Recommendations on MCI from the Third and Fourth Canadian Consensus Conferences on Diagnosis and Therapy of Dementia/ Quatrieme Conférence Canadienne Consensuelle sur la Démence 2012.

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Disclosure Statement

Dr. Chertkow has been a paid consultant for:

Bristol-Myers Squibb

Dr. Chertkow like the MoCA but receives no renumeration for its use.

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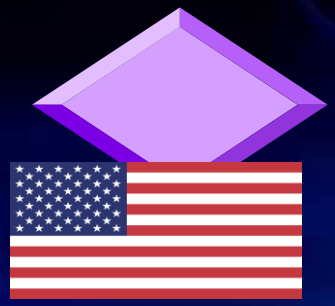
Background

- Canada: Small enough to get the experts in one room.
- Four times since 1990- consensus conferences of Canadian dementia experts from psychiatry, geriatric medicine, neurology.
- Results impact on drug coverage, government policy, teaching of residents across the country.



innovation [e.g. Amyloid PET] → FDA → availability and use → Variable Uptake

innovation [e.g. Amyloid PET] → Health Canada → 12 provincial payers → Use or not

12 provincial payers → Public hospital services

Expert Panels,guidelines, Consensus Conferences

Focus of fourth CCCDTD (2012)

- New definitions and conceptualization of AD and MCI
- Availability of biomarkers (CSF, amyloid and functional MRI neuroimaging) and how to handle them.
- Ethical concerns about clinical use (misuse) of biomarkers
- Target audience: non dementologist specialists, family physicians- for best care

CLINICAL PRACTICE GUIDELINES/CONCENSUS STATEMENTS

Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4)

Serge Gauthier, MD, Christopher Patterson, MD, Howard Chertkow, MD, Michael Gordon, MD, Nathan Herrmann, MD, Kenneth Rockwood, MD, Pedro Rosa-Neto, MD, PhD, Jean-Paul Soucy, MD on behalf of the CCCDTD4 participants*

Can Geriatr J 2012; 15(4): 120-6

Full set of articles to published in special edition
Of Alzheimer's Research and Therapy

- *Alzheimer's Research & Therapy* 2013, 5(Suppl 1):
- Volume 5 Supplement 1
- Background documents to the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4)
- Montreal, Canada, 4 May 2012
- Edited by Serge Gauthier, Christopher Patterson and Howard Chertkow
-
- Introduction
- Christopher Patterson, Serge Gauthier
-
- Definitions of dementia and predementia states in Alzheimer Disease and Vascular Cognitive Impairment –Howard Chertkow, Howard Feldman, H. , Claudia Jacova,C., & Fadi Massoud.
-
- Clinical applications of neuroimaging in patients with Alzheimer's disease:
- Jean-Paul Soucy, Robert Bartha, Christian Bocti, Michael Borrie, Amer M Burhan, Robert Laforce, Pedro Rosa-Neto
-
- Fluid biomarkers for diagnosing dementia: rationale- Pedro Rosa-Neto, Ging-Yuek Hsiung, Mario Masellis, on behalf of the CCDTD4 participants
-

Who participated?

Steering Committee

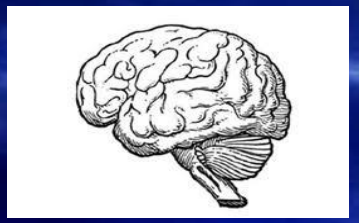
- **Christopher Patterson (Co-Chair)-geriatrician**
- **Serge Gauthier (Co-Chair)-neurologist**
- **Howard Chertkow-neurologist**
- **Michael Gordon (Ethics consultant) –geriatrician**
- **Pedro Rosa-Neto-neurologist**
- **Ken Rockwood –geriatrician**
- **Jean-Paul Soucy-nuclear med.**

Participants

Twenty-four academic physicians

- 8 neurologists, 8 geriatricians, 6 psychiatrists
- 2 family

- Building upon 1989 & 1999 cccd
- Posting background papers to website
- Comments added on line
- Voting online
- Advanced dissemination strategy (specific $) CMAJ, Alzheimer's & Dementia



Montréal, May 4-5

2012

- Adherence to AGREE template (21/22 criteria)
- Use of GRADE evidence classification
- Ethics consultant and consumer involvement
- Advanced knowledge translation strategy (DKTN, publications, web based)
- No industry funding

Process for achieving consensus:

- Consensus = 80% of CCCD participants (web based plus attendees)
- Partial consensus = 60-79%
- Recommendation may be amended
- Less than 60%: option to drop or rewrite recommendation, opposing view
- Recommendations may be subsequently abbreviated for clarity

- Hypothesis: If there is consensus in the medical community of experts, the government will listen

AGREE Collaboration (Appraisal of Guidelines, research and Evaluation)

1. Scope and purpose: specific statement & description target population
2. Stakeholder involvement
3. Rigour of development: search strategy, criteria for selecting evidence, linkage to recommendations, external review
4. Clarity and presentation
5. Applicability: organization, cost, monitoring
6. Editorial independence: isolation from funding sources, conflict of interest declaration

Qual Saf Health Care 2003 12:18-23

Definitions of dementia/AD and pre-dementia states

NIA-AA Working Groups:

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

Guy M. McKhann, David S. Knopman, Howard Chertkow, et al., Alzheimer's & Dementia, 2011

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

Marilyn S. Albert, Steven T. DeKosky, et al., Alzheimer's & Dementia, 2011

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

Reisa A. Sperling, Paul S. Aisen, *et al.*, Alzheimer's & Dementia, 2011

“The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging and the Alzheimer’s Association workgroup”-Guy M. McKhann, David S. Knopman, Howard Chertkow, et al., Alzheimer's & Dementia, 2011

•Revision of clinical criteria

1. Criteria for dementia of all causes
2. Probable AD – core clinical criteria (amnestic vs. non-amnestic presentations such as logopenic PPA, Post. Cort. Atrophy, frontal/executive).
   - - increased level of certainty with causative genes, documented decline

1. Possible AD core clinical criteria
   - Atypical course or
   - Etiologically mixed (Vascular, extrapyramidal, other neuro illness)
2. Probable/ possible AD with biomarkers (“evidence of the AD pathophys”).

Canadian Consensus?

We recommend the adoption of the 2011 NIA-AA criteria proposed by the working group for:

	For
Dementia	**All**
Probable and possible AD	**All**

Canadian Consensus?

For

We recommend the 2011 ASA/AHA recommendations for the diagnosis of VCI, VaD

All

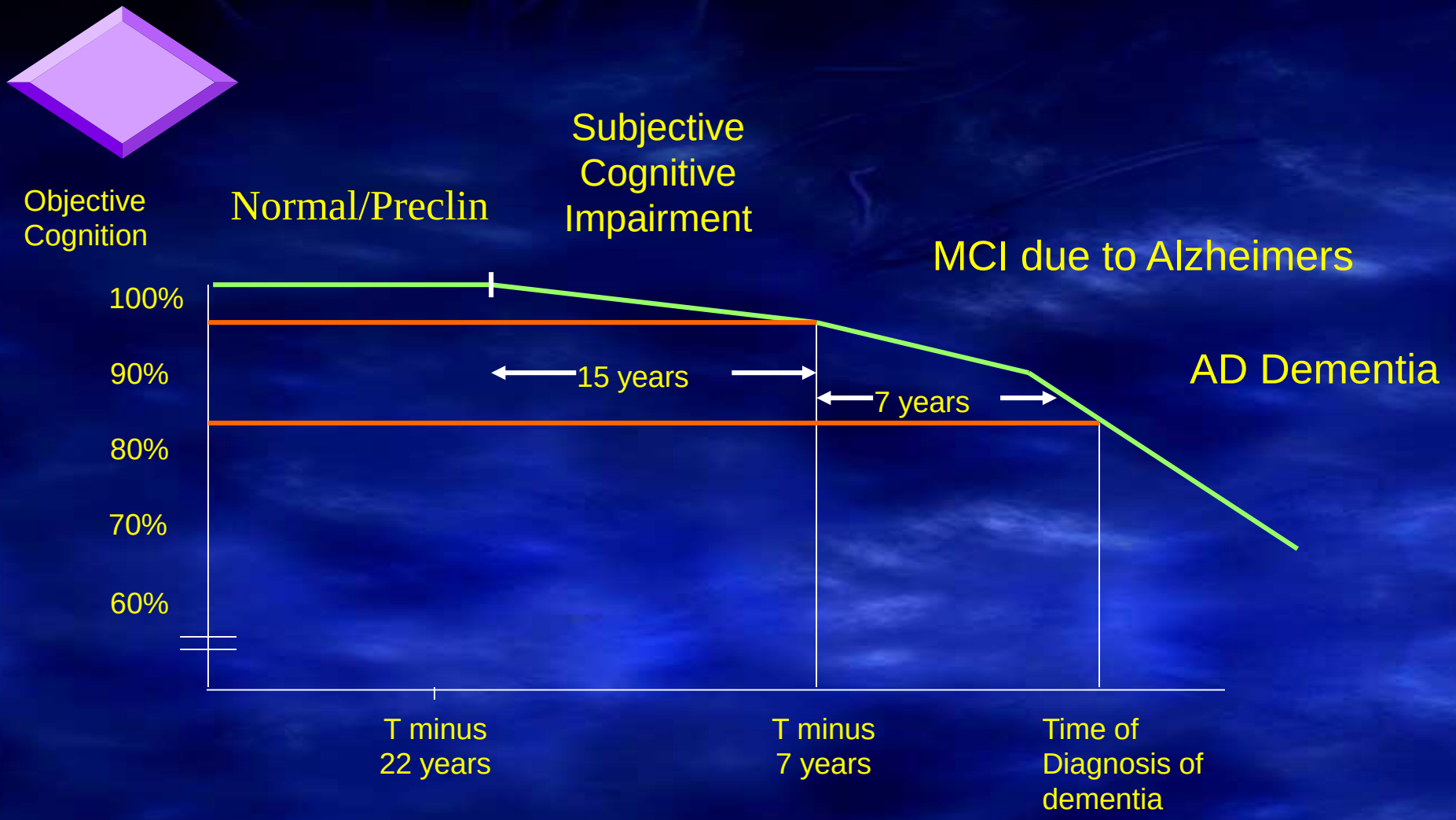
How do we diagnose dementia now?

Normal

Mild Cognitive Impairment

Dementia

Functional impairment



When does AD begin?
B. Reisberg, IPA meeting, 2009

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup
Marilyn S. Albert, Steven T. DeKosky, et al., Alzheimer's & Dementia, 2011

- **Need to identify individuals in earliest AD stages**
  - **For new treatment, drug development**
  - **"It is ..important to incorporate this continuum of impairment into clinical and research practice."**
- **Standardize clinical criteria for MCI**
- **Delineate "MCI of the Alzheimer's type"**

- **"MCI- Research criteria incorporating biomarkers"- biomarker evidence of AD**
- **Recognition that MCI is frequently AD**

Albert et al.: Biomarkers in MCI

Clinical diagnosis category **MCI due to AD Core clinical criteria**	**BoM probability of AD etiology** **Uninformative**	**Abeta (CSF or PET)** **Unavailable or conflicting or indeterminate**	**Neuronal injury (MRI, FDG PET, CSF tau)** **Unavailable or conflicting or indeterminate**	
MCI due to AD Intermediate likelihood	Intermediate	Positive Unavailable	Unavailable Positive	
MCI due to AD High likelihood	Highest	Positive	Positive	
MCI –unlikely due to AD	Lowest	Negative	Negative	

Positive Biomarkers are found in some cognitively normal elderly subjects.

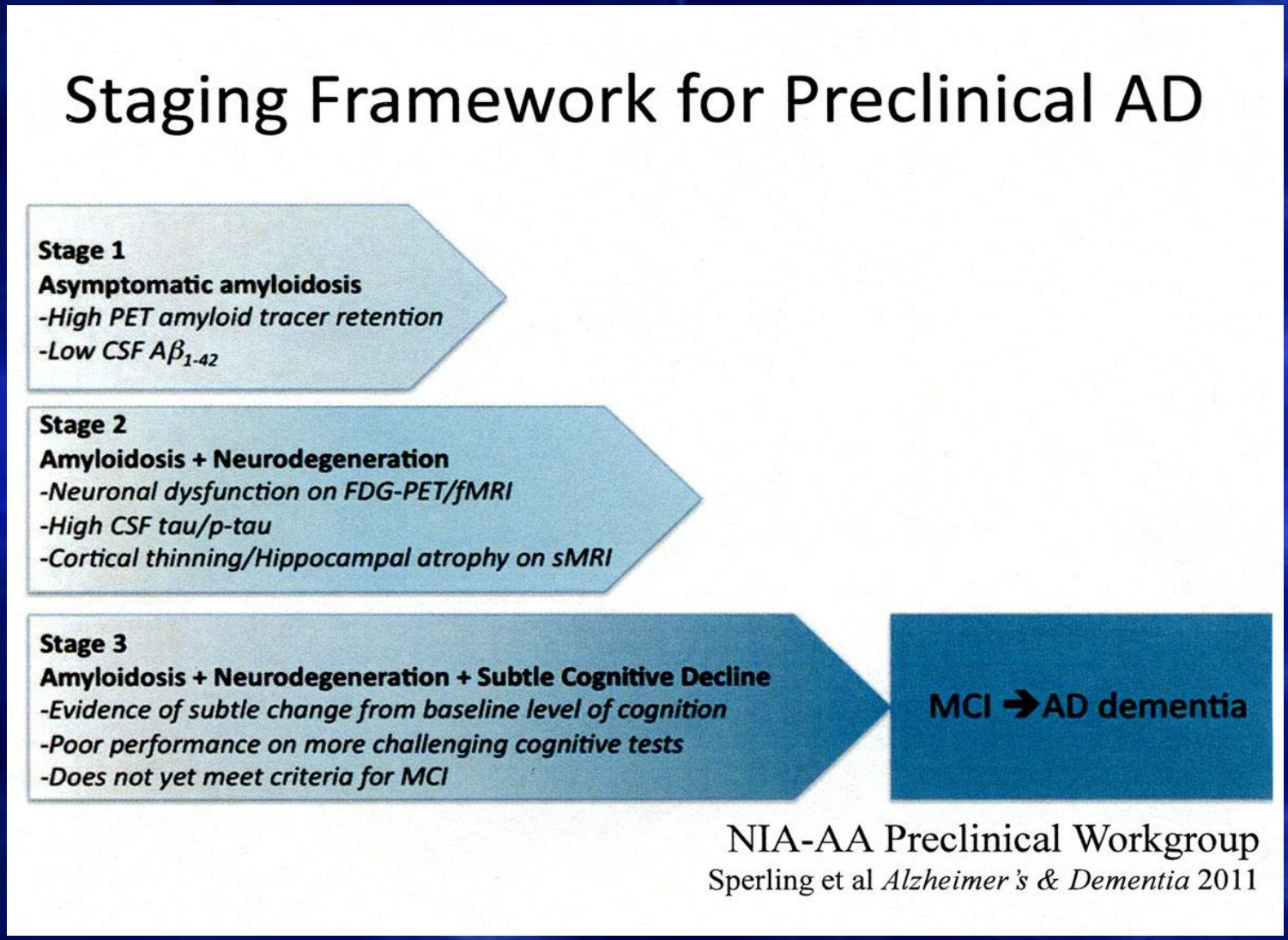
Morris et al (2010), Ann Neuro, 67: 122-131

Normal Elderly Controls- Percentage with +ve biomarkers (AD range):

- **PIB PET + 15.5%**
- **ABeta42 CSF – 28%**
- **Tau CSF – 6.6%**
- **phospho tau 181 CSF – 4.2%**
- **BUT DO THESE PREDICT WITH TOTAL SENSITIVITY AND SPECIFICITY WHO WILL GO ON TO ALZHEIMER'S DISEASE?**
- **Not yet known!**

"Toward defining the preclinical stages of Alzheimer's disease"

Sperling,Aisen, *et al.*, Alzheimer's & Dementia, 2011



Alternative approach to MCI and biomarker positive elderly- the "International Working Group (IWG)".

- Dubois et al, 2008:Proposal- Use term MCI if no biomarkers. But MCI (genuine memory loss) plus specific "abnormal biomarker" [PET, CSF, MRI] = "prodromal AD"
- For individuals with no cognitive complaints, yet showing abnormal biomarkersrecommend term "Asymptomatic at-risk for AD".
  - Individuals have increased risk of progressing
  - They may still die with normal cognition
  - Prognostic certainty of biomarkers is still unclear
-

Dubois "International Working Group"

Proposed lexicon for Cognitive spectrum -(IWG)

	AD diagnosis	Presence of impairment on specified memory tests	Evidence of biomarkers in vivo	Additional requirements
Typical AD	Yes	Required	Required	None
Atypical AD	Yes	Not required	Required	Specific clinical presentation
Prodromal AD	Yes	Required	Required	Absence of dementia
AD dementia	Yes	Required	Required	Presence of dementia
Mixed AD	Yes	Required	Required	Evidence of comorbid disorders
Preclinical AD				
Asymptomatic at risk for AD	No	Not present	Required	Absence of symptoms of AD
Presymptomatic AD	No	Not present	Not required	Absence of symptoms of AD and presence of monogenic AD mutation
Mild cognitive impairment	No	Not required	Not required	Absence of symptoms or biomarkers specific for AD

AD=Alzheimer's disease.

Table 2: Comparative features of the different conditions described in the new lexicon according to the new research criteria framework[6]

Dubois B et al. Lancet Neurol 2010; 9: 1118

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Canadian Consensus?

We recommend the adoption of the 2011 NIA-AA criteria proposed by the working group for:

Criteria for MCI

For

All

Canadian Consensus on MCI, normal terminology

Recommendation:

For

We recommend the IWG definition of "asymptomatic at-risk for AD" states for **research purpose**.

All

We recommend **reassessment** of the utility of the concept of prodromal AD in the future when AD-PP biomarkers are available, validated, and ready for use in Canada. This term has advantages.

All

Clinical categories

Normal function:
- **No complaints of cognitive loss**
- **Testing is within normal limits**

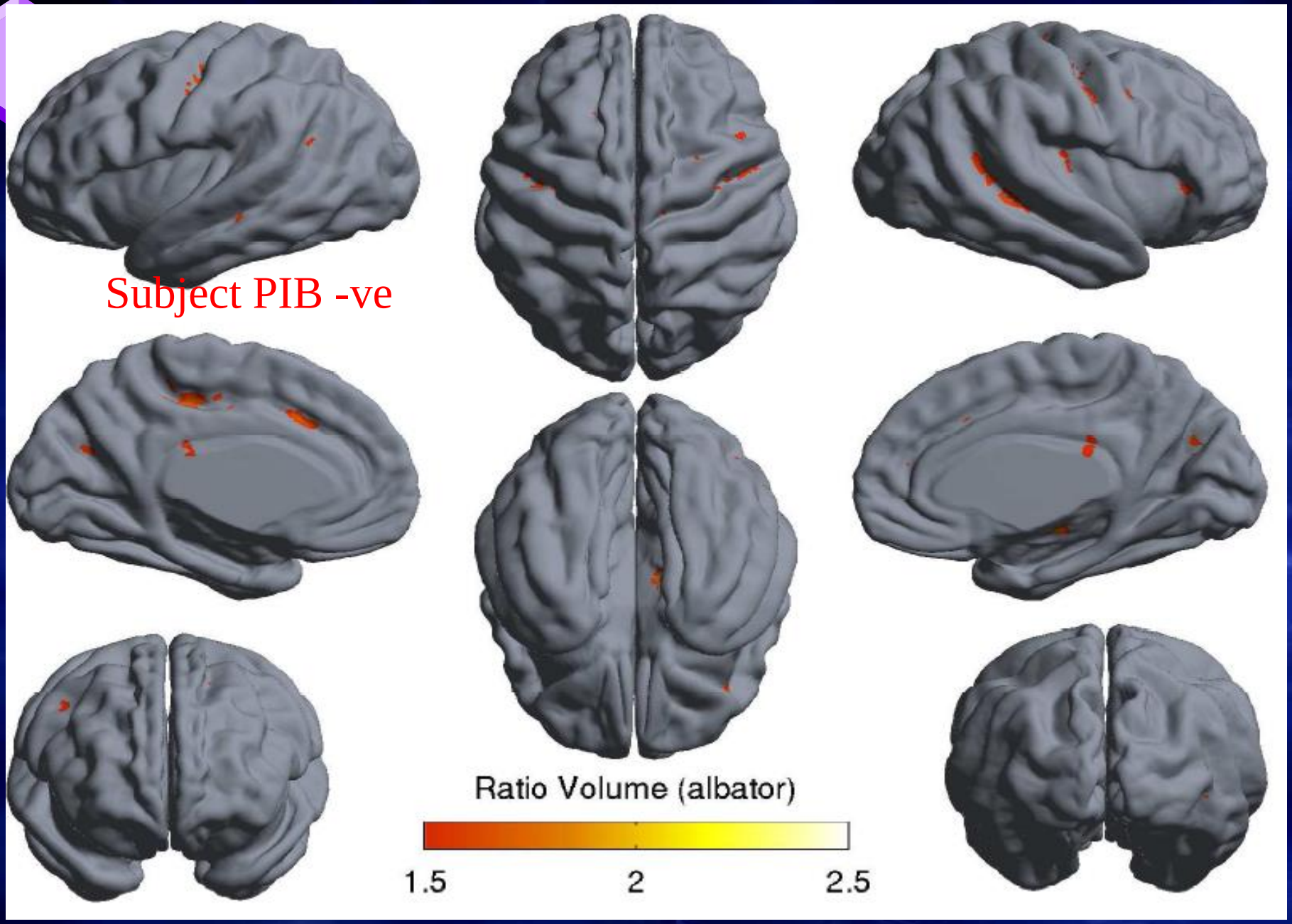
Subjective complaints only:
- **Patient or family complains of loss**
- **Testing is within normal limits**

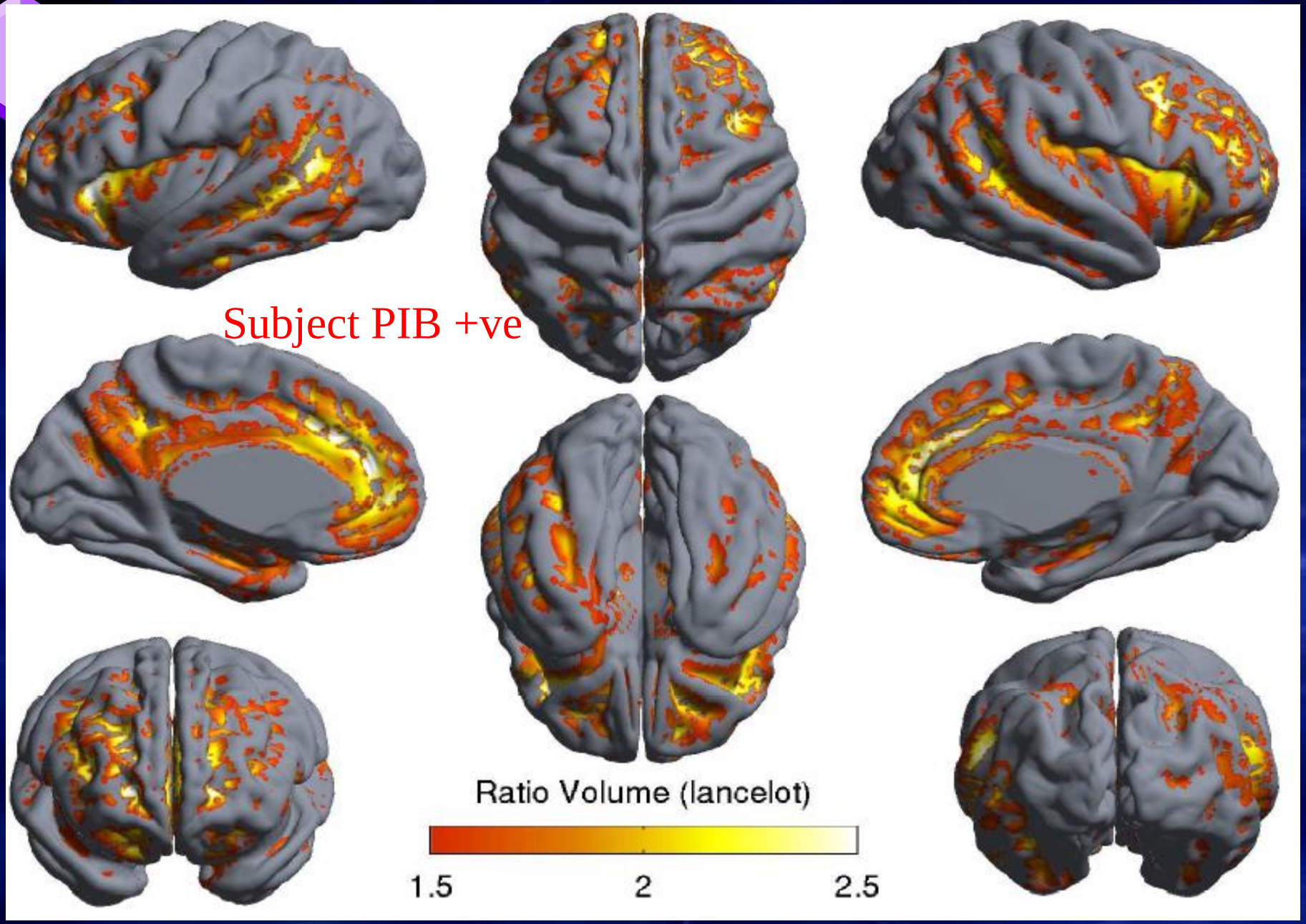
Mild Cognitive Impairment:
- **Patient or family complains of loss**
- **Objective mild impairment in cognition**
- **Not sufficient to be dementia**

Dementia:
- **Significant decline in two or more cognitive domains**
- **Sufficient to impair day to day function**

Converging evidence from both genetic at-risk and age at-risk cohorts that the pathophysiological AD begins years, perhaps more than a decade, prior to the diagnosis of dementia

What about the role of amyloid imaging?


Subject PIB -ve
Ratio Volume (albator)
1.5
2
2.5


Subject PIB +ve
Ratio Volume (lancelot)
1.5
2
2.5

Canadian Consensus against amyloid PET in normal individuals

Given that the presence of brain amyloid in normal people is of uncertain significance, the CCCD **discourages** the use of amyloid imaging in individuals without memory loss, **outside** of the research setting .

For All

The medical community should be clear in its discussions with patients, the media and the general population that presence of brain amyloid in **normal** people is of **unclear** significance at the present time.

All

Neuroimaging - Amyloid Imaging

At present, there is **no clinical indication** for amyloid imaging in cognitively normal individuals, initial investigation of cognitive complaints, differentiating AD from other Aβ - associated dementia (e.g. DLB, CAA), differentiating between AD clinical variants (e.g. classic amnestic AD vs. PCA or lvPPA), and differentiating between non-AD causes of dementia (e.g. molecular subtypes of FTLD).

For

All

Neuroimaging - Amyloid Imaging

For

All

Amyloid imaging is not currently approved in Canada. Should amyloid imaging become available in Canadian clinicians in the future, it must **not be considered a routine** test and we recommend it as an adjunct to a comprehensive evaluation for complex atypical presentations in referral to tertiary care Memory Clinics when a more accurate clinical diagnosis is needed (Grade 1B).

Neuroimaging - Amyloid Imaging

Although amyloid imaging represents a promising technique in the evaluation of dementia, there are many unknowns that could impact on its diagnostic utility and therefore we recommend that its use be restricted to research at present (Level 1C).

Health Policy recommendation:

Based on current evidence we recommend that Health Canada approves the use of amyloid imaging in tertiary care dementia clinics.

	For	Against
All	63%	37%

Summary

- Clinical definitions for AD, MCI can incorporate biomarker information
- Canadians prefer “asymptomatic, at risk for AD” to “Preclinical AD”.
- Biomarker studies will clarify when “MCI of the Alzheimer Type” is really “prodromal AD”.
- Canadian community is less enthusiastic about clear role for amyloid imaging, even for difficult cases! Serious concern about overuse and misinterpretation.
- Pressure for earlier diagnosis will be driven by availability of new disease modifying drugs and preventive therapies

Dr. Howard Chertkow’s Cognitive Neuroscience Team