DIAGNOSIS OF MCI AND DEMENTIA DUE TO AD IN CANADA

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CONFLICTS OF INTEREST

- Member of scientific advisory committes of Advantage Therapeutics, Alzheon, Amyriad Therapeutics, Biogen, Cerveau, Eisai, Enigma, Lilly, Lundbeck, Medesis, Roche, Sharon Francis Foundation, TauRx
- Editor-in-chief of JPAD
- Member of the CCD 2023 organizing committee

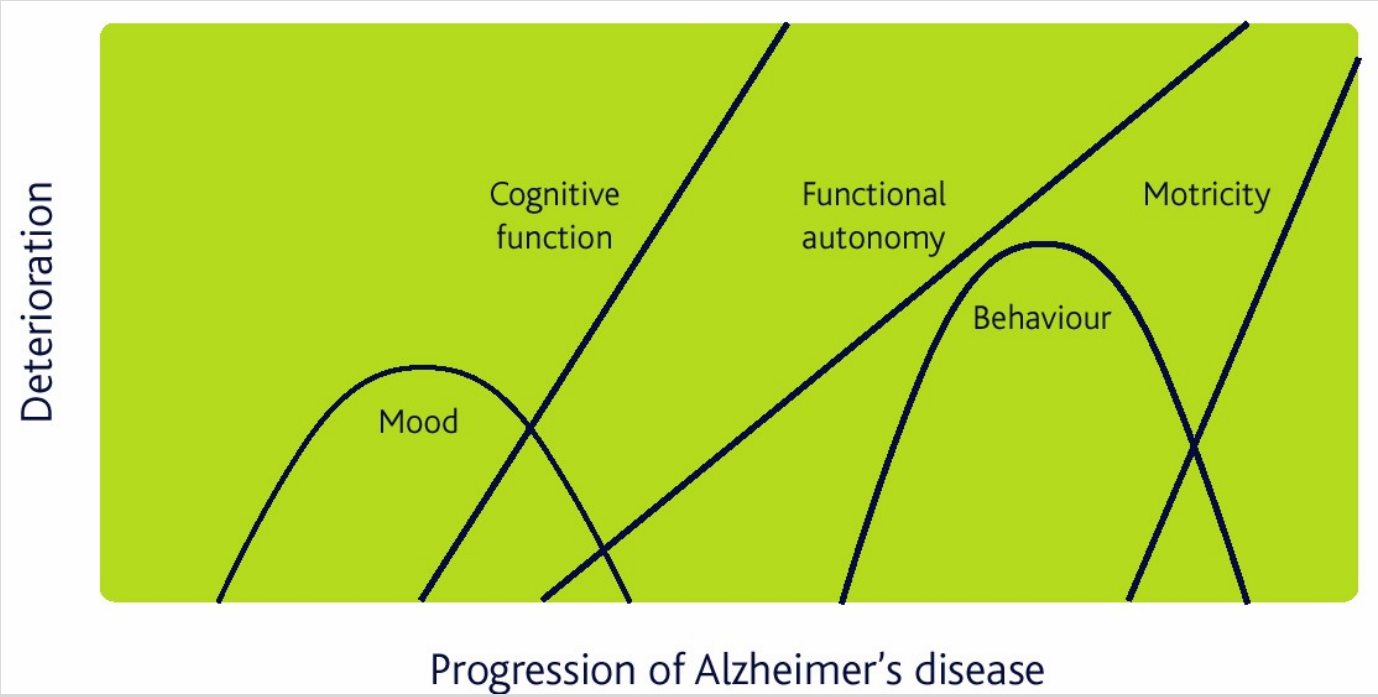
OBJECTIVES

- Study the natural history of cognitive decline with age using AD as template
- Review the step-by-step approach to diagnosis
- Extract from the World Alzheimer Report 2021 costs for the diagnosis
- Explore new plasma biomarkers
- Extrapolate on the resources needed across Canada for a more structured approach to diagnosis

PRESENTATION

- **Natural history of age-associated cognitive decline**
- Clinical assessment and complementary tests
- Costs of diagnostic tests in 2021, in Québec
- New plasma biomarkers
- Near future changes in diagnosis of AD

PROGRESSION OF SYMPTOMS IN "TYPICAL"ALZHEIMER'S DISEASE



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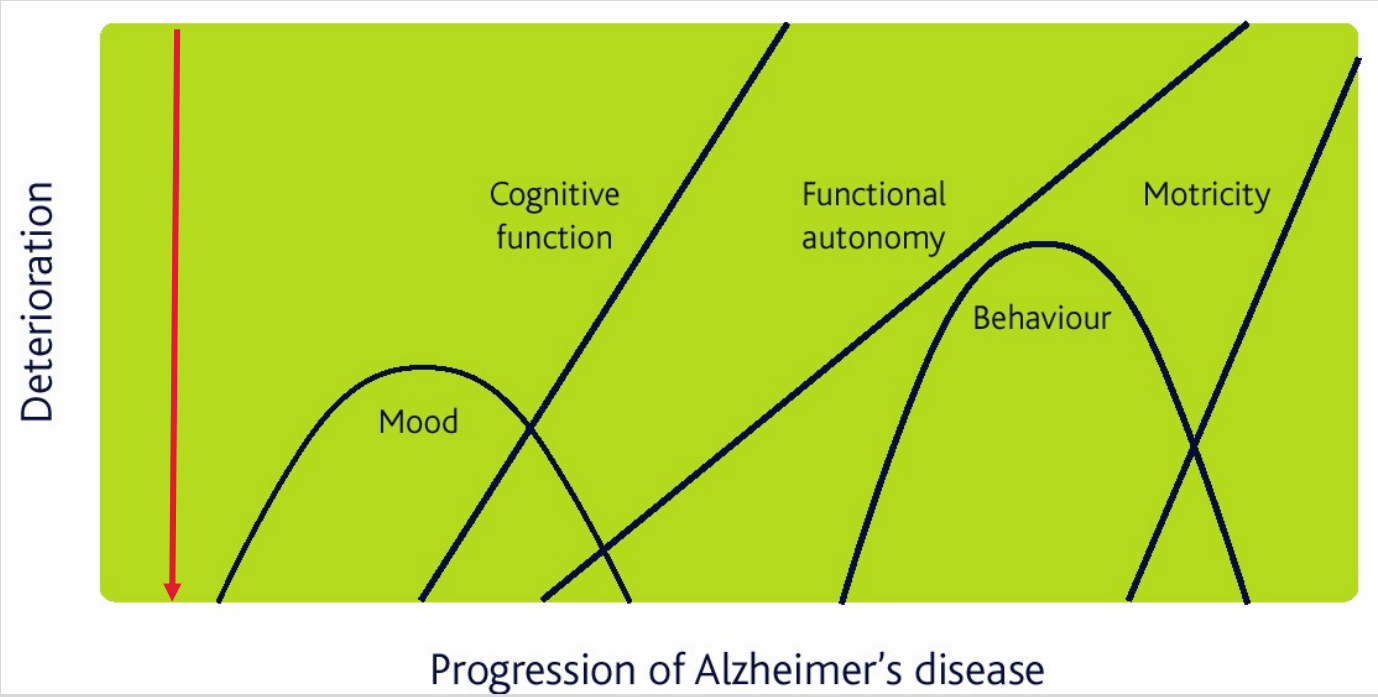
Subjective Cognitive Decline (SCD)



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Mild Behavioral Impairment (MBI)

Change in behavior or personality with **emergence** ≥ age 50 and **persistence** for ≥6 months

Five domains

- Drive and Motivation (apathy)
- Emotional Dysregulation (mood/anxiety)
- Impulse Dyscontrol (agitation, response inhibition)
- Social Inappropriateness
- Thoughts and Perception (psychosis)

MBI Checklist

Mild Behavioral Impairment Checklist (MBI-C)

Date: _____

Rated by: ☐ Clinician ☐ Informant ☐ Subject

Location: ☐ Clinic ☐ Research

Label

Circle "Yes" **only** if the behavior has been present for at least **6 months** (continuously, or on and off) and is a **change** from her/his longstanding pattern of behavior. Otherwise, circle "No".

Please rate severity: **1 = Mild** (noticeable, but not a significant change); **2 = Moderate** (significant, but not a dramatic change); **3 = Severe** (very marked or prominent, a dramatic change). If more than 1 item in a question, rate the most severe.

	YES	NO	SEVERITY
This domain describes interest, motivation, and drive			
Has the person lost interest in friends, family, or home activities?	Yes	No	1 2 3
Does the person lack curiosity in topics that would usually have attracted her/his interest?	Yes	No	1 2 3
Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?	Yes	No	1 2 3
Has the person lost motivation to act on her/his obligations or interests?	Yes	No	1 2 3
Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?	Yes	No	1 2 3
Does she/he no longer care about anything?	Yes	No	1 2 3
This domain describes mood or anxiety symptoms			
Has the person developed sadness or appear to be in low spirits? Does she/she have episodes of tearfulness?	Yes	No	1 2 3
Has the person become less able to experience pleasure?	Yes	No	1 2 3
Has the person become discouraged about their future or feel that she/he is a failure?	Yes	No	1 2 3
Does the person view herself/himself as a burden to family?	Yes	No	1 2 3
Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)?	Yes	No	1 2 3
Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?	Yes	No	1 2 3
This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward			
Has the person become agitated, aggressive, irritable, or temperamental?	Yes	No	1 2 3
Has she/he become unreasonably or uncharacteristically argumentative?	Yes	No	1 2 3
Has the person become more impulsive, seeming to act without considering things?	Yes	No	1 2 3
Does the person display sexually disinhibited or intrusive behaviour, such as touching (themselves/others), hugging, groping, etc., in a manner that is out of character or may cause offence?	Yes	No	1 2 3
Has the person become more easily frustrated or impatient? Does she/he have troubles coping with delays, or waiting for events or for their turn?	Yes	No	1 2 3
Does the person display a new recklessness or lack of judgement when driving (e.g. speeding, erratic swerving, abrupt lane changes, etc.)?	Yes	No	1 2 3
Has the person become more stubborn or rigid, i.e., uncharacteristically insistent on having their way, or unwilling/unable to see/hear other views?	Yes	No	1 2 3
Is there a change in eating behaviors (e.g., overeating, cramming the mouth, insistent on eating only specific foods, or eating the food in exactly the same order)?	Yes	No	1 2 3
Does the person no longer find food tasteful or enjoyable? Are they eating less?	Yes	No	1 2 3
Does the person hoard objects when she/he did not do so before?	Yes	No	1 2 3
Has the person developed simple repetitive behaviors or compulsions?	Yes	No	1 2 3
Has the person recently developed trouble regulating smoking, alcohol, drug intake or gambling, or started shoplifting?	Yes	No	1 2 3
This domain describes following societal norms and having social graces, tact, and empathy			
Has the person become less concerned about how her/his words or actions affect others? Has she/he become insensitive to others' feelings?	Yes	No	1 2 3
Has the person started talking openly about very personal or private matters not usually discussed in public?	Yes	No	1 2 3
Does the person say rude or crude things or make lewd sexual remarks that she/he would not have said before?	Yes	No	1 2 3
Does the person seem to lack the social judgement she/he previously had about what to say or how to behave in public or private?	Yes	No	1 2 3
Does the person now talk to strangers as if familiar, or intrude on their activities?	Yes	No	1 2 3
This domain describes strongly held beliefs and sensory experiences			
Has the person developed beliefs that they are in danger, or that others are planning to harm them or steal their belongings?	Yes	No	1 2 3
Has the person developed suspiciousness about the intentions or motives of other people?	Yes	No	1 2 3
Does she/he have unrealistic beliefs about her/his power, wealth or skills?	Yes	No	1 2 3
Does the person describe hearing voices or does she/he talk to imaginary people or "spirits"?	Yes	No	1 2 3
Does the person report or complain about, or act as if seeing things (e.g. people, animals or insects) that are not there, i.e., that are imaginary to others?	Yes	No	1 2 3

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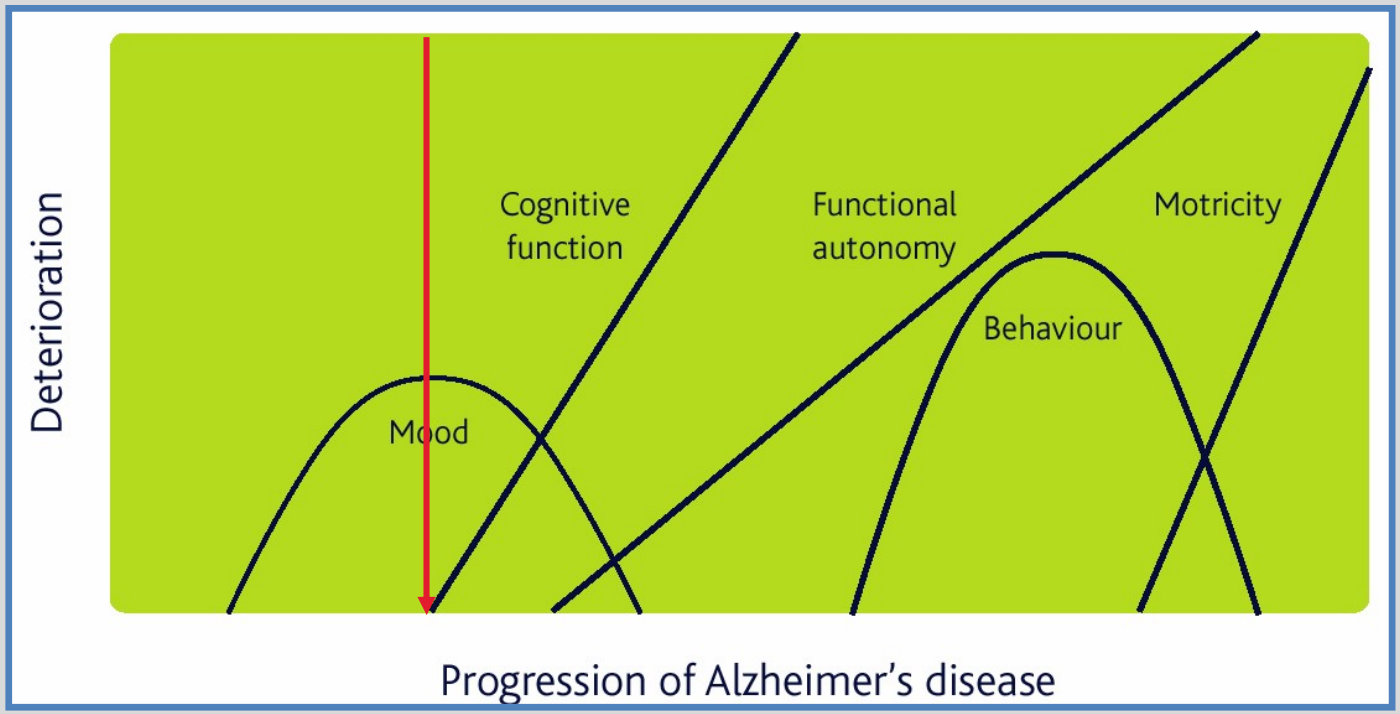
AD: MILD BEHAVIOURAL IMPAIRMENT STAGE



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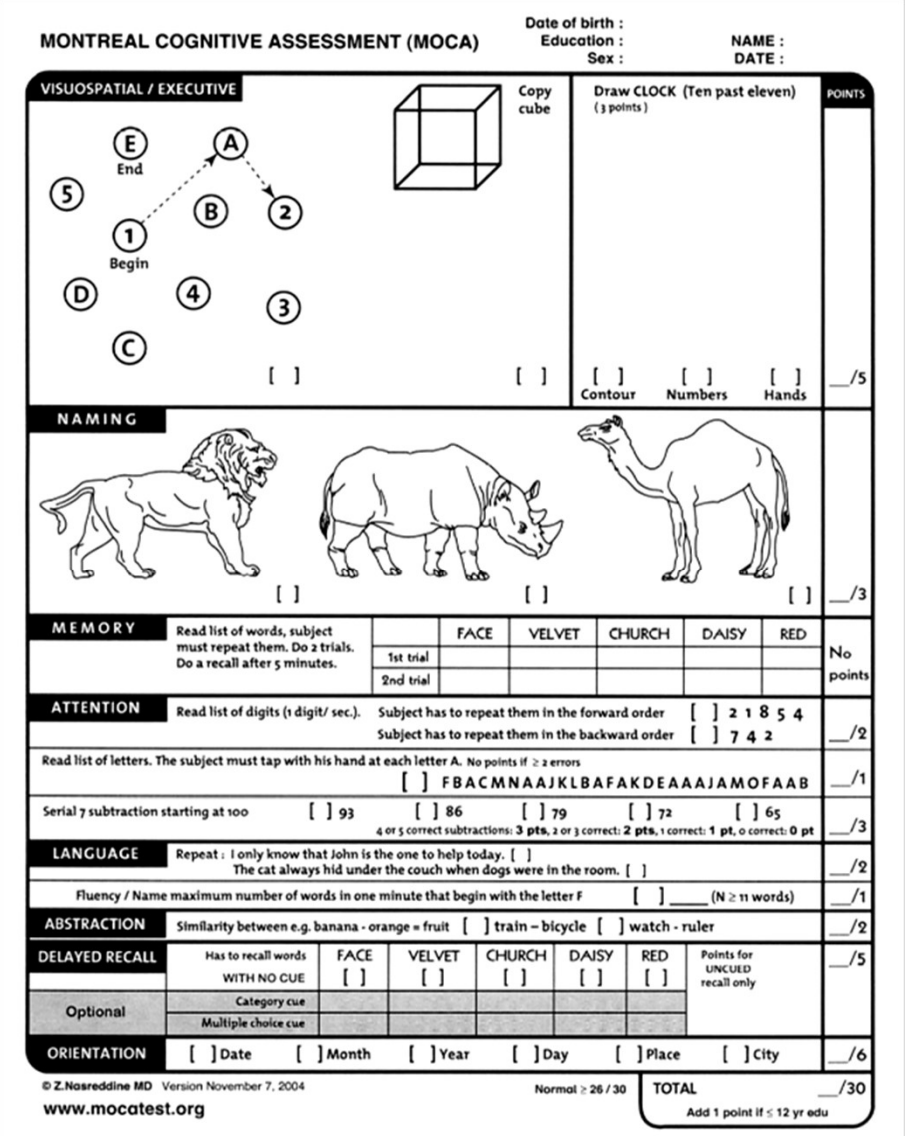
- One-page
- 30-point scale
- 10 minutes to administer

www.mocatest.org



MONTREAL COGNITIVE ASSESSMENT (MOCA)

Date of birth :
Education :
Sex :

NAME :
DATE :

VISUOSPATIAL / EXECUTIVE — Copy cube — Draw CLOCK (Ten past eleven) (3 points) — POINTS

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ]

[ ] Contour [ ] Numbers [ ] Hands /5

NAMING

[ ] [ ] [ ] /3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

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 /2

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

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B /1

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** /3

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. [ ] /2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) /1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler /2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

/5

ORIENTATION — [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City /6

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Normal ≥ 26 / 30

TOTAL /30

Add 1 point if ≤ 12 yr edu

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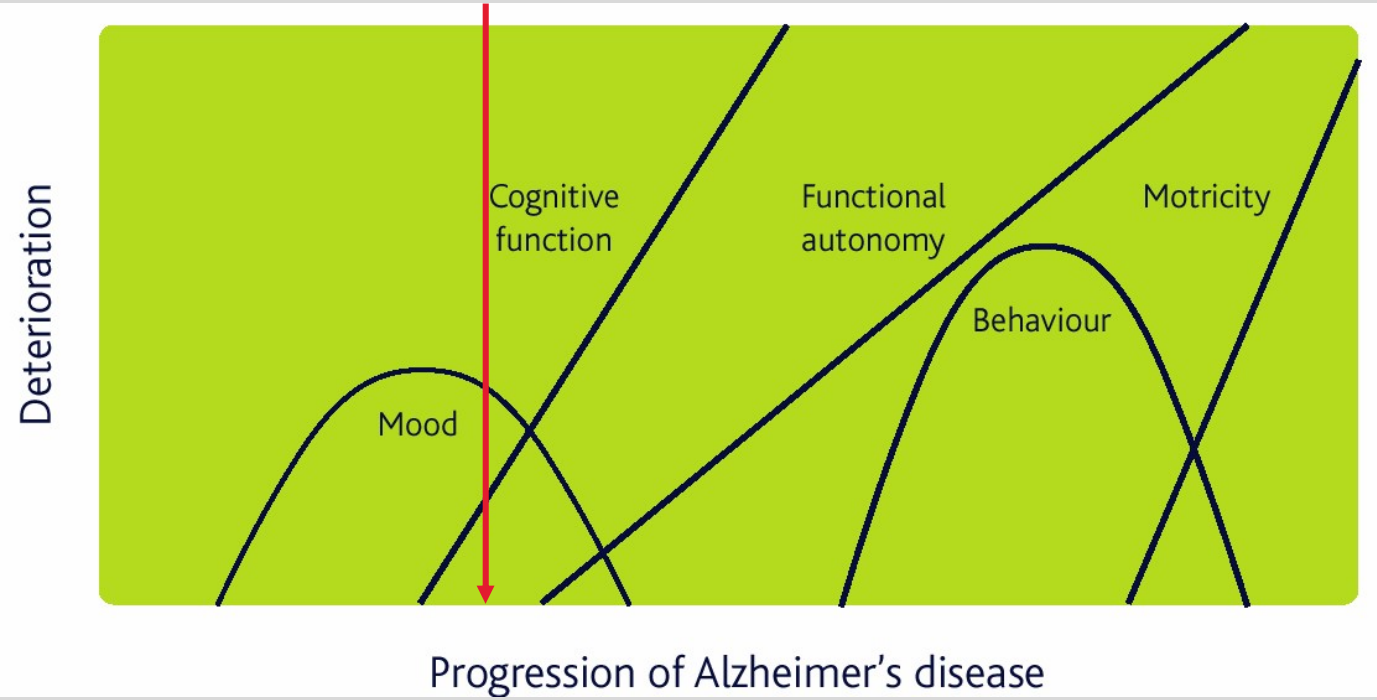
AD: MILD COGNITIVE IMPAIRMENT STAGE



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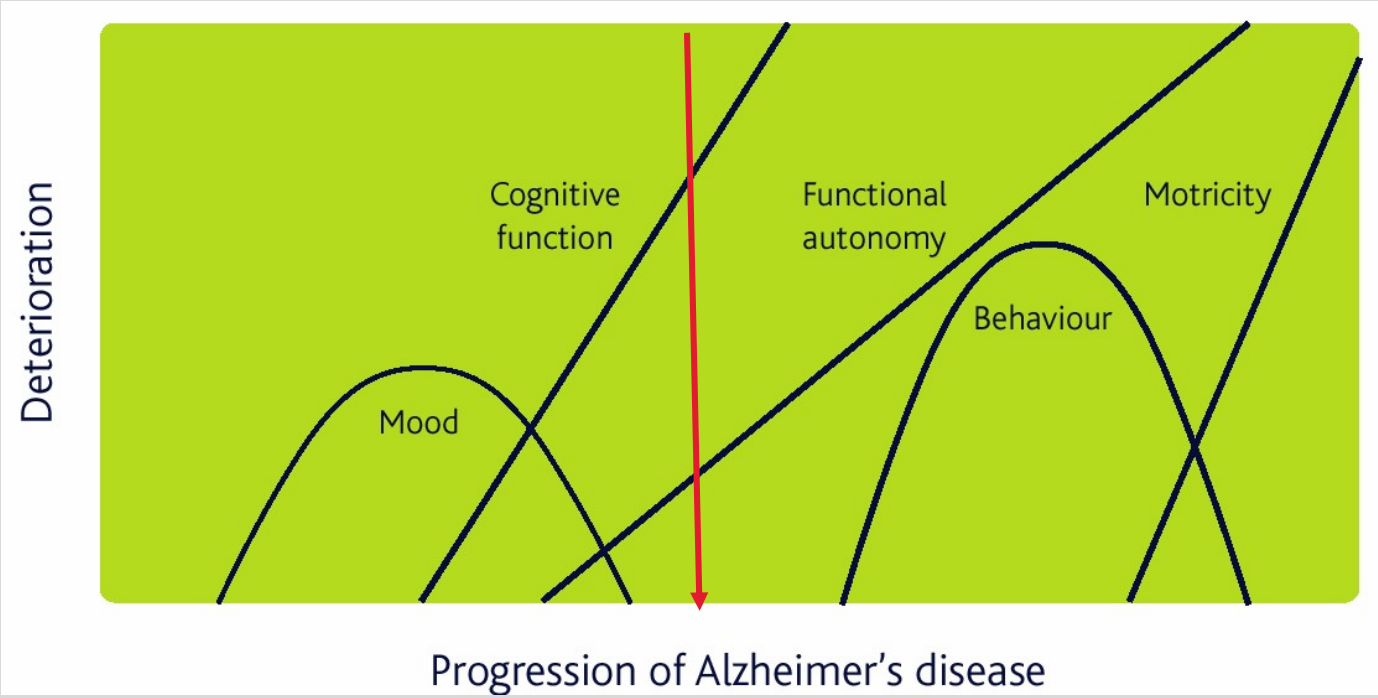
CLINICAL DEFINITION OF MAJOR NEUROCOGNITIVE DISORDER (DEMENTIA)

- Decline in intellectual abilities (memory plus one other cognitive domain)
- Interfering with social or occupational life
- There may be little insight and reporting is done by family
- There may be concomitant anxiety and depression

AD: MILD DEMENTIA STAGE



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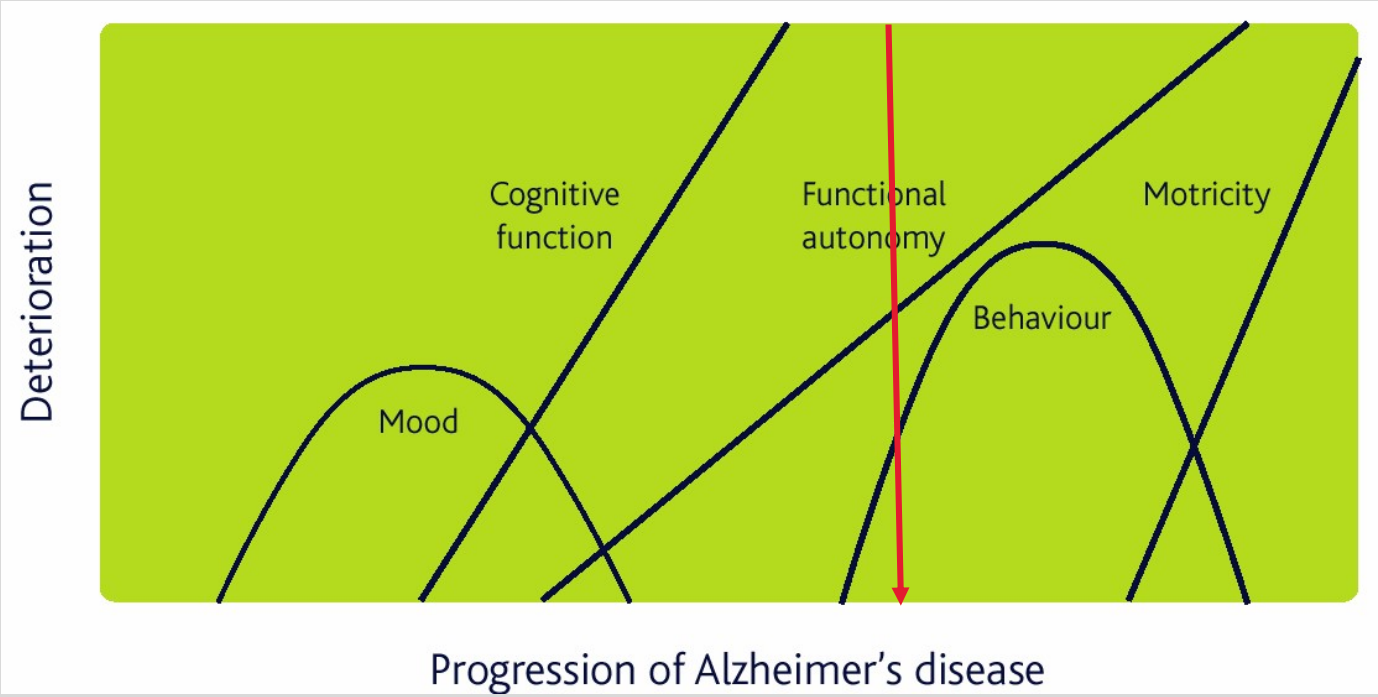
AD: MODERATE DEMENTIA STAGE



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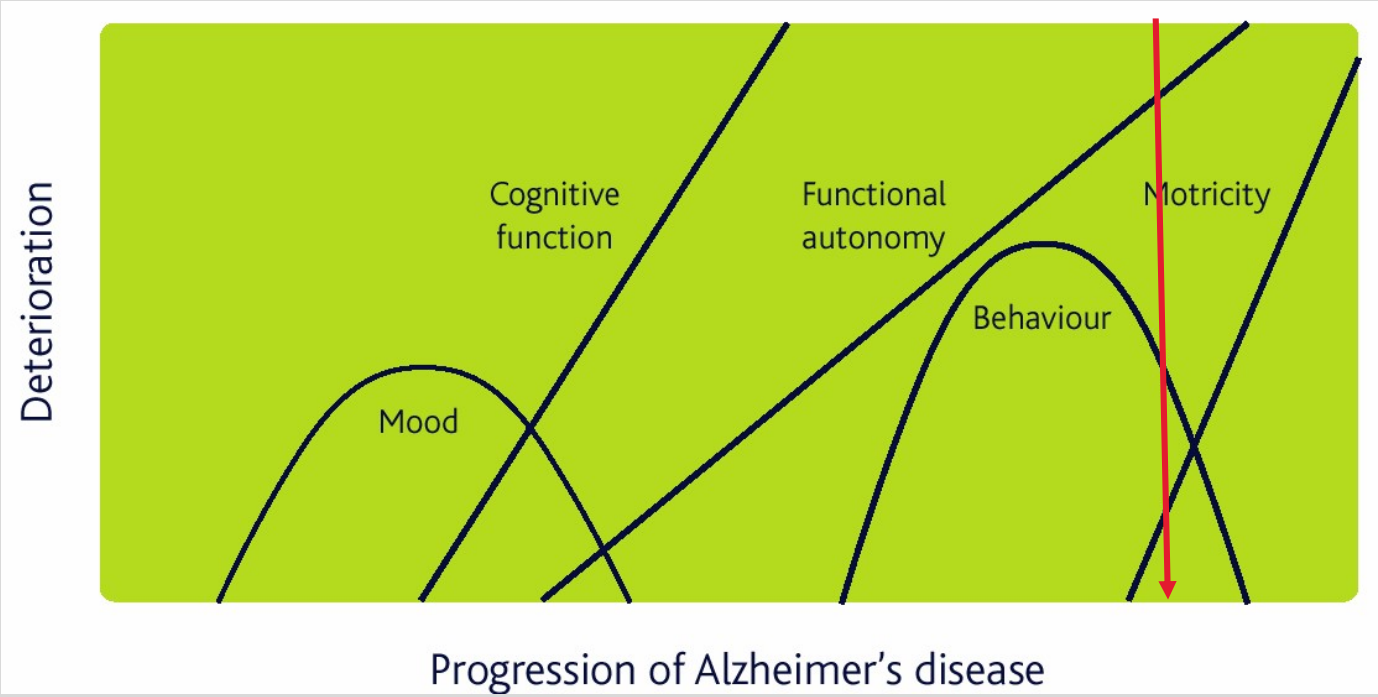
AD: SEVERE DEMENTIA STAGE



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PRESENTATION

- Natural history of age-associated cognitive decline
- **Clinical assessment and complementary tests**
- Costs in 2021, in Québec
- New plasma biomarkers
- Near future changes in diagnosis of AD

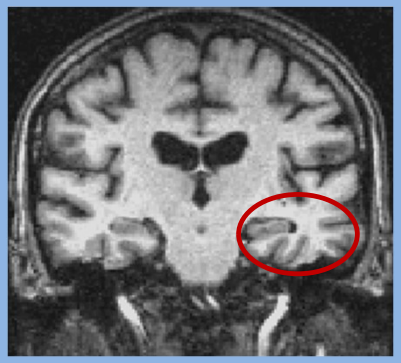
CLINICAL ASSESSMENT

- History with reliable informant is key to diagnosis
- Physical & neurological examination
- MMSE & MoCA
- Usually two visits

LABORATORY/IMAGING WORKUP OF DEMENTIA

- Recommended blood work: B12, CBC, calcium, electrolytes, glucose, TSH
- Brain CT or MRI optional but done in most cases, looking for strokes, tumors and hydrocephalus, and more relevant to dementia: size of the hippocampi

MRI IN AD



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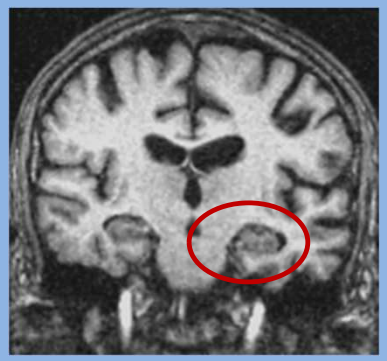
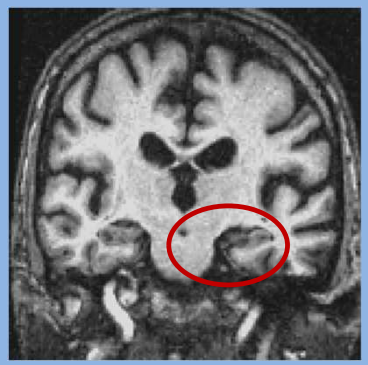


1



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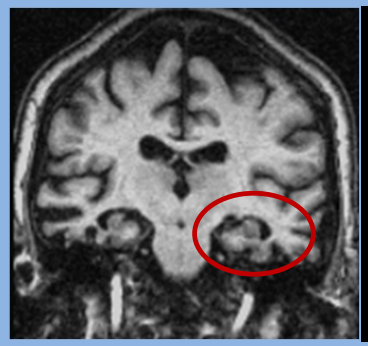

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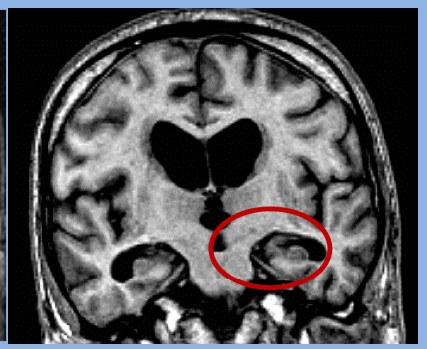


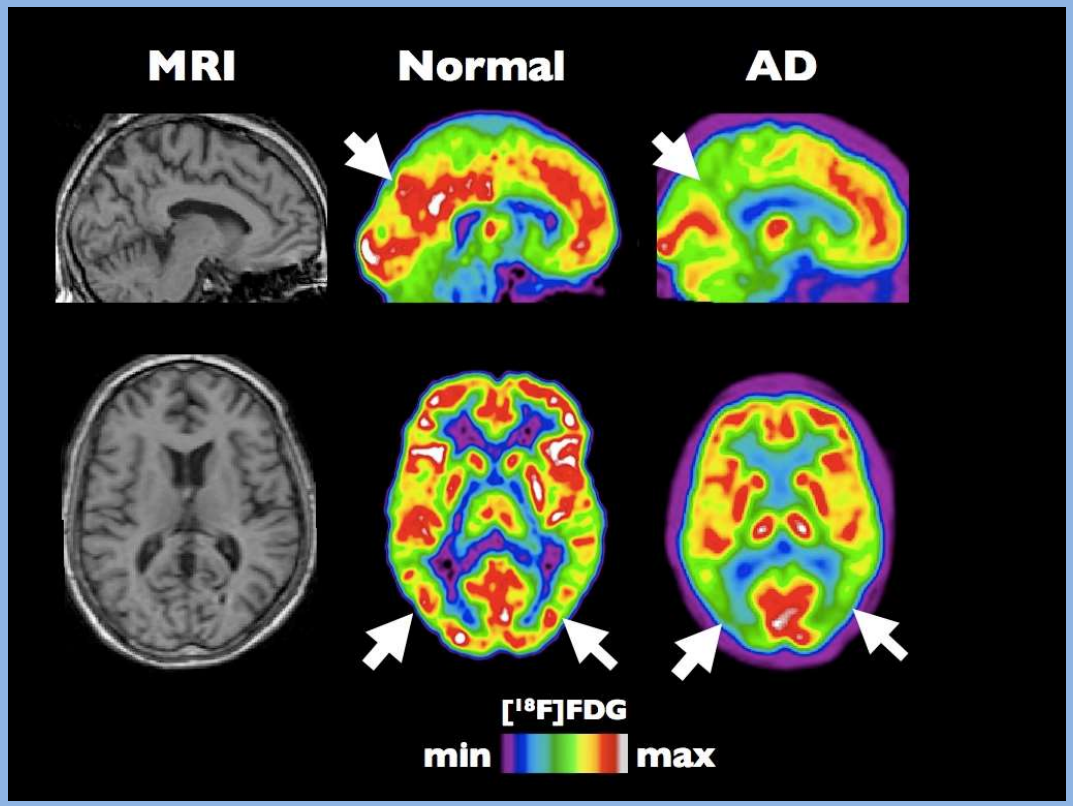
4

Rated area

SPECIAL DIAGNOSTIC TESTS

- Brain PET scan using FDG
- Commonly done for young (<65) persons, mild and/or atypical symptoms
- Gives a map of where glucose is being used across the brain
- Patterns of regions with low glucose utilization support certain diagnosis, notably Alzheimer's disease and Lewy Body Dementia

[18F]FDG OF NORMAL vs AD

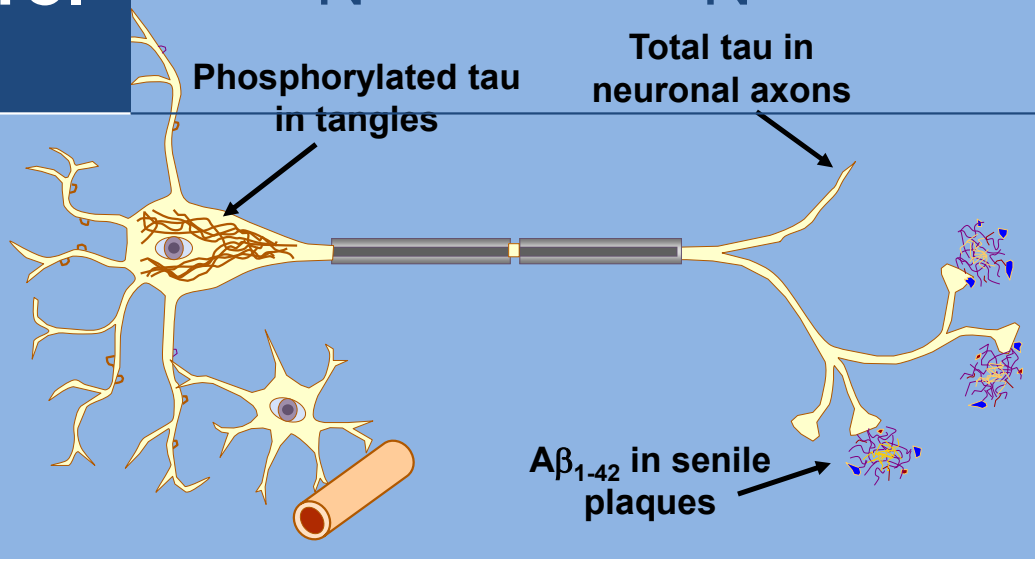


SPECIAL DIAGNOSTIC TESTS

- Spinal fluid examination requires a lumbar puncture
- Offered in specialized clinics for young (<65) persons, mild and/or atypical symptoms
- The levels of specific proteins are measured and can give a biological confirmation of the diagnosis of Alzheimer's disease

SPINAL FLUID (CSF) IN AD

	Aβ42	Tau	Ptau
AD	↓↓	↑↑	↑↑
MCI	↓ or N	↑ or N	↑ or N
Control	N	N	N



SPECIAL DIAGNOSTIC TESTS

- Amyloid PET if special conditions including an equivocal FDG scan

PUTTING ALL THE INFORMATION AVAILABLE TOGETHER - 1

- Is there clear evidence of cognitive decline?
- Does it interfere with daily life?
- Is there depression?
- Are there other conditions explaining some of the symptoms?
- Are there drugs with side effects?

DIAGNOSTIC CRITERIA FOR PROBABLE AD

- Dementia established clinically, eg deficit in two or more areas or cognition, interfering with daily life, progressing gradually
- No disturbance of consciousness
- Onset between 40 and 90 (below 65: early onset)
- Absence of other brain or systemic disease that could account for the dementia

CRITERIAS FOR VASCULAR DEMENTIA (VaD)

- Decline in two or more cognitive abilities interfering with daily life but not caused by the physical effects of stroke
- Evidence of stroke by history, physical exam or brain imaging
- Temporal relationship between dementia and stroke (within 3 months of a stroke)

CRITERIAS FOR DEMENTIA WITH LEWY BODIES (DLB)

- Progressive intellectual decline interfering with daily life
- One or two of
    * fluctuations of cognition
    * visual hallucinations
    * spontaneous parkinsonism
- Supportive features: REM Behavior Disorder, neuroleptic hypersensitivity

CRITERIAS FOR PARKINSON DISEASE DEMENTIA (PDD)

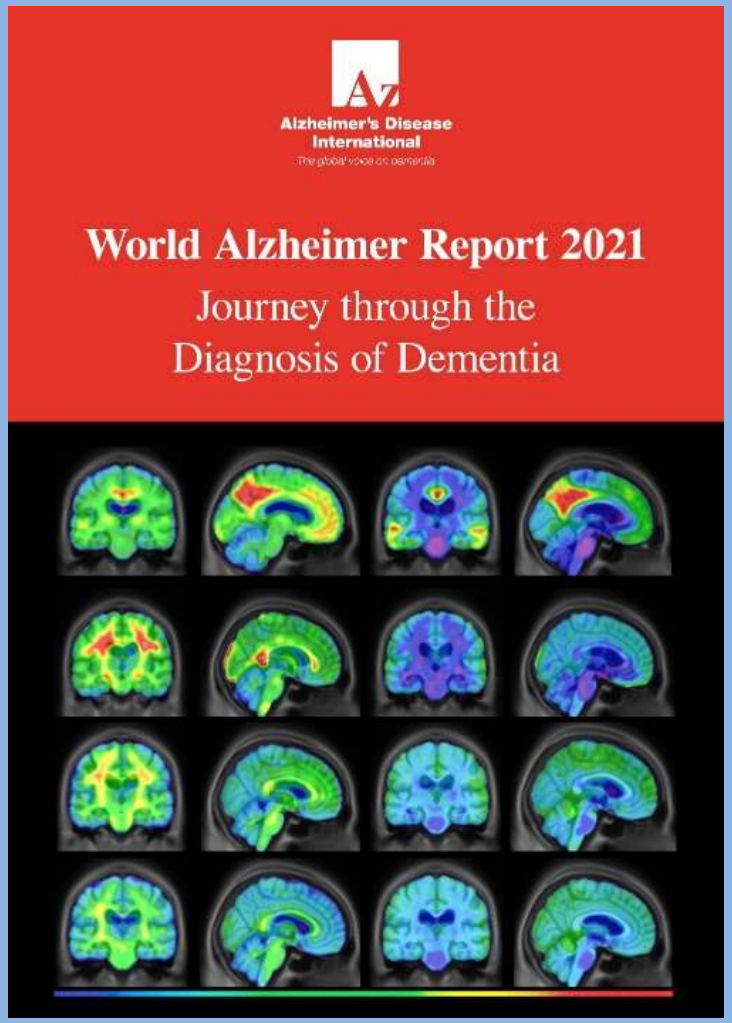
- Idiopathic PD (2 of rigidity, bradykinesia, resting tremor)
- Impairment of attention, executive and visuo-spatial abilities
- Often with visual hallucinations

PUTTING ALL THE INFORMATION AVAILABLE TOGETHER - 2

- At this stage of disease the most likely diagnosis is …
- Disclosure issues: will the patient have a catastrophic reaction, versus the right to know and plan ahead

PRESENTATION

- Natural history of age-associated cognitive decline
- Clinical assessment and complementary tests
- **Costs in 2021, in Québec**
- New plasma biomarkers
- Near future changes in diagnosis of AD



www.alzint.org/worldreport

Current costs of dementia diagnosis related to visits (Table 1a) and procedures (Table 1b) in a hospital outpatient clinic, in the province of Quebec, Canada, under a universal publicly funded Medicare system.

Table 1a. Assessments by physicians (First visit and one follow-up visit for persons over the age of 65)

	First Visit	Follow-up Visit
Family practitioner	100.00	50.00
Neurologist	320.00	77.00
Psychiatrists	359.00	140.00
Geriatricians	350.00	250.00
Geneticists	323.00	105.00
	PUBLIC	**PRIVATE**
Assessments by other healthcare professionals		
Genetic counsellor	140.00	Not available
Neuropsychologist	500.00	2,300.00

Table 1b. Laboratory tests		
	PUBLIC	PRIVATE
Blood Tests		
Complete Blood Count (CBC)	1.30	52.00
Sedimentation rate	1.60	39.00
Thyroid Stimulation Hormone (TSH)	1.60	89.00
T4	1.80	79.00
Electrolytes	2.10	69.00
Calcium	0.80	35.00
Blood Urea Nitrogen (BUN)	0.70	29.00
Creatinine	0.70	37.00
Glycemia	0.70	37.00
Haemoglobin A1c (HbA1c)	3.20	62.00
Alanine Aminotransferase (ALT)	0.70	31.00
B12	2.50	62.00
Folate	3.30	59.00
Cholesterol total, HDL, LDL, Triglycerides	5.30	79.00
Homocysteine	10.80	129.00
Syphilis serology	3.50	69.00
Human Immunodeficiency Virus (HIV) screen	4.90	69.00

Table 1b. Laboratory tests		
	PUBLIC	PRIVATE
Electroencephalography (EEG)		
Routine awake EEG	300.00	450.00
Spinal Fluid		
Lumbar puncture (procedure and kit)	205.00	205.00
Measure of A-Beta, Total tau and P-Tau	400.00	1349.00USD
Brain imaging		
Non contrast computer tomography (CT)	34.00	300.00
Non contrast magnetic resonance imaging (MRI)	320.00	650.00
Positron Emission Tomography (PET) with fluorodeoxyglucose (PET-FDG)	636.00	1,750.00
PET with amyloid ligand florbetaben	3,000.00	Not available
Genetic Testing		
APOE	43.00	219.00
PS1, PS2, APP	890.00 USD	890.00 USD

CLINICAL ASSESSMENT

- History with reliable informant is key to diagnosis
- Physical & neurological examination
- MMSE & MoCA
- Usually two visits

$100 for GP, $320 for a neurologist, $359 for a psychiatrist, $350 for a geriatrician

LABORATORY/IMAGING WORKUP OF DEMENTIA

- Recommended blood work: B12, CBC, calcium, electrolytes, glucose, TSH
  $9

- Brain CT or MRI optional but done in most cases, looking for strokes, tumors and hydrocephalus, and more relevant to dementia: size of the hippocampi
  $34 or $320

SPECIAL DIAGNOSTIC TESTS

- Brain PET scan using FDG
- Commonly done for young (<65) persons, mild and/or atypical symptoms
- Gives a map of where glucose is being used across the brain
- Patterns of regions with low glucose utilization support certain diagnosis, notably Alzheimer's disease and Lewy Body Dementia

$636

SPECIAL DIAGNOSTIC TESTS

- Spinal fluid examination requires a lumbar puncture
- Offered in specialized clinics for young (<65) persons, mild and/or atypical symptoms
- The levels of specific proteins are measured and can give a biological confirmation of the diagnosis of Alzheimer's disease

LP, $205; Analysis, US$1349

SPECIAL DIAGNOSTIC TESTS

- Amyloid PET if special conditions including an equivocal FDG scan

$3,000

SUMMARY OF DIAGNOSIS COSTS

- Diagnosis by GP with the minimal complementary tests. **$202**
- Diagnosis by neurologist if required by current CCCDTD criteria of early (65) or atypical presentation, unmanagable behavior, request by patient or family, or interest in research

$726 with MRI only, $1,362 with IRM and FDG-PET, $2,643 with MRI and CSF, $4,362 with MRI, FDG-PET, TEP-FDG and amyloid PET

PRESENTATION

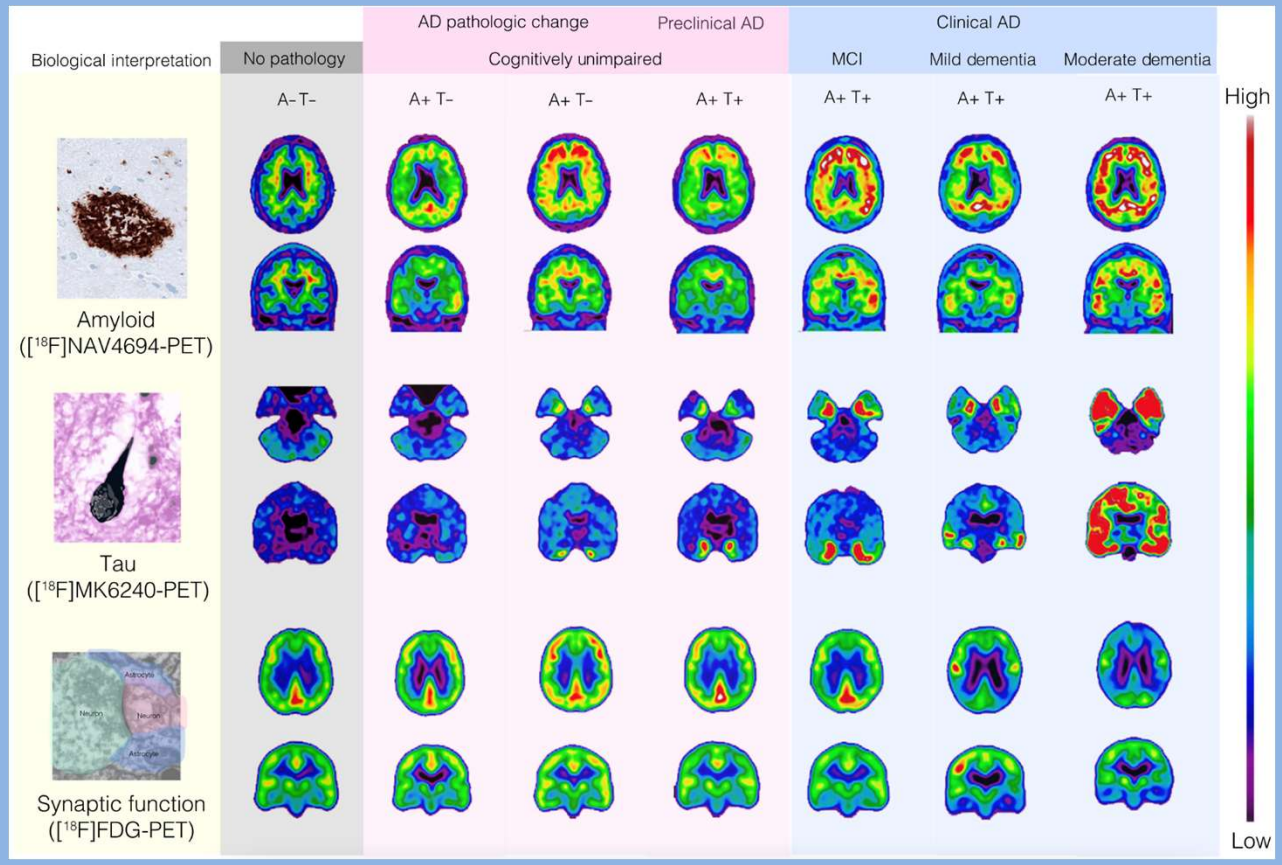
- Natural history of age-associated cognitive decline
- Clinical assessment and complementary tests
- Costs in 2021, in Québec
- **New plasma biomarkers**
- Near future changes in diagnosis of AD

ATN BIOLOGICAL DEFINITION OF AD

- Amyloid (A) — Amyloid PET or CSF
- Tau (T) — Tau PET or CSF
- Neurodegeneration (N) — MRI or FDG PET or CSF

MCI or dementia due to AD: A(+), T(+), N(+)

Adapted from Jack et al. NIA-AA Research framework: towards a biological definition of AD. Alzheimer's & Dementia 2018; 14(4), 535-62


Biological interpretation
No pathology
AD pathologic change
Preclinical AD
Cognitively unimpaired
Clinical AD
MCI
Mild dementia
Moderate dementia
A- T-
A+ T-
A+ T-
A+ T+
A+ T+
A+ T+
A+ T+
High
Low
Amyloid
([18F]NAV4694-PET)
Tau
([18F]MK6240-PET)
Synaptic function
([18F]FDG-PET)

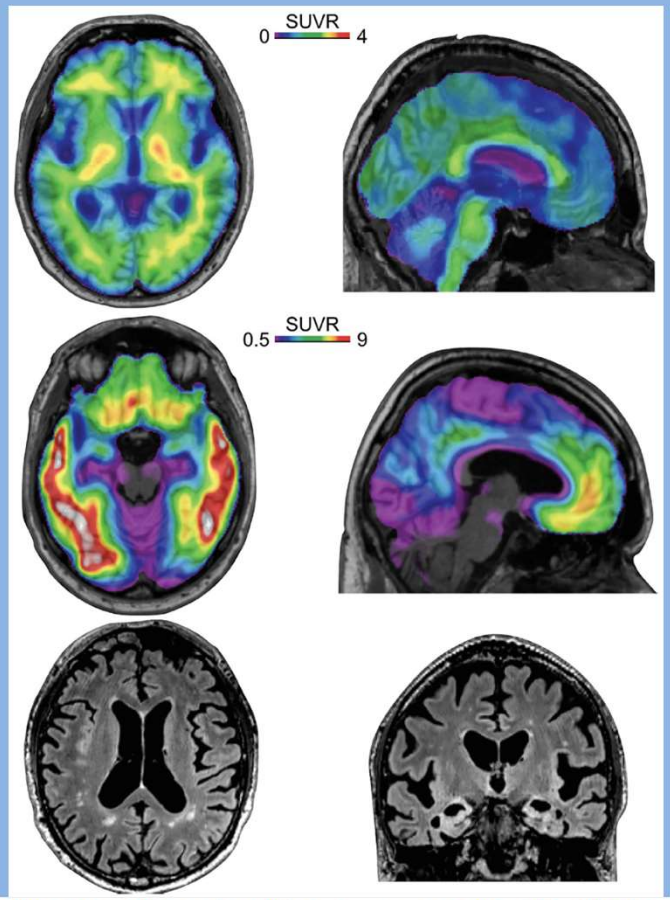


Figure. Amyloid positron emission tomography (PET), tau PET, and MRI from a man, age 80, with mild dementia (CDR 1) after a gradual cognitive decline over 5 years and clinical diagnosis of probable AD. The amyloid PET is read as negative, the tau PET positive on the temporal lobe, precuneus, inferior parietal cortex, orbitofrontal cortex, and amygdala (Braak V). The MRI shows mild general and hippocampal atrophy (Scheltens 4-5), White matter hyperintensities (WMH) are limited to the periventricular regions (Fazekas 1). This individual has a neurofibrillary tangle predominant dementia.

Gauthier & Rosa-Neto. Practical Neurology 2019; 18(5): 60-63

Plasma p-tau is a novel, promising blood-based biomarker for Alzheimer's disease

Plasma p-tau levels are increased in AD

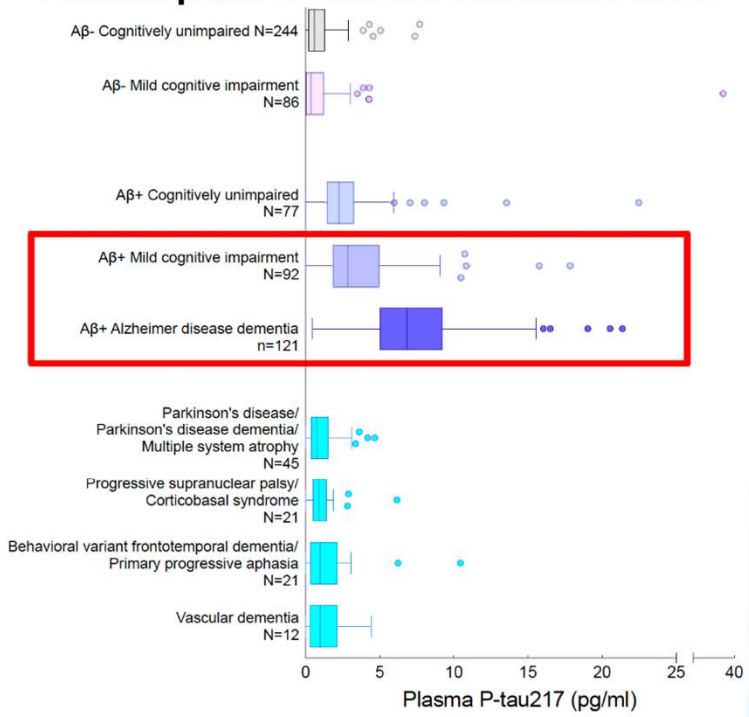


Figure adapted from Palmqvist S, et al. *JAMA*. 2020;324:772–781.[1]

Approximative ordering of Alzheimer's disease biomarker changes during the disease course

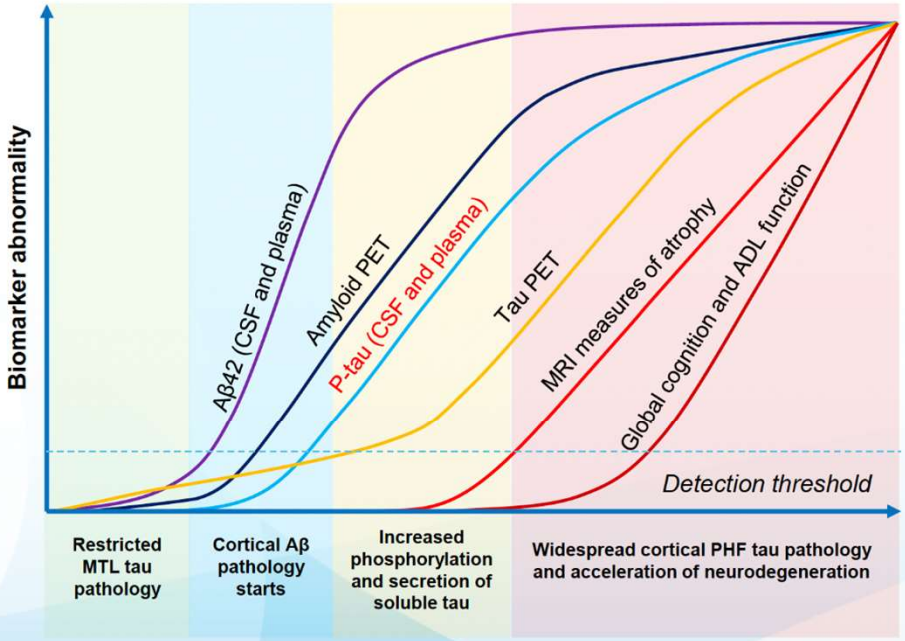


Figure adapted from Hansson O. *Nat Med*. 2021;27:954–963.[2]

Aβ, amyloid beta; ADL, activities of daily living; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; MTL, medial temporal lobe; p-tau, phosphorylated tau; PET, positron emission tomography; PHF, paired helical filaments; t-tau, total tau. 1. Palmqvist S, et al. *JAMA*. 2020;324:772–781; 2. Hansson O. *Nat Med*. 2021;27:954–963.

PRESENTATION

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- **Near future changes in diagnosis of AD**

NEAR FUTURE CHANGES IN DIAGNOSIS OF AD

- Plasma isoforms pTau 181 and/or 217 could be used in primary care to screen persons with a clinical diagnosis of AD most likely to be ATN+. Estimated cost **$200**. May require adding ApoE genotype **$43**.
- Fast track consultation in neurology or other clinician with expertise in AD, if younger than 65 and/or interest in research or access to approved DMD.
- Cost savings for CSF analysis if done in Canada. $400 instead of US$1,349, thus **$1331 total** for two clinical visits by a neurologist, MRI and CSF

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REVIEW ARTICLE

Remote cognitive and behavioral assessment: Report of the Alzheimer Society of Canada Task Force on dementia care best practices for COVID-19

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CONCLUSIONS

- There is clear interest in the general public for earlier and accurate diagnosis of MCI and early dementia
- Possible utility of self screening on line with validated instruments
- Manpower issues could be managed by training of interested GP and other health professionals in the use of structured assessments for cognition, ADL and mood/behavior changes
- ATN characterization could be made cost-effective using CT or MRI, plasma biomarkers and CSF analysis in sequence