severity of dementia and the order in which patients have difficulty with different sections of the Blessed Dementia Scale; from early to late: H, E, I, G, & F. Major deviations to this pattern may suggest another disease.

Other tests. Useful if the pattern from the BDS is unclear:

Word Fluency: Intact individuals generate more words to categories (animals, vegetables, fruits; 12-15 or > for each), than letters (F, A, S; 10-12 or > for each); early AD patients show opposite pattern, i.e. can generate more words to letters than categories. (This is the only test that uses the patient as their own control.)

Instructions: “Tell me all the words that you can think of in 1 minute that begin with a certain letter. You cannot use names or different forms of the same words. For example, if the letter was ‘R’ you could not say Richard or Roger or Rochester, because those are names. You could say ‘run’ but then you could not say ‘runs,’ ‘running,’ or ‘ran’ because those are different forms of the same word. The first letter is F....” Prompt patients if they do not give any words for any 15 second block. For efficiency, only do as many letters as needed to establish pattern or normality. For categories: “Now we’re going to do the same thing only different. I want you to tell me all the words you can think of that are all in the same category (which I will give you). The words can begin with any letters. You can say both big subcategories, as well as small individual items. For example, if the category was ‘furniture,’ you could not only say ‘tables,’ ‘desks,’ and
‘chairs,’ but also ‘armchair,’ ‘high chair,’ ‘rocker,’ ‘recliner,’ etc. The first category is ‘animals’…” Again, prompt patients after no response for 15 seconds, and only do as many categories as necessary to either establish a pattern or normality.

**Attention:** *Simple* (always intact in early AD): Digit span forwards, 1 to 20, months forwards, registration (remembering words etc. w/o distraction for 30-60 seconds).

**Attention:** *Complex* (may be impaired in early AD): Digit span backwards, 20 to 1, months backwards, calculations.

**Memory** (always impaired in early AD): (note: registration must be intact) drilled word span (= to 1 less than digit span forwards), story “Bill and Tom went fishing…”, others. If they don’t get the words on free recall, check cued recall and recognition.

**Remote Memory** (often intact in early AD): Presidents, personal information.

**Language** (usually intact early, except for naming): naming high and low frequency objects (watch & band, pencil & point), writing sentence, comprehension, repetition, (empty speech late).

**Visuospatial** (may be impaired in early AD): copy figure

F. Laboratory tests: TSH, RPR, B12, Lyme titre (CBC, lytes, BUN, Cr, glucose, LFTs, Ca, alb)

G. Imaging: MR is better for judging atrophy (esp. hippocampal), better for small vessel disease, better for evaluating for unusual conditions. CT is adequate, and better for agitated patients. (Everyone deserves at least one image in the course of their disease. E.g. a subdural on top of AD may explain the patient’s current presentation—AD patients don’t remember their falls!)

H. Additional w/u:

**Behavioral Neurology Evaluation:** (1.5-2 hrs over 1-2 visits with neurologist who has additional training in dementias.) Review history, imaging, interviews with patient & caregiver, general and neurological examinations, 20-30 minute cognitive exam. Especially important for complicated patients or those seeking second opinion of specialist. (Will follow patient if you desire.)

**Neuropsychological Evaluation:** (1-1.5 hrs with neuropsychologist (Ph.D.) + 3-6 hrs with technician for cognitive testing, over 1-3 visits.) Helpful if after your own thorough w/u including 15-20 min cognitive exam it is necessary to better characterize the existing deficit to make a diagnosis. E.g. to help determine the contributions of depression to a memory disorder, or to help evaluate someone who has an above average IQ and educational background such that although they perform normally on your office tests, you still suspect they are impaired. [Caution: all neuropsychologists are NOT equal when it comes to diagnosing dementia; only refer your patients to ones with experience in dementias.]

**Brain PET or SPECT:** Nuclear medicine test. Useful for confirming diagnosis of atypical dementia, or AD in a young patient (< age 65). In AD Expect temporal and parietal hypoperfusion. Moderate sensitivity and specificity. In correct clinical setting, areas of medial temporal, temporal, or parietal hypoperfusion suggests AD regardless of the official interpretation. PET and SPECT scans (unlike MRI) will often show significant changes from one year to the next, making them a useful follow-up test in the setting of previous negative work-up. In frontotemporal dementia, PET and SPECT shows
abnormalities in frontal lobes; in corticobasal degeneration there are abnormalities in parietal lobes; in Lewy body disease there are abnormalities similar to AD but also in occipital lobes; in primary progressive aphasia abnormalities are in left perisylvian areas. Some pathologies yield multifocal patterns: e.g., Lyme disease, cerebral vasculitis.

I. Apply new criteria for AD and MCI due to AD (see review from Budson & Solomon, 2012, at end of handout)


A. D/c or change anticholinergic agents, sedatives, etc.

B. To enhance cognition:

1. **donepezil (Aricept)**. Cholinesterase inhibitor. Main side effects are: anorexia, nausea, & diarrhea (occur infrequently, <1 out of 10), also vivid dreams. (Additionally, need to use non-cholinergic paralytic agent for anesthesia; i.e. no succinyl choline) Start with 5mg QD, increase to 10 mg after 4-6 weeks if tolerated. 23 mg tablet available for moderate to severe AD; data suggests it may improve cognition but side-effects (anorexia, nausea, vomiting, diarrhea) also more common. Low income assistance program available. Produces a noticeable improvement in most patients. FDA approved for mild, moderate, and severe AD.

2. **rivastigmine (Exelon)**. Cholinesterase inhibitor. Side-effects are more than donepezil in capsule form, but rivastigmine is now available in a QD patch which has comparable efficacy and fewer side-effects than any drug in this class. Start 4.6 mg/24 hr patch; can increase to 9.5 mg/24 hr patch after one month. The rivastigmine patch is FDA approved for mild to moderate AD and mild to moderate dementia associated with Parkinson’s disease (Lewy Body Dementia).

3. **galantamine (now generic, formerly Razadyne, formerly Reminyl)**. Cholinesterase inhibitor. Similar to Donepezil. Usually least expensive. Immediate release (IR) and extended release (ER) formulations available; ER is both easier to use and has fewer side-effects (due to lower serum peak levels). ER: Start with 8 mg QD and increase after 4 weeks to 16 mg QD. Can also go to 24 mg QD. IR: 4 mg bid and increase after 4 weeks to 8 mg bid. Can also go to 12 mg bid.

**References for cholinesterase inhibitors:**

- Improves cognition, participation in activities of daily living, & global function in mild to moderate patients with AD:
  - Donepezil: Neurology 1998;50:136
  - Rivastigmine: BMJ 1999;318:633
  - Galantamine: Neurology 2000;54:2261
- Improves cognition & behavior in mild to moderate and moderate to severe patients with AD
Galantamine: Neurology 2000;54:2269
Delay to nursing home placement by up to 2 years:
Donepezil: J Am Ger Soc 2003;51:937
Reduces healthcare expenditures because treatment costs are offset by reductions in other healthcare expenditures.
Galantamine: Neurology 2000;57:972
Donepezil: Dementia and Geriatric Cognitive Disorders 2003;15:44
Reduces caregiver time by over 1 hour per day
Mild Cognitive Impairment
Vascular Dementia
Galantamine: Lancet 2002;359:1283
Donepezil: Neurology 2003;61:479
Lewy Body Dementia
Rivastigmine: Lancet 2000;356:2031
Neuropsychiatric inventory meta-analysis
JAMA 2003;289:210
Responders and non-responders
25-30% show an improvement equivalent to a 1 year reversal of symptoms
50-60% show an improvement equivalent to a 6-month reversal of symptoms
10-15% show either less than a 6-month reversal of symptoms or no significant improvement
NEJM 2004;351:56.
How long to use them?
Studies suggest at least 4 to 5 years (CNS Drugs 2004;18:757)
Recommend: continue as long as there is quality of life to preserve.
In patients with moderate or severe Alzheimer’s disease, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over the course of 12 months. (NEJM 2012; 366: 893-903)

See Figure for Treatment outcomes curves.
Treatment expectations for cholinesterase inhibitors:
• Small but noticeable improvements:
  – Less time spent looking for keys, glasses, etc.
  – Repeats self less often
  – Dwells in past less
  – Easier time keeping track of conversation
  – More engaged, outgoing
• Will decline over time even if the cholinesterase is working.

Treatment side effects:
• Gastrointestinal effects
  – Anorexia
  – Nausea/vomiting
  – Diarrhea
• Vivid dreams
  – Take in AM or earlier PM dose
• Other cholinergic symptoms
  – Rarely slows heart rate
  – Muscle cramps
  – Increased salivation
  – Rhinorrhea
  – Can exacerbate existing ulcers (but not known to cause them)

   Cholinesterase inhibitor. Similar (perhaps fewer) side effects. 100 mcg of
huperzine A BID is equivalent to 5 mg donepezil QHS. Effects are somewhat less impressive. (Obviously, this drug should not be used with other cholinesterase inhibitors.) http://www.nutrapharm.com/

5. Memantine (Namenda). Two mechanisms: 1. Uncompetitive antagonist at the NMDA glutamate receptor. 2. Dopamine agonist. Approved for use in moderate to severe patients (MMSE 15/Blessed 15 or worse). Works well with cholinesterase inhibitors—both are better than either one alone. Improves both cognition and behavior—particularly agitation. Side-effects uncommon, < 1 out of 10. Main side-effect is drowsiness, confusion, and dizziness which is dose related, often transient, and worse in milder patients. A few patients have experienced changes in blood pressure. Pills are 10 mg. Start at half a pill, then increase weekly by half a pill: ½ qd, then ½ bid, then ½ in AM and 1 in PM, then 1 bid. Can prescribe memantine “titration pack” disp #1 sig. Use as directed, followed by memantine 10 mg BID disp #60. Latest retrospective data analysis suggest that combination therapy, memantine plus a cholinesterase inhibitor, is superior to either medication alone.
   • References for memantine:
     o N Engl J Med 2003; 348:1333
     o Int J Geriatr Psychiatry 1999;14:135
     o JAMA 2004; 291:317
     o Alzheimer Dis Assoc Disord. 2008 Jul-Sep;22(3):209-21


7. Ritalin. A useful stimulant when attention or encoding deficits are prominent, or when fatigue, somnolence, and poor energy are issues. Also great when there is a problem with napping during the day and consequent wandering at night—much better to use a stimulant in the morning than a sleeper at night. I use the 20 mg of the sustained release formulation. Can also use Concerta 18 mg or modafinil 100 mg.

8. On-going clinical trials.

C. To slow down disease progression:
   1. Lower homocysteine: Folate, B6, B12 (NEJM 2002;346:476) Can use Folgard (Folate 0.8 mg, B6 10 mg, B12 115 mcg)
   2. Statins
   3. Clinical trials.

D. Managing Agitation. For additional information see Section IV of Budson & Solomon, Memory Loss: A Practical Guide for Clinicians, Philadelphia: Elsevier Inc., 2011. Try to determine the underlying cause of agitation:
   1. Agitation is often due to anxiety
      i. Start with sertraline (Zoloft) 50 to 100 mg or citalopram (Celexa) 20 to 40 mg (others not as good.)
   2. Manage sleep cycle disturbances
      i. Limit naps
      ii. Methylphenidate (Ritalin) SR 20 mg or modafanil (Provigil) in AM if needed.
   3. Daytime agitation
i. Risperidone (Risperdal) start 0.25 mg QD
4. Nighttime agitation
   i. Trazodone start 50 mg QHS
   ii. Quetiapine (Seroquel) start 25 mg QHS
8. Refer to psychiatry if needed.
E. Social Work referral often helpful for helping patients and families deal with diagnosis, day programs, nursing home and other long term care placement.
F. Early on, Cognitive Occupational Therapy can be especially helpful for those with a bit of insight, to provide alternative strategies.
   1. Patients with very mild AD have accident rates similar to 16 to 19 year old drivers (Neurology 2000;54:2205)
   2. Have family members ride as passengers; when they feel uncomfortable patient is not safe to drive.
   3. Rehabilitation hospitals have driving evaluations ($250 to $500)

IV. Case histories

A. 81M whose children want to know if there is anything that could be done to improve his memory. Patient admits memory difficulties but cannot provide any details. 8 years ago he began getting lost repeatedly, and he mailed out letters using Christmas seals rather than postage stamps. In the last 6-12 months he has been unable to learn new information and has language difficulties including word finding difficulties and saying sentences that do not make sense. PE: mild snout and grasp. MSE: speech empty of content, word finding difficulties, and difficulty with complex grammatical commands. MMSE 13: (missing 3/3 recall, orientation, attention/calculations, pentagons). MRI….

B. 73F who c/o word finding difficulties over the past 6-12 months. Her son has also noticed that she has had to increasingly writing things down over the past 5 years in order to remember them. PE: unremarkable. MMSE 24: (missing 2/3 recall, orientation). MRI….

C. 72M with mild memory difficulties. CEO of a large company. Trouble remembering his schedule—secretary needed to remind him. Trouble remembering the content of meetings; needed to take more notes. Gradual worsening over the last two years. Never forgot anything critically important. No trouble with words or other things. Isolated problems with memory on testing. Physical exam normal. MMSE 29 (missing 1/3 recall). MRI normal.
D. 78M with memory difficulties and inappropriate behavior. 3-4 years ago had difficulty remembering things and became confused in unfamiliar places. 1 year ago began uncharacteristic behaviors: secretly watching pornography channels on cable TV, and telling sexually explicit jokes in front of his daughters. He became depressed. He lost interest in his hobbies. Often paced and moved around the house without purpose. Frequently lost his temper over minor things. PMH: on coumadin for atrial fibrillation, Paxil and trazodone for depression. FHx: dementia in mother in her 80’s. PE: bilateral paratonia. Reflexes 3+ w/ ankle clonus. Right sided Babinski; equivocal left. Prominent jaw jerk. MMSE 22 (missing 1/3 recall, orientation, attention calculations). Word fluency: 2 F words, 3 A words. MRI unremarkable. SPECT….

E. 65M p/w cognitive difficulties. Professor of English on medical leave. Forgetful for about 1 year, often confused, unable to use TV remote. Distorts memories and make false accusations. Also, less volume in voice, less expression in face, & slowness of gait. ROS: “Silent” nocturnal visual hallucinations, mainly of people. Also perceptual difficulties uncorrected by glasses. PMH: DM, HTN, depression, insomnia, mild sleep apnea. PE: Masked facies, mild grasp and palmomental reflexes, increased tone with maneuvers, +cogwheeling but no rest tremor. MMSE 29 (pentagons). MRI… SPECT…

F. 74M w/ 6 year h/o cognitive and functional decline. Problems began with “small TIAs,” e.g. he suffered a sudden decline in one day of his speech, handwriting and gait which subsequently improved, but not back to baseline. Although he has a Ph.D. from MIT, he currently has difficulty with simple calculations, remembering a short list of items, and finding his way around a familiar street. He will cry and laugh either inappropriately or with the least provocation. ROS: frequent urinary incontinence and occasional fecal incontinence. FHx: Maternal aunt diagnosed with AD in her early 70s. PE: Diminished joint position sense, graphesthesia, stereognosis. Bilateral extensor plantar reflexes. MMSE: 28 (missing 2/3 recall). Neuropsychological evaluation revealed compromised frontal lobe functioning (poor sustained and complex attention, mild impulsivity, set loss, and perseveration); his memory performance was variable—sometimes performing in the average or above average range, at other times he had extremely poor spontaneous recall with preservation of recognition. MRI….

G. 76F with poor cognition over 6 to 12 months. She had very impaired attention; it was difficult for her to focus on a conversation. She was incontinent of urine. Memory testing showed very poor recall but preservation of recognition. Her physical exam was notable for a “magnetic” gait disorder, grasp, and palmomental reflexes. CT scan….
NAME ________________________________

A. CHANGES IN PERFORMANCE OF EVERYDAY ACTIVITIES

| Inability to perform household tasks | 0 .5 1 |
| Inability to cope with small sums money | 0 .5 1 |
| Inability to remember a short list of items | 0 .5 1 |
| Inability to find way about indoors | 0 .5 1 |
| Inability to find way about familiar street | 0 .5 1 |
| Inability to interpret surroundings | 0 .5 1 |
| Impairment of regard for feelings of others | 0 .5 1 |
| Impairment of emotional control | 0 .5 1 |
| Coarsening of affect | 0 .5 1 |
| Impairment of emotional control (e.g. increased petulance and irritability) | 0 .5 1 |
| Hilarity in inappropriate situations | 0 .5 1 |
| Impairment of regard for feelings of others (e.g. depression) | 0 .5 1 |
| Sexual misdemeanor (de nova in old age) | 0 .5 1 |

B. CHANGES IN HABITS

| Eating: cleanly with proper utensils | 0 |
| messily with spoon only | 1 |
| simple solids (no utensils) | 2 |
| has to be fed | 3 |
| Occasionally misplaced buttons | 1 |
| wrong sequence, forgets items | 2 |
| unable to dress | 3 |
| Dressing: unaided | 0 |
| Tendency to dwell in the past | 0 .5 1 |

Sphincter Control: Complete | 0 |
| Occasionally wets bed | 1 |
| Frequently wets bed | 2 |
| Doubly incontinent | 3 |

C. CHANGES IN PERSONALITY

1. Increased rigidity | 0 1 |
2. Increased egocentricity | 0 1 |
3. Impairment of regard for feelings of others | 0 1 |
4. Coarsening of affect | 0 1 |
5. Impairment of emotional control (e.g. increased petulance and irritability) | 0 1 |
6. Hilarity in inappropriate situations | 0 1 |
7. Diminished emotional control (e.g. depression) | 0 1 |
8. Sexual misdemeanor (de nova in old age) | 0 1 |

D. CHANGES IN INTEREST AND DRIVES

1. Hobbies relinquished | 0 1 |
2. Diminished initiative or growing apathy | 0 1 |
3. Purposeless hyperactivity | 0 1 |

LEFT SCORE ________________

DATE ________________________  No. _______________

E. INFORMATION

| Name | 0 1 |
| Age | 0 1 |
| Time (hour) | 0 1 |
| Time of day | 0 1 |
| Day of Week | 0 1 |
| Date | 0 1 |
| Month | 0 1 |
| Season | 0 1 |
| Year | 0 1 |
| Place: Name | 0 1 |
| Street | 0 1 |
| Town | 0 1 |
| Type of Place (e.g. Hospital, home etc.) | 0 1 |
| Recognition of persons | 0 1 2 |
| Occupation | 0 1 |
| School Attended | 0 1 |
| Place of Birth | 0 1 |
| Date of Birth | 0 1 |
| Season | 0 1 |
| Year | 0 1 |
| Town | 0 1 |
| Street | 0 1 |
| Place: | 0 1 |
| Type of Place | 0 1 |
| Name of employer | 0 1 |
| Name of sibling or spouse | 0 1 |
| Name of any town where patient worked | 0 1 |
| Occupation | 0 1 |
| School Attended | 0 1 |
| Place of Birth | 0 1 |
| Date of Birth | 0 1 |
| Season | 0 1 |
| Year | 0 1 |
| Town | 0 1 |
| Street | 0 1 |
| Place: | 0 1 |
| Type of Place | 0 1 |
| Name of employer | 0 1 |
| Name of sibling or spouse | 0 1 |
| Name of any town where patient worked | 0 1 |

F. PERSONAL MEMORY

| Dates of WWI (1914-1918) | 0 1 |
| Dates of WWII (1939-1945) | 0 1 |
| President of the United States | 0 1 |
| Vice President of the United States | 0 1 |
| (Mr.) John Brown | 0 1 2 |
| 42 West (Street) | 0 1 2 |
| Cambridge, (MA) | 0 1 |

G. NONPERSONAL MEMORY

| Months backward | 0 1 2 |
| Counting 1-20 | 0 1 2 |
| Counting 20-1 | 0 1 2 |

RIGHT SCORE ________________
**VISUOSPATIAL / EXECUTIVE**

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

**MEMORY**

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

<table>
<thead>
<tr>
<th>1st trial</th>
<th>2nd trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ATTENTION**

Read list of digits (1 digit/sec.). Subject has to repeat them in the forward order

[ ] 2 1 8 5 4

Subject has to repeat them in the backward order

[ ] 7 4 2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors


Serial 7 subtraction starting at 100

[ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

**LANGUAGE**

Repeat: I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] (N ≥ 11 words)

**ABSTRACTION**

Similarity between e.g. banana - orange = fruit [ ] train - bicycle [ ] watch - ruler

**DELAYED RECALL**

Has to recall words WITH NO CUE

FACE [ ] VELVET [ ] CHURCH [ ] DAISY [ ] RED [ ]

Points for UNCUED recall only

**ORIENTATION**

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City
Montreal Cognitive Assessment  
(MoCA)

Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. **Alternating Trail Making:**
   
   **Administration:** The examiner instructs the subject: "Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)]."

   **Scoring:** Allocate one point if the subject successfully draws the following pattern: 1–A–2–B–3–C–4–D–5–E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. **Visuoconstructional Skills (Cube):**

   **Administration:** The examiner gives the following instructions, pointing to the cube: “Copy this drawing as accurately as you can, in the space below”.

   **Scoring:** One point is allocated for a correctly executed drawing.
   - Drawing must be three-dimensional
   - All lines are drawn
   - No line is added
   - Lines are relatively parallel and their length is similar (rectangular prisms are accepted)

   A point is not assigned if any of the above-criteria are not met.

3. **Visuoconstructional Skills (Clock):**

   **Administration:** Indicate the right third of the space and give the following instructions: “Draw a clock. Put in all the numbers and set the time to 10 after 11”.

   **Scoring:** One point is allocated for each of the following three criteria:
   - Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
   - Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
   - Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centred within the clock face with their junction close to the clock centre.

   A point is not assigned for a given element if any of the above-criteria are not met.
4. **Naming:**

**Administration:** Beginning on the left, point to each figure and say: “Tell me the name of this animal”.

**Scoring:** One point each is given for the following responses: (1) camel or dromedary, (2) lion, (3) rhinoceros or rhino.

5. **Memory:**

**Administration:** The examiner reads a list of 5 words at a rate of one per second, giving the following instructions: “This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn’t matter in what order you say them.” Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: “I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time.” Put a check in the allocated space for each word the subject recalls after the second trial.

At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, “I will ask you to recall those words again at the end of the test.”

**Scoring:** No points are given for Trials One and Two.

6. **Attention:**

**Forward Digit Span:** **Administration:** Give the following instruction: “I am going to say some numbers and when I am through, repeat them to me exactly as I said them”. Read the five number sequence at a rate of one digit per second.

**Backward Digit Span:** **Administration:** Give the following instruction: “Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order.” Read the three number sequence at a rate of one digit per second.

**Scoring:** Allocate one point for each sequence correctly repeated, (N.B.: the correct response for the backwards trial is 2-4-7).

**Vigilance:** **Administration:** The examiner reads the list of letters at a rate of one per second, after giving the following instruction: “I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand”.

**Scoring:** Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).
Serial 7s: Administration: The examiner gives the following instruction: “Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop.” Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond “92 – 85 – 78 – 71 – 64” where the “92” is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

7. **Sentence repetition:**

   Administration: The examiner gives the following instructions: “I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]: I only know that John is the one to help today.” Following the response, say: “Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]: The cat always hid under the couch when dogs were in the room.”

   Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today;" substituting "hides" for "hid", altering plurals, etc.).

8. **Verbal fluency:**

   Administration: The examiner gives the following instruction: “Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready? [Pause] Now, tell me as many words as you can think of that begin with the letter F. [time for 60 sec]. Stop.”

   Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject’s response in the bottom or side margins.

9. **Abstraction:**

   Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: “Tell me how an orange and a banana are alike”. If the subject answers in a concrete manner, then say only one additional time: “Tell me another way in which those items are alike”. If the subject does not give the appropriate response (fruit), say, “Yes, and they are also both fruit.” Do not give any additional instructions or clarification.

   After the practice trial, say: “Now, tell me how a train and a bicycle are alike”. Following the response, administer the second trial, saying: “Now tell me how a ruler and a watch are alike”. Do not give any additional instructions or prompts.
Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:

- Train-bicycle = means of transportation, means of travelling, you take trips in both;
- Ruler-watch = measuring instruments, used to measure.

The following responses are not acceptable: Train-bicycle = they have wheels; Ruler-watch = they have numbers.

10. **Delayed recall:**

**Administration:** The examiner gives the following instruction: “I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember. Make a check mark (✓) for each of the words correctly recalled spontaneously without any cues, in the allocated space.

**Scoring:** Allocate 1 point for each word recalled freely without any cues.

**Optional:**
Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (✓) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, “Which of the following words do you think it was, NOSE, FACE, or HAND?”

Use the following category and/or multiple-choice cues for each word, when appropriate:

- **FACE:**
  - category cue: part of the body
  - multiple choice: nose, face, hand
- **VELVET:**
  - category cue: type of fabric
  - multiple choice: denim, cotton, velvet
- **CHURCH:**
  - category cue: type of building
  - multiple choice: church, school, hospital
- **DAISY:**
  - category cue: type of flower
  - multiple choice: rose, daisy, tulip
- **RED:**
  - category cue: a colour
  - multiple choice: red, blue, green

Scoring: No points are allocated for words recalled with a cue. A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

11. **Orientation:**

**Administration:** The examiner gives the following instructions: “Tell me the date today”. If the subject does not give a complete answer, then prompt accordingly by saying: “Tell me the [year, month, exact date, and day of the week].” Then say: “Now, tell me the name of this place, and which city it is in.”

**Scoring:** Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

**TOTAL SCORE:** Sum all subscores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.

**Quick Start**

<table>
<thead>
<tr>
<th>New Guidelines</th>
<th>These new guidelines:</th>
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<tbody>
<tr>
<td></td>
<td>• Update the widely used Alzheimer’s disease (AD) guidelines established in 1984</td>
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<tr>
<td></td>
<td>• Expand existing guidelines for diagnosing mild cognitive impairment (MCI) due to AD</td>
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<td></td>
<td>• Expand the spectrum of AD to include presymptomatic (preclinical), mildly symptomatic but pre-dementia (MCI), as well as symptomatic with dementia (AD) stages</td>
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<td></td>
<td>• Establish a framework for researchers (and eventually clinicians) to use biomarkers to aid in the diagnosis of preclinical AD, MCI due to AD, and AD dementia.</td>
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<table>
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<tr>
<th>Guidelines for Diagnosis of AD dementia (probable and possible)</th>
<th>Probable AD dementia core clinical criteria:</th>
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<tbody>
<tr>
<td></td>
<td>• Dementia</td>
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<tr>
<td></td>
<td>• Insidious onset and worsening symptoms</td>
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<td></td>
<td>• Initial deficits in either:</td>
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<td></td>
<td>o memory and at least one other cognitive area (amnestic presentation – most common)</td>
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<tr>
<td></td>
<td>o language, visuospatial function, or executive function and at least one other cognitive area (nonamnestic presentation)</td>
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<tr>
<td></td>
<td>• Diagnosis of probable AD dementia should not be made in the presence of:</td>
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<td></td>
<td>o significant cerebrovascular disease, Lewy Body disease, or behavioral variant of frontotemporal dementia or the semantic or nonfluent / agrammatic types of primary progressive aphasia.</td>
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<tr>
<td></td>
<td>o another active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.</td>
</tr>
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</table>

Possible AD dementia criteria:  

• *Atypical course* meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline  

• *Etiologically mixed presentation* meets all core clinical criteria for AD dementia but has evidence of (a) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) features of Dementia with Lewy bodies other than the dementia itself; or (c) evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition.
### Guidelines for Diagnosis of MCI due to AD

These new guidelines:

- Establish clinical and cognitive criteria
  - Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)
  - Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)
  - Preservation of independence in functional abilities
  - Not demented

- Examine etiology of MCI consistent with AD pathophysiological process
  - Rule out vascular, traumatic, medical causes of cognitive decline, where possible
  - Provide evidence of longitudinal decline in cognition, when feasible
  - Report history consistent with AD genetic factors, where relevant

### Use of Biomarkers in AD

- There are two types of biomarkers:
  - Markers of amyloid-beta (Aβ) protein deposition in the brain
    - low CSF Aβ42
    - positive PET amyloid imaging
  - Markers of downstream neurodegeneration
    - elevated cerebrospinal fluid tau (total and phosphorylated)
    - decreased metabolism in temporal and parietal cortex on 18F-fluorodeoxyglucose (FDG) positron emission tomography
    - atrophy on MRI in temporal (medial, basal, and lateral) and medial parietal cortex

- Changes in biomarkers that indicate the earliest stages of the disease before cognitive and behavioral changes occur
- These biomarkers are not to be used alone by the practicing clinician to render a diagnosis of MCI or AD, but rather can be used in conjunction with existing criteria for clinical diagnosis for AD or MCI to add confidence to the diagnosis

### Implications for the Practicing Clinician

Although these new guidelines do not suggest a fundamental difference in the way clinicians will diagnose AD dementia and MCI due to AD, they do encourage clinicians to:

- Recognize that AD is the end of a long process, spanning years or perhaps decades, leading to death of brain cells, cognitive loss, and ultimately dementia.
- Diagnose (and perhaps treat) AD at the earliest possible stage. At present this would be the MCI stage, but eventually will include preclinical AD.
- Begin to consider using biomarkers in the diagnosis of all stages
of AD. For now, most biomarkers will only be used in research studies (both for diagnostic purposes and to evaluate the efficacy of disease modifying treatments), but some either are available to clinicians now (e.g., CSF Aβ42 and tau) or will be in the near future (e.g., amyloid PET scans).

- Evaluate patients with dementia to determine its etiology with special attention paid to amnestic and nonamnestic presentations of AD.
- Remember that they will soon see a significant increase in patients in their practices with AD. There are currently 5.4 million patients in the US with AD dementia and perhaps an equal amount with MCI. Because of the aging population, these numbers could triple in the next 50 years.

### Rationale for new criteria

Updating the prior criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (ADRA) work group in 1984, new clinical criteria have recently been published for Alzheimer’s disease (AD) and mild cognitive impairment (MCI) due to the AD pathophysiological process (MCI due to AD). Four articles in the journal *Alzheimer’s & Dementia* in 2011 describe these criteria and the underlying rationale for them. The first is an introduction that gives the background of why new criteria are needed (Jack et al., 2011). The second discusses in detail the hypothesis that the AD pathophysiological process starts years and perhaps decades prior to the onset of clinical symptoms and dementia. It also brings up the concept of “preclinical” AD (Sperling et al., 2011). The third discusses both clinical and research criteria for MCI due to AD (Albert et al., 2011). Finally, the fourth describes new clinical and research criteria for AD (McKhann et al., 2011). We will focus on new clinical criteria, the area that will be of greatest use to practicing clinicians, and briefly touch on the research criteria and theoretical issues.

As discussed in these articles (particularly Jack et al., 2011 and Sperling et al., 2011), the new criteria were developed due to the recognition of a number of important factors that have changed since 1984:

1. It is now believed that the AD pathophysiological process starts years prior to detectable cognitive changes and perhaps decades prior to the onset of clinical dementia (Figure 1).
2. There are many patients whose cognition is not normal for age but also do not meet criteria for dementia.
3. Other causes of dementia such as frontotemporal dementia, vascular dementia, and dementia with Lewy bodies are now understood to be more likely mistaken for AD than are thyroid disorders and B12 deficiency.
4. The genetics of AD are now better understood.
5. Putative biomarkers of AD are now available in some centers.
6. New criteria are needed for clinical trials and other research.
7. New treatments are being developed that are specific for the AD pathophysiological process, making it more important that patients truly have that process prior to the initiation of this type of specific treatment.
Figure 1. Postulated temporal lag between the deposition of Aβ in amyloid plaques from an autopsy series and the development of clinical AD dementia based upon three epidemiological studies (From Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):280-92.).

As described by Sperling et al. (2011), one commonly used model of AD is that many factors including age, genetics, the environment, and others combine to lead to the accumulation of amyloid beta (Aβ) in the brain, which in turn produces synaptic dysfunction, tangle formation, and neuronal death, all of which ultimately lead to cognitive decline (Figure 2).

Given that the events in this pathological cascade sequence likely take years or decades from the accumulation of Aβ to the development of dementia or even MCI, there must be a prior “preclinical” stage of AD (Figure 3).

Table 1 presents several biomarkers of Aβ or neurodegeneration that are currently in use. Based upon the current scientific model regarding when different events occur in the AD pathophysiological process (Figure 4), Sperling et al. (2011) discussed three stages of preclinical AD to be considered for research, based upon biomarkers and cognitive change. Stage 1 is asymptomatic cerebral amyloidosis, which could be determined by the presence of a biomarker sensitive to Aβ, in the absence of any marker of neurodegeneration or evidence of subtle cognitive change. Stage 2 is asymptomatic cerebral amyloidosis plus neurodegeneration in the absence of subtle cognitive change. Finally, stage 3 is amyloidosis plus neurodegeneration plus subtle cognitive or behavioral decline. Guided by these theoretical underpinnings, the new clinical and research criteria are next presented.
Figure 2. Hypothetical model of AD pathophysiological cascade sequence. (From Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement. 2011 May;7(3):280-92.)

Table 1: Putative biomarkers for AD currently being used

(1) Markers of amyloid-beta (Aβ) protein deposition in the brain
   a. low CSF Aβ42
   b. positive PET amyloid imaging

(2) Markers of downstream neurodegeneration
   a. elevated cerebrospinal fluid tau (total and phosphorylated)
   b. decreased metabolism in temporal and parietal cortex on ¹⁸fluorodeoxyglucose (FDG) positron emission tomography
   c. atrophy on MRI in temporal (medial, basal, and lateral) and medial parietal cortex

Figure 4. Model of how the different stages of AD may be detected by changes in various biological, cognitive, and clinical markers. (From Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):280-92.)

Criteria for all-cause dementia & Alzheimer's disease

First, a distinction has been made between AD pathology, now termed the AD pathophysiological process, and the clinical disease that arises as a consequence of the pathophysiological process, now termed AD dementia.

Second, criteria for the diagnosis of “all-cause” dementia is proposed, that is, criteria for dementia that would encompass dementia due to any number of causes including (but
not limited to) AD, dementia with Lewy bodies, vascular dementia, and frontotemporal dementia. In addition to making the distinction between the general “all-cause” dementia and AD dementia specifically, the general criteria are now much more detailed and use examples to help the clinician understand how the criteria should be operationalized (Box 1). These criteria are followed by an explanation of the distinction between dementia and MCI, namely, that dementia signifies a significant decline from prior level of functioning that interferes with function at work or usual daily activities, whereas MCI does not.

**Box 1. Criteria for all-cause dementia**

Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder;
4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a “bedside” mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.
5. The cognitive or behavioral impairment involves a minimum of two of the following domains:
   a. Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
   b. Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
   c. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.
   d. Impaired language functions (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.
   e. Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

Third, three new criteria for AD dementia are then presented: (1) probable AD dementia, 
(2) possible AD dementia, and (3) probable or possible AD dementia with evidence of 
the AD pathophysiological process. The first two criteria are intended to be for clinical 
use, whereas the third is intended for research use.

The clinical criteria for probable AD dementia can be found in Box 2. These criteria 
differ from those of the NINCDS-ADRDA in that there are now specific presentations. 
An amnestic presentation as the most common is described first, followed by three 
specific nonamnestic presentations: language, visuospatial, and executive presentations.

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**Box 2. Core clinical criteria for probable AD dementia**

**Probable AD dementia is diagnosed when the patient**

1. Meets criteria for dementia described in Box 1, and in addition, has the following 
   characteristics:
   
   A. Insidious onset. Symptoms have a gradual onset over months to years, not 
      sudden over hours or days;
   
   B. Clear-cut history of worsening of cognition by report or observation; and

   C. The initial and most prominent cognitive deficits are evident on history and 
      examination in one of the following categories.
      
      a. Amnestic presentation; the most common syndromic presentation of AD 
         dementia. The deficits should include impairment in learning and recall of 
         recently learned information. There should also be evidence of cognitive 
         dysfunction in at least one other cognitive domain, as defined in Box 1.
      
      b. Nonamnestic presentations:
         
         • Language presentation: The most prominent deficits are in word-finding, 
            but deficits in other cognitive domains should be present.
         
         • Visuospatial presentation: The most prominent deficits are in spatial 
            cognition, including object agnosia, impaired face recognition, 
            simultanagnosia, and alexia. Deficits in other cognitive domains should be 
            present.
         
         • Executive dysfunction: The most prominent deficits are impaired 
            reasoning, judgment, and problem solving. Deficits in other cognitive 
            domains should be present.
   
   D. The diagnosis of probable AD dementia should not be applied when there is 
      evidence of (a) substantial concomitant cerebrovascular disease, defined by a 
      history of a stroke temporally related to the onset or worsening of cognitive 
      impairment; or the presence of multiple or extensive infarcts or severe white 
      matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies 
      other than dementia itself; or (c) prominent features of behavioral variant 
      frontotemporal dementia; or (d) prominent features of semantic variant primary 
      progressive aphasia or nonfluent / agrammatic variant primary progressive 
      aphasia; or (e) evidence for another concurrent, active neurological disease, or a 
      non-neurological medical comorbidity or use of medication that could have a 
      substantial effect on cognition.

**Probable AD dementia with increased level of certainty**

**Probable AD dementia with documented decline**

• Diagnosis of probable AD plus evidence of progressive cognitive decline on
subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations.

**Probable AD dementia in a carrier of a causative AD genetic mutation**
- Diagnosis of probable AD plus evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2).


After these basic criteria are presented there are additional criteria described for two varieties of “Probable AD with increased level of certainty.” If there is a decline documented by subsequent examinations by informant history and/or cognitive testing, patients meet the criteria for “probable AD with documented decline.” If there is evidence of a genetic mutation causing AD (the amyloid precursor protein (APP), presenilin 1 (PSEN1) or presenilin 1 (PSEN2) genes), patients meet the criteria for “probable AD in a carrier of a causative AD genetic mutation.” (Note that the workgroup determined that carrying an apolipoprotein E (ApoE) €4 allele was not sufficient to be in this category).

The clinical criteria for possible AD dementia can be found in Box 3. The term “possible” is used instead of “probable” in two scenarios. One is if the cognitive deficits look like AD but there is an atypical course of the disease: either sudden onset or no definite decline. The second is if there is evidence for a mixed etiology of the dementia, such that the patient meets criteria for probable AD dementia but there is also evidence of significant vascular disease, features of dementia with Lewy bodies, or other disease or condition that could be contributing to the patient’s dementia.

**Box 3. Core clinical criteria for possible AD dementia**

A diagnosis of possible AD dementia should be made in either of the following circumstances:

**Atypical course**
- Atypical course meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline

**Or**

**Etiologically mixed presentation**
- Etiologically mixed presentation meets all core clinical criteria for AD dementia but has evidence of (a) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) features of Dementia with Lewy bodies other
than the dementia itself; or (c) evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition


The next idea that is introduced is that of research criteria for “probable AD dementia with evidence of the AD pathophysiological process.” These research criteria increase the certainty that the patient’s clinical dementia is due the AD pathophysiological process by adding biomarker evidence to the probable AD dementia criteria. The biomarkers fall into two categories, markers of amyloid-beta (Aβ) protein deposition in the brain and markers of downstream neurodegeneration, (see Table 1, above).

If one of these two biomarker categories is positive, the “biomarker probability of AD etiology” rises to “intermediate,” and if both categories are positive the probability becomes “high.” The authors are specific that they do not advocate obtaining AD biomarkers for routine clinical purposes at the present time, although they do note that they may be used when they are available and deemed appropriate by the clinician.

Research criteria for “Possible AD dementia with evidence of the AD pathophysiological process” are next discussed. This section may be confusing because it does not correspond to the “Possible AD dementia” section as discussed above. Whereas that section discusses situations in which the cognitive deficits look like AD dementia but either the course of the disease is atypical or there may be a secondary contributing etiology, this section states that the category should be used for persons who meet clinical criteria for a non-AD dementia but have either biomarker evidence of the AD pathophysiological process, or meet the neuropathological criteria for AD after autopsy. Presumably the general idea is that in possible AD dementia, with or without biomarkers, the presentation is in some way atypical. In any event, if both of the biomarker categories described in Table 1 are positive, then there is a “high” biomarker probability of AD etiology but it does not rule out a second etiology contributing to the dementia. No mention is made of how to interpret a single positive biomarker in this setting.

Pathophysiologically proven AD is next discussed, consisting simply of the unchanged criteria of patients meeting both the clinical and neuropathological criteria for AD.

The criteria for dementia unlikely to be due to AD is then discussed, which requires one of the following (adapted from McKhann et al., 2011):

1. Does not meet clinical criteria for AD dementia
2. Regardless of meeting clinical criteria for probable or possible AD dementia
   a. There is sufficient evidence for an alternative diagnosis such as HIV dementia, dementia of Huntington’s disease, or others that rarely overlap with AD
   b. Biomarkers for both Aβ and neuronal degeneration are negative.

Criteria for Mild Cognitive Impairment due to the Alzheimer’s disease pathophysiological process
In the article by Albert et al. (2011) the criteria for MCI due to AD are presented. These criteria refer to the symptomatic phase of the AD pathophysiological process but before the individual develops the functional impairment that defines dementia. MCI due to AD is thus one of many causes of MCI. Both core clinical criteria for the diagnosis of MCI due to AD and clinical research criteria are presented.

As the authors start their discussion on the core clinical criteria they point out that, in addition to these criteria, clinical judgment must be used to distinguish between normal cognition and MCI, and between MCI and dementia. The clinical criteria are divided into two parts. First, criteria are presented for the clinical and cognitive syndrome of MCI, and second, criteria are presented regarding the etiology of the MCI syndrome being consistent with AD. A summary of these criteria can be found in Box 4.

Note that the bullets in Box 4 under the “Establish clinical and cognitive criteria” heading correspond closely to the clinical criteria presented in Box 4.1 in the main text of our book. These clinical and cognitive criteria are essentially the same, and more information regarding them can be found in Chapter 4. Different is that, in order to have the etiology of the MCI consistent with AD pathophysiological process, inclusion and exclusion criteria are presented to (1) exclude patients who have other causes of MCI, (2) include patients with a decline in cognition over time, and (3) include patients who have mutations in one of the three genes associated with early familial AD described above (amyloid precursor protein (APP), presenilin 1 (PSEN1) or presenilin 1 (PSEN2)).

Box 4. Summary of clinical and cognitive evaluation for MCI due to AD

**Establish clinical and cognitive criteria**

- Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)
- Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)
- Preservation of independence in functional abilities
- Not demented

**Examine etiology of MCI consistent with AD pathophysiological process**

- Rule out vascular, traumatic, medical causes of cognitive decline, where possible
- Provide evidence of longitudinal decline in cognition, when feasible
- Report history consistent with AD genetic factors, where relevant


Selected additional aspects of the new clinical criteria mentioned in Albert et al. (2011) include:

- An emphasis on change over time being present.
• Typically (but not always) scoring 1 to 1.5 standard deviations below the mean on cognitive tests compared to age and education matched peers.
• Cognitive evaluation should include tests of memory as well as executive functions, language, visuospatial skills, and both simple and divided attention.
• An example of formal cognitive tests mentioned include: Rey Auditory Verbal Learning Test (memory), the Trail Making Test Parts A & B (executive function), the Boston Naming Test, letter and category fluency (language), figure copying (spatial skills), and digit span forward (attention).
• Note is made that many of the commonly used test do not have norms for individuals aged 90 and older, and have only been validated in a few different cultures.
• Informal techniques to evaluate cognition are also mentioned, but concern is raised that they will not be sensitive enough to detect changes in the early stages of MCI.
• To rule out etiologies other than AD, signs and symptoms of other disorders should be sought for, such as extensive vascular disease on imaging studies, symptoms of dementia with Lewy bodies, and others.
• Note is made that those individuals who meet clinical, cognitive, and etiology criteria for MCI and have one or two apolipoprotein E (ApoE) ε4 alleles are more likely to progress to AD than those without an ε4 allele.

Research criteria for MCI due to AD incorporating biomarkers are next presented. The biomarkers discussed include those in Table 1, above. Two valuable reasons to add biomarkers is that they may help determine (1) the underlying etiology of the MCI and (2) the likelihood and time course of an individual with MCI becoming more impaired or demented. An important point discussed is that biomarkers that detect Aβ protein deposition are most useful in determining underlying etiology, whereas biomarkers that detect neuronal degeneration and injury are most useful in determining prognosis and progression. In this article elevated levels of tau are noted to be useful for determining both the underlying etiology and prognosis. Adding biomarkers to the core clinical diagnosis of MCI due to AD is analogous to adding them to the core clinical diagnosis of AD: If one of these two biomarker categories is positive, the “biomarker probability of AD etiology” rises to “intermediate,” and both categories must be positive for the “highest” probability. The “lowest” probability is present if both categories are negative.

**Implications for the Practicing Clinician**
These new guidelines do not suggest a fundamental difference in the way clinicians will diagnose AD dementia or MCI due to AD. For now, diagnosis of these disorders will continue to be primarily clinical. The new guidelines also do not recommend any specific treatment strategies. Implicitly or explicitly, however, they do encourage clinicians to:
• Recognize that AD is the end of a long process, spanning years or perhaps decades, leading to death of brain cells, cognitive loss, and ultimately dementia.
• Diagnose (and perhaps treat) AD at the earliest possible stage. At present this would be the MCI stage, but eventually will include preclinical AD.
• Begin to consider using biomarkers in the diagnosis of all stages of AD. For now, most biomarkers will only be used in research studies (both for diagnostic purposes and to evaluate the efficacy of disease modifying treatments), but some either are available to clinicians now (e.g., CSF Aβ42 and tau) or will be in the near future (e.g., amyloid PET scans).
• Evaluate patients with dementia to determine the cause of the dementia with special attention paid to amnestic and nonamnestic presentations of AD.
• Remember that they will soon see a significant increase in patients in their practices with AD. There are currently 5.4 million patients in the US with AD dementia and perhaps an equal amount with MCI. Because of the aging population, these numbers could triple in the next 50 years.

Conclusion
Today, these new criteria allow the practicing clinician to diagnose AD dementia and MCI due to AD with more clarity, providing greater certainty of the diagnosis for patients and families. In the future, these criteria will provide practitioners with the tools they need to know which patients are appropriate for the disease-modifying medications which are being developed to slow or even stop the AD pathophysiologic process.

References