치매임상시험평가의 전망

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Focuses of this session

1. Emerging disease-modifying drugs for AD /dementia
2. Biomarkers as potential outcome measure for disease-modifying trials
   - Neuroimaging
   - Other biomarkers

AD / Dementia drug effects

- Symptomatic effect
  - Cognitive symptom
  - Global
  - BPSD
  - IADL / basic ADL
  - Parkinsonism
  - Others: QOL, Caregiver burden, etc

- Disease modifying effect
  - Modifying (stop or slow) biological diseases process itself

Potential disease-modifying therapies under investigation for AD

From Cummings et al. (2007) Neurology

Antiamyloid approaches*
Immunization/vaccination[107,108]
Beta-secretase inhibitors[109,110]
Gamma-secretase inhibitors/modulators[111-113]
Antifibrillization agents[114,115]
Statins[116,117]
PPAR-gamma agonists[118,119]
Protein-metal attenuating compounds[120-122]
Muscarinic M1 agonists[123-125]
Neuroprotective approaches
Nerve growth factor and related therapies[126-128]
Antioxidants[129,130]
Astrocyte modulators[131-133]
Homocysteine-lowering therapies[134,135]
Anti-inflammatory agents[59,136]
NMDA receptor antagonists[137,138]
Ampakines [139-141]
Tau-related therapies (e.g., GSK3β inhibitors)[142,143]
Caspase inhibitors[144,145]
Monoamine oxidase inhibitors[146,147]
Nicotine acetylcholine receptor agonists[148,149]
Cholinesterase inhibitors [150-152]
Neurorestorative approaches
Neurotrophin/nerve growth factor [126,153,154]
Cell transplantation[155,156]
Stem cell–related strategies[157,158]

Primary outcome measures in current AD/dementia trials

- Cognition (esp., ADAS-cog)
- Function (esp., CIBIC, etc)
- Others

- Emergence of cognitive symptoms
- Conversion from amnestic MCI to diagnosable dementia
- Loss of instrumental ADL
- Emergence of BPSD
- Nursing home placement
- Loss of self-care ADL
- Death

General limitations of cognition and function as a outcome measures in AD/dementia related trials

- Cannot easily distinguish Ds-modifying vs. Sx effect
  - → Design-based methods*
    - : difficult to perform, higher drop-out rate
    - : thus require more time and funds
- Relatively poor test-retest reliability (ICC=0.5~0.8)
  - → Reduce statistical power, requiring increased sample size
- Some medication with Ds-modifying effect may not have an impact on cognition or function in the short term.
  - → Especially in primary prevention trials

Any alternative outcome measures (surrogate markers) to overcome these limitations?

Advantage of Neuroimaging (or other biomarker) as a outcome measure in AD/dementia related trials

- Obtains information directly from the brain
- Much higher test-retest reliability
  : ICC > 0.95 for hippocampus volume measuring
- Has high “face validity” as an index of disease progression
- To some extent, have been quantitatively validated by correlation with cognition/function, and correlation with neuropathology

FDA Modernization Act (1997)

[Although FDA has not used imaging endpoints for approval of AD treatment]

"a fast tract product may be approved if it has an effect on a **surrogate marker** that is **reasonably likely** to predict a clinical benefit in the treatment of serious and life-threatening illnesses (including AD)"

Biomarkers with potential roles in AD / dementia clinical trials

- Neuroimaging
  - Structural MRI
  - Functional imaging
  - Molecular imaging
- Biochemical measures
  - CSF $A\beta_{42}$
  - CSF tau or p-tau
  - Others

Basic requirements of a useful biomarker for AD/dementia trials

1. The assay must have excellent sensitivity and test-retest reliability.
2. The biomarker should reflect a key feature of AD pathology or a mechanism of disease.
3. The longitudinal pattern of change in the biomarker and variability of that change should be adequately described.

Potential uses for biomarkers in drug development

1. For selection of homogeneous patients group (in inclusion or exclusion criteria)
2. As an early indicator that an investigational drug is reaching its target and is having the intended effect (biological disease modification effect)
3. For indirect assessments of effects on disease progression (“surrogate marker”)

Structural imaging : MRI

- Serial volumetric MRI
  - Can provide surrogate markers of disease progression using serial MRI
- Advantage of MRI
  - Non-invasive
  - even with repeated imaging, no adverse effects

    (if excluding subjects with pacemaker or metallic implant)
  - Widely disseminated and relatively inexpensive

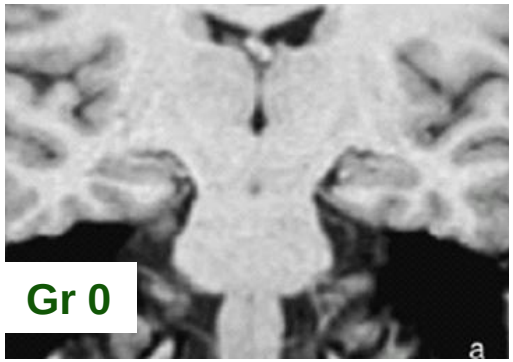
Longitudinal **volumetric** MRI studies

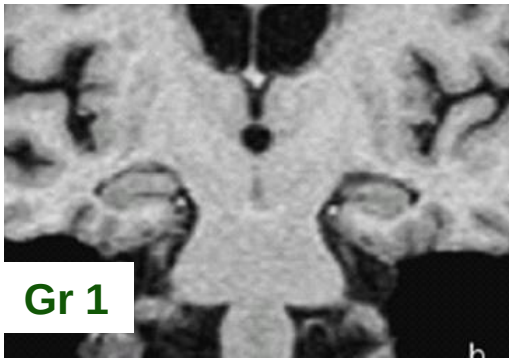
TABLE 2. Longitudinal Volumetric Magnetic Resonance Imaging Studies in Alzheimer Disease[8–11,14–20,92]

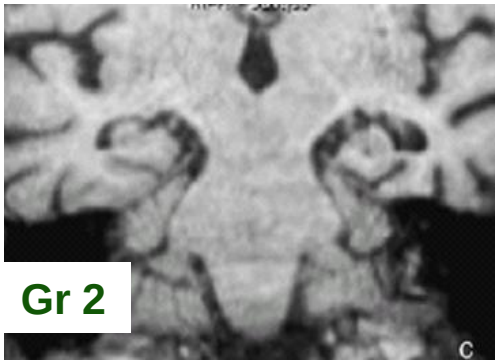
Source	Region	N (Control/Alzheimer Disease [AD])
Kaye et al, 1997	Hippocampi	18/12 (preclinical AD)
	Parahippocampal gyri	
	Temporal lobes*	
	Intracranial volume	
Jack et al, 1998, 2004	Hippocampi*	24/24 and 55/64
	Entorhinal cortex*	
	Temporal horns*	
	Whole brain*	
	Ventricle*	
Fox et al, 2000	Whole brain*	18/18
Laakso et al, 2000	Hippocampi	8/27
Teipel et al, 2002	Corpus callosum*	10/21
Bradley et al, 2002	Whole brain*	32/5
	Ventricle*	
	Ventricle/brain ratio*	
Wang et al, 2002	Cerebrum*	14/14
	Lateral ventricles*	
	Temporal lobes*	
Du et al, 2003, 2004	Entorhinal cortex*	23/21 and 25/21
	Hippocampus*	
Schott et al, 2003	Entorhinal cortex*	20/5 (presymptomatic AD)
	Hippocampus*	
	Temporal lobe*	
	Brain*	
Thompson et al, 2004	Hippocampus*	14/12
	Ventricle*	

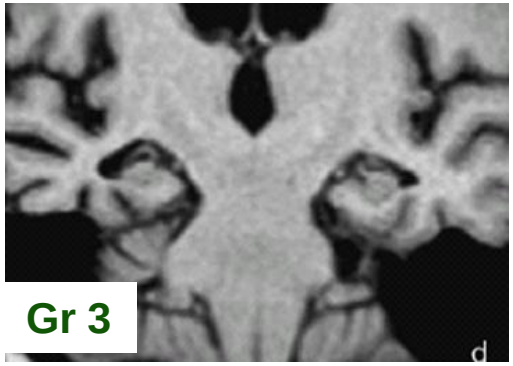
*There were statistically significant differences between patients with Alzheimer disease and controls.

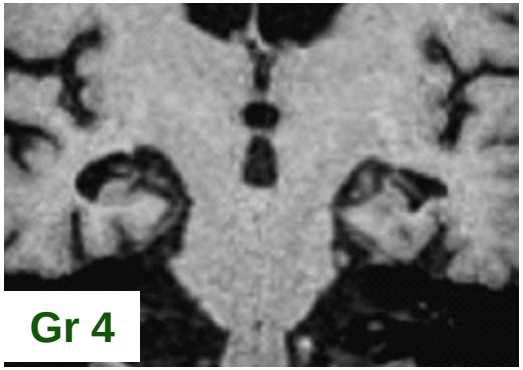
Visual assessment of MTA



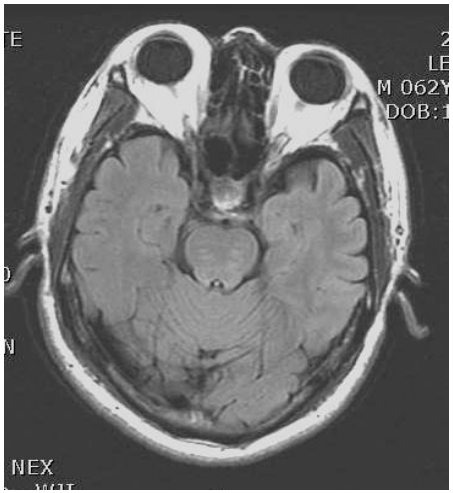


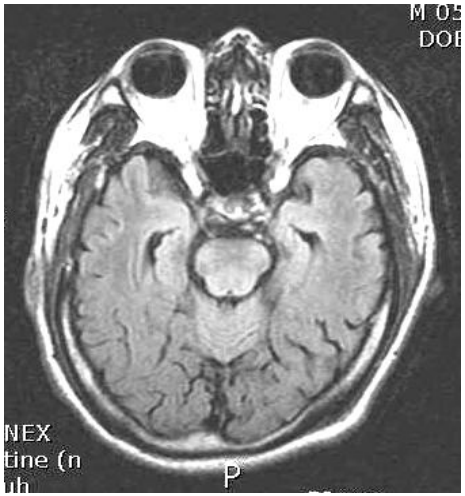


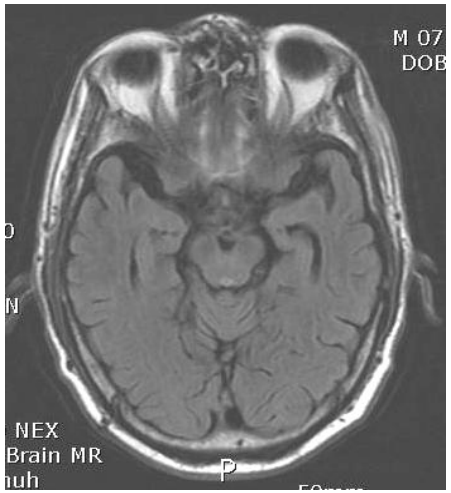


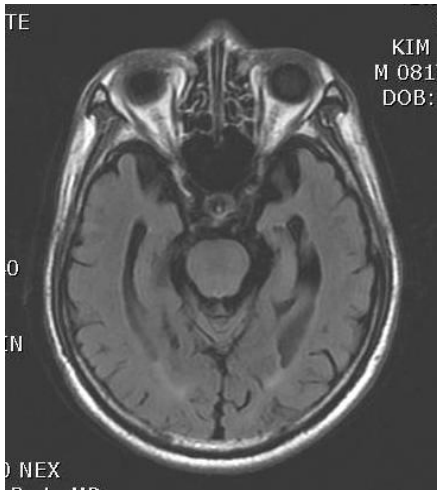


Scheltens (1992) JNNP

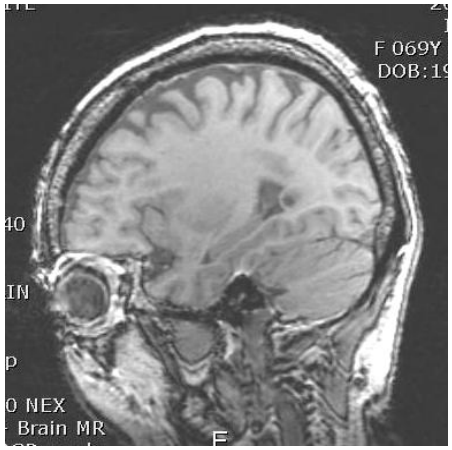


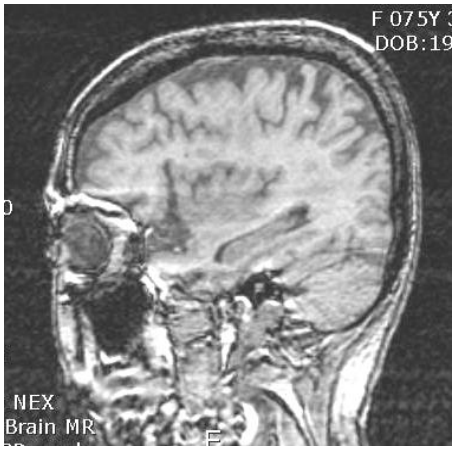


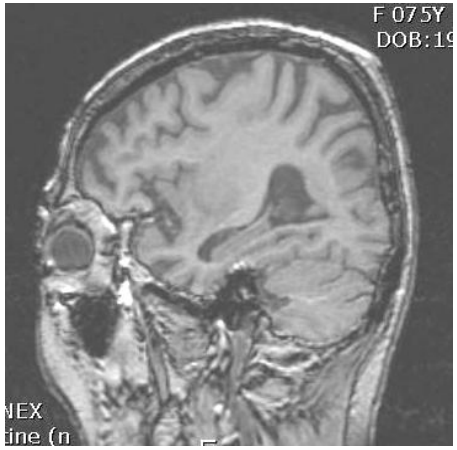


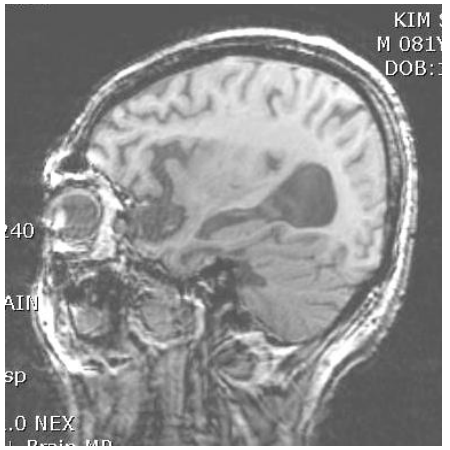


Grade 0 **Grade 1** **Grade 2** **Grade**





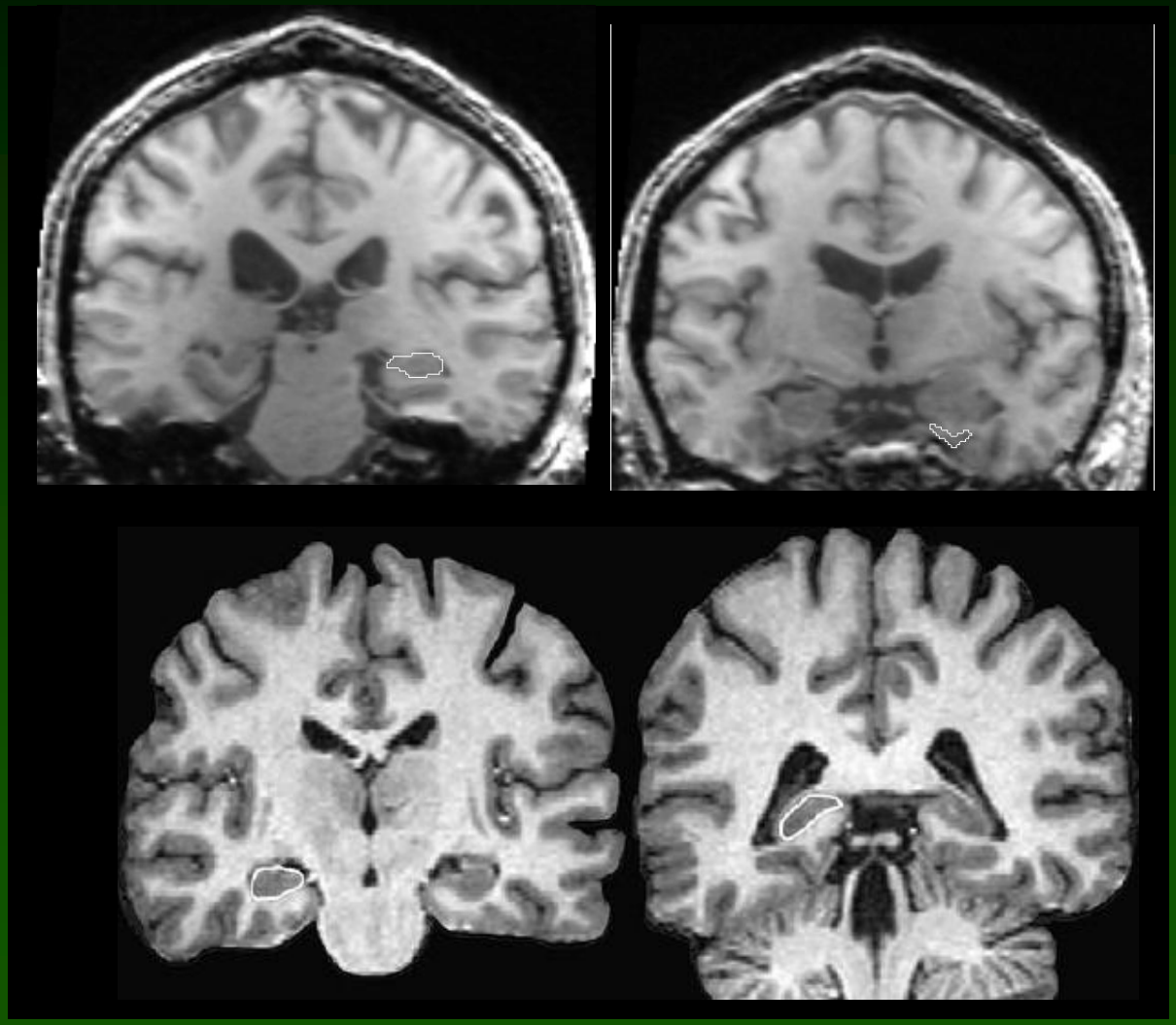




SNUH NP Dementia Clinic

KCGP2007

Manual tracing of hippocampus or ERC



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Brain Boundary Shift Integral (BSI) method

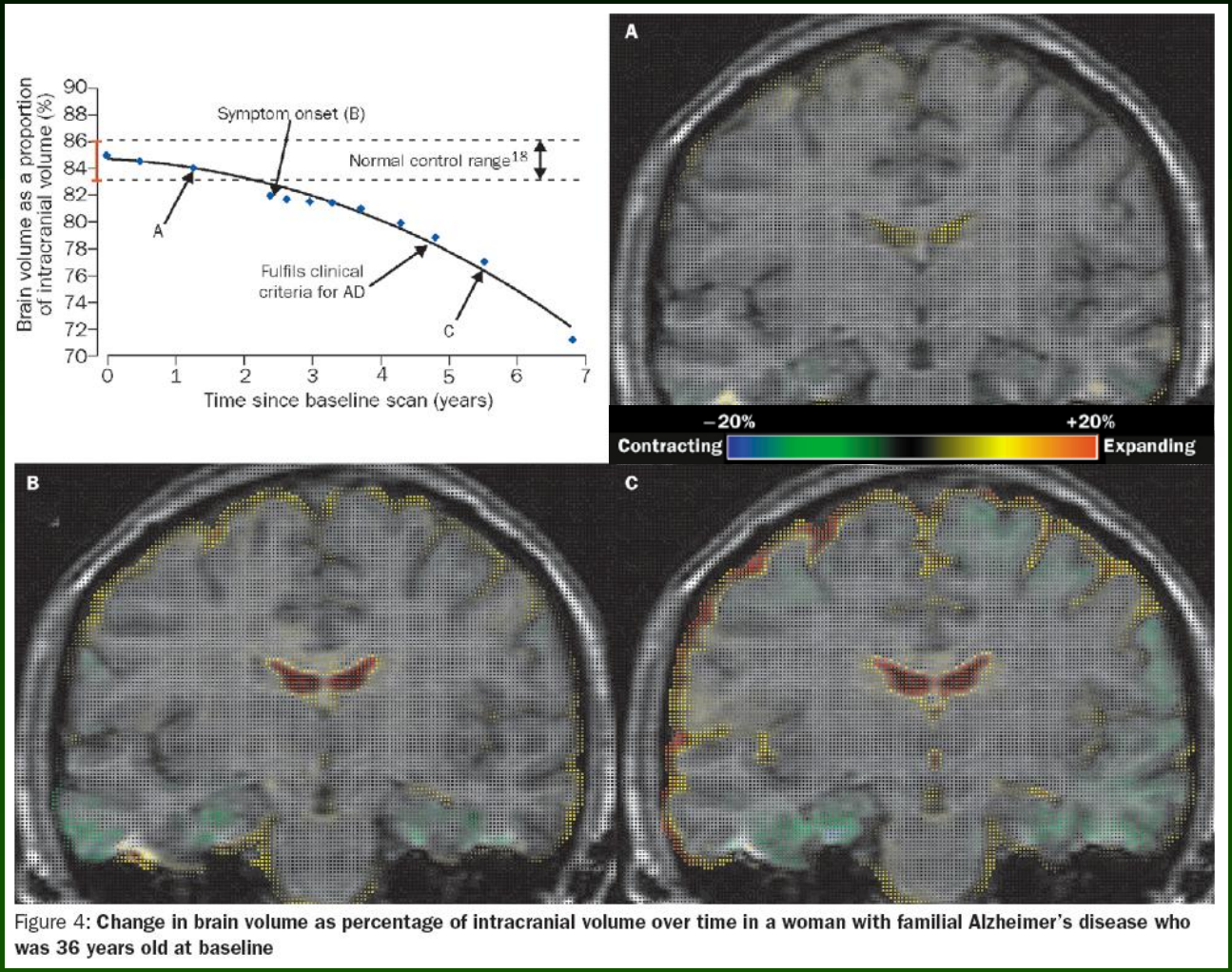


Figure 4: **Change in brain volume as percentage of intracranial volume over time in a woman with familial Alzheimer's disease who was 36 years old at baseline**

Fox et al. (2001) Lancet

Comparison of estimated number of subjects per arm between cognitive tests and MRI volume measures

- To detect a 50% reduction in the rate of decline over one year

Measures	ADAS-cog	MMSE	Hippocampus volume	Temporal horn volume
Subjects number per arm	320	241	21	54

Jack et al. (2003) Neurology

Lesson from Aβ immunization (AN1792) trial

- More brain volume loss in antibody responder group, in spite of better cognitive performance, than placebo group

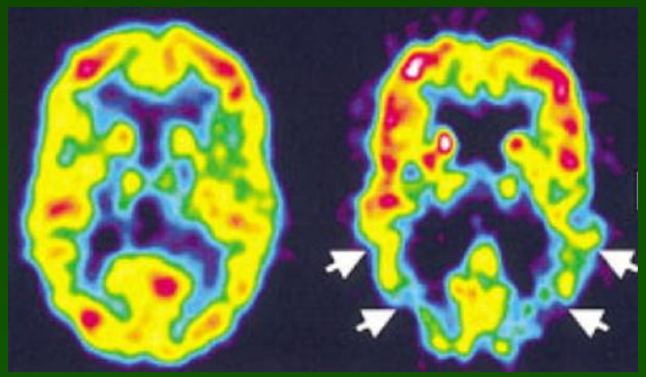
	n	Observed mean (SD) change from baseline
Whole-brain volume boundary shift integral, %		
Placebo	52	2.04 (1.74)
Antibody responder	38	3.12 (1.98)
Ventricular volume boundary shift integral,† %		
Placebo	56	0.48 (0.40)
Antibody responder	45	1.10 (0.75)

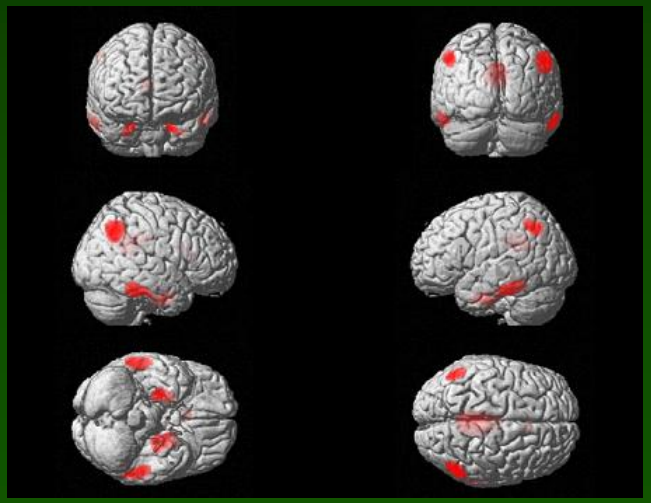
► Biomarker changes in observational studies do not always predict changes seen in therapeutic trials.

Fox et al. (2005) Neurology

FDG-PET

- rCMRglu reflects reginal synaptic activity
- Parietal and temporal cortex typically affected
  - Relative sparing of primary sensorimotor and visual cortex
  - Sparing of striatum, thalamus and cerebellum





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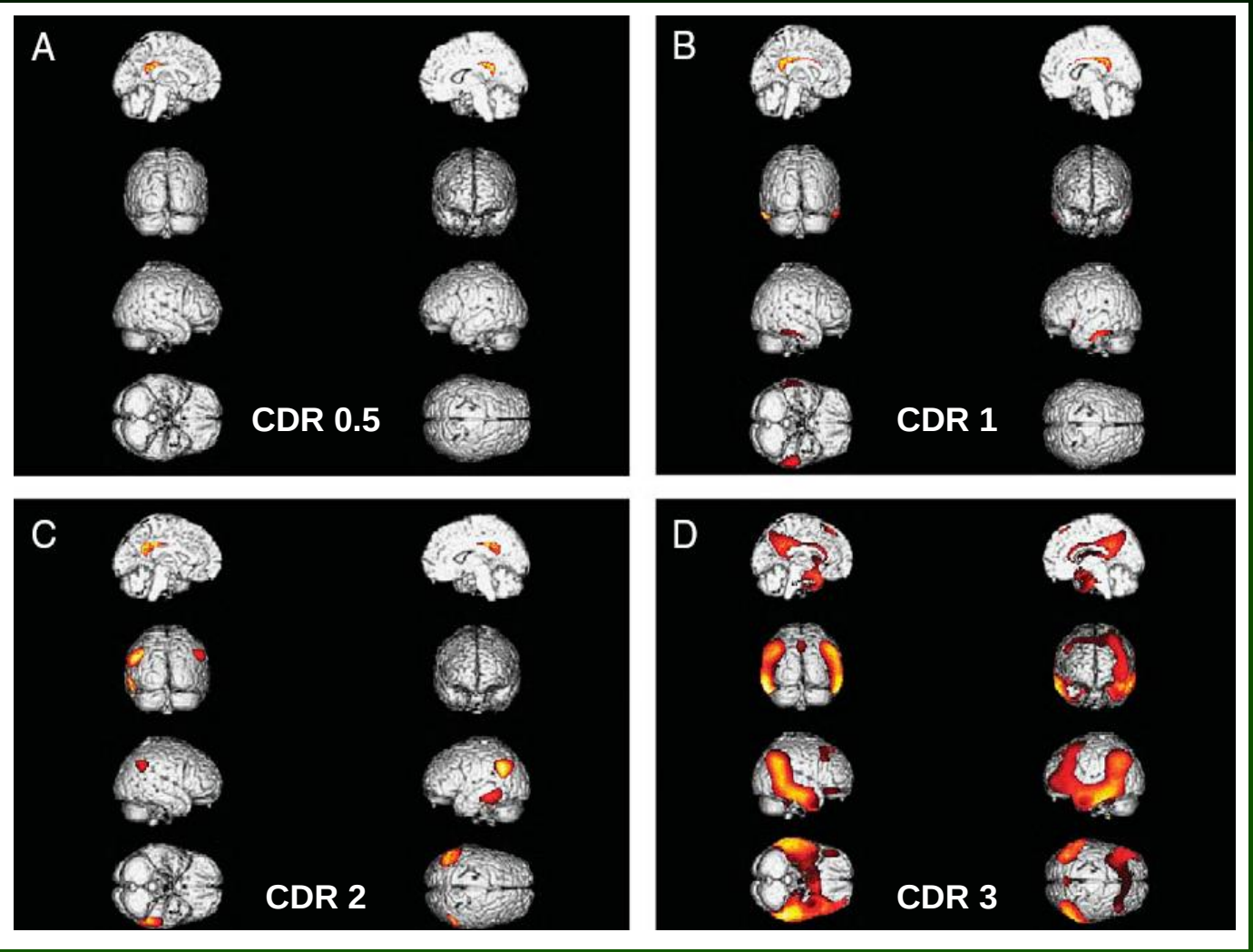
Diagnostic accuracy of FDG-PET for Alzheimer's disease

- Compared with neuropathological confirmation of presence or absence of AD

Basis of AD diagnosis	Sensitivity	Specificity
Clinical evaluation, probable AD	66% ± 17%	77% ± 23%
Clinical evaluation, probable + possible AD	90.5% ± 5.5%	55.5% ± 5.5%
^{18}F-FDG PET, AD pattern	91.5% ± 3.5%	70% ± 3%

Silverman (2004) J Nucl Med

Topographic progression pattern of rCMRglu decline according to AD progression



Chu et al.(2007) ADAD

Estimated number of subjects per arm when using FDG-PET as a outcome measure

- To detect an effect with 80% power over one year

	Treatment Effect			
	20%	**30%**	**40%**	**50%**
Frontal	85	38	22	14
Parietal	217	97	55	36
Temporal	266	119	68	44
Cingulate	343	153	87	57
Combined	62	28	16	10

► Comparable with MRI and almost 1/10 of size based on clinical measures

Adapted from Alexander et al. (2002) Am J Psychiatry

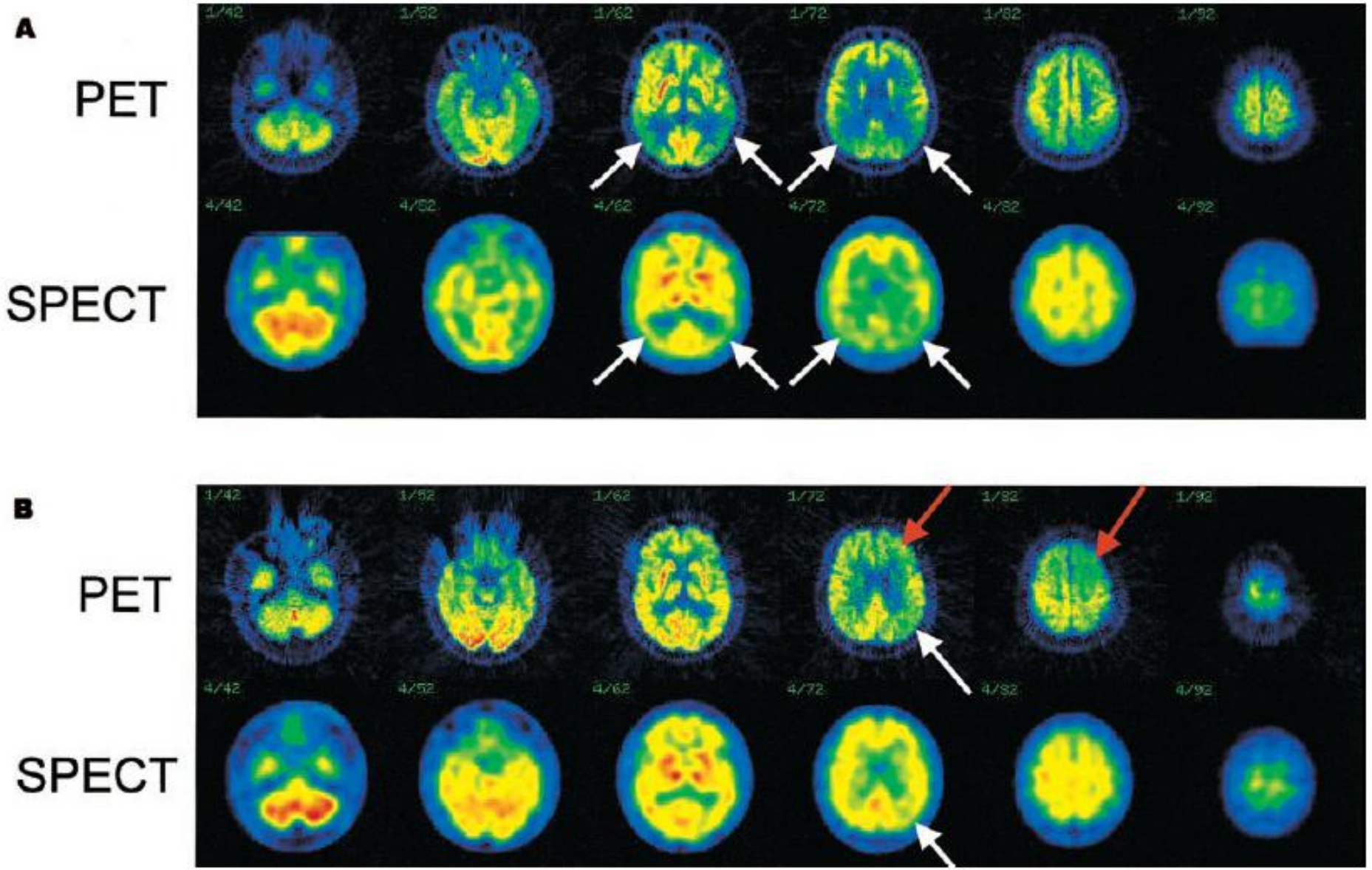
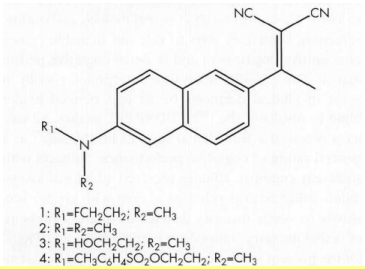


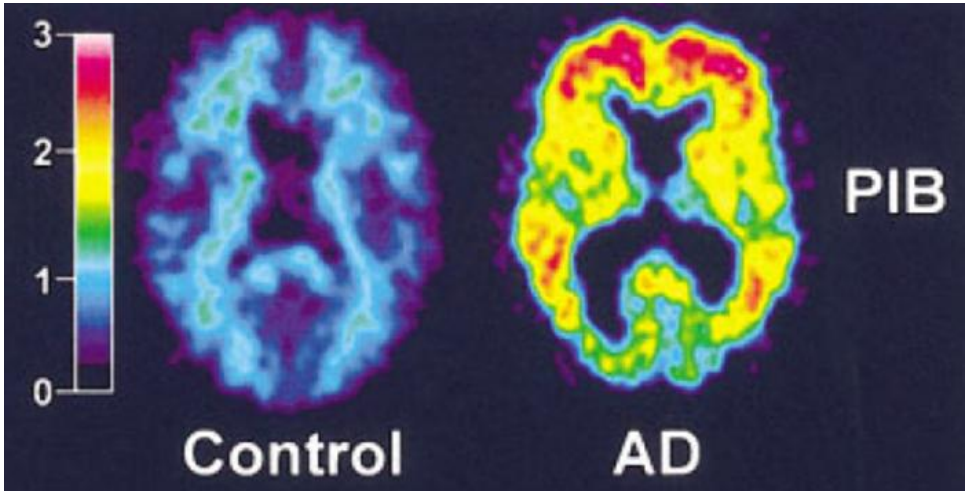
FIGURE 3. (A) Good correspondence between PET and SPECT is shown by spatially normalized original images of AD patient (MMSE score = 19, *r* of *z* maps = 0.62), particularly with respect to reduced uptake in temporoparietal association cortex (white arrows). (B) Discordance is found in another patient (MMSE score = 21, *r* = 0.35), with impaired frontal uptake for PET (red arrows) but not for SPECT.

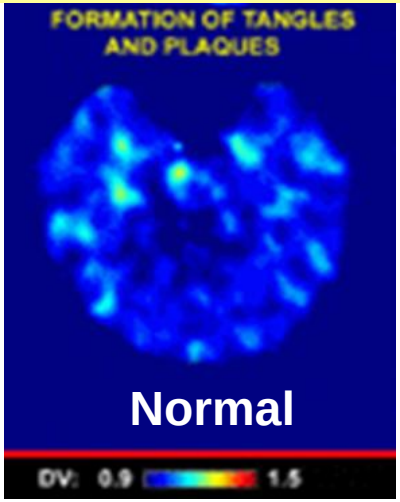
Herholz et al. (2002) J Nucl Med

PET Molecular Imaging



Stabilization therapies, esp. those targeting amyloid deposition, might focus on PET with such ligands as a major outcome measure.





Shoghi-Jadid et al (2002) AJGP; Klunk et al.(2004) Ann Neurol

Limitations of PET molecular imaging

- Little longitudinal data have been obtained yet.
  - Impossible to estimate sample size estimation
- Amyloid load (measured by PIB PET activity) appears to plateau in moderate to severe dementia
  - May not be an appropriate for studies at this stage of the disease

CSF $A\beta_{42}$, tau and p-tau

- CSF $A\beta_{42}$
  - ↓ (40~50%) in AD, compared with control
  - Correlate to AD severity
  - But stable over intervals as long as 1 yr
- CSF total tau
  - ↑ (2~3 fold) in AD
  - Weak correlation with cognitive score change
  - But stable over intervals as long as 1 yr
- CSF p-tau (3 species: p-thr231, p-ser199 and p-thr181)
  - All ↑ in AD and even MCI
  - Progressively decline with ds. progression (long. study)

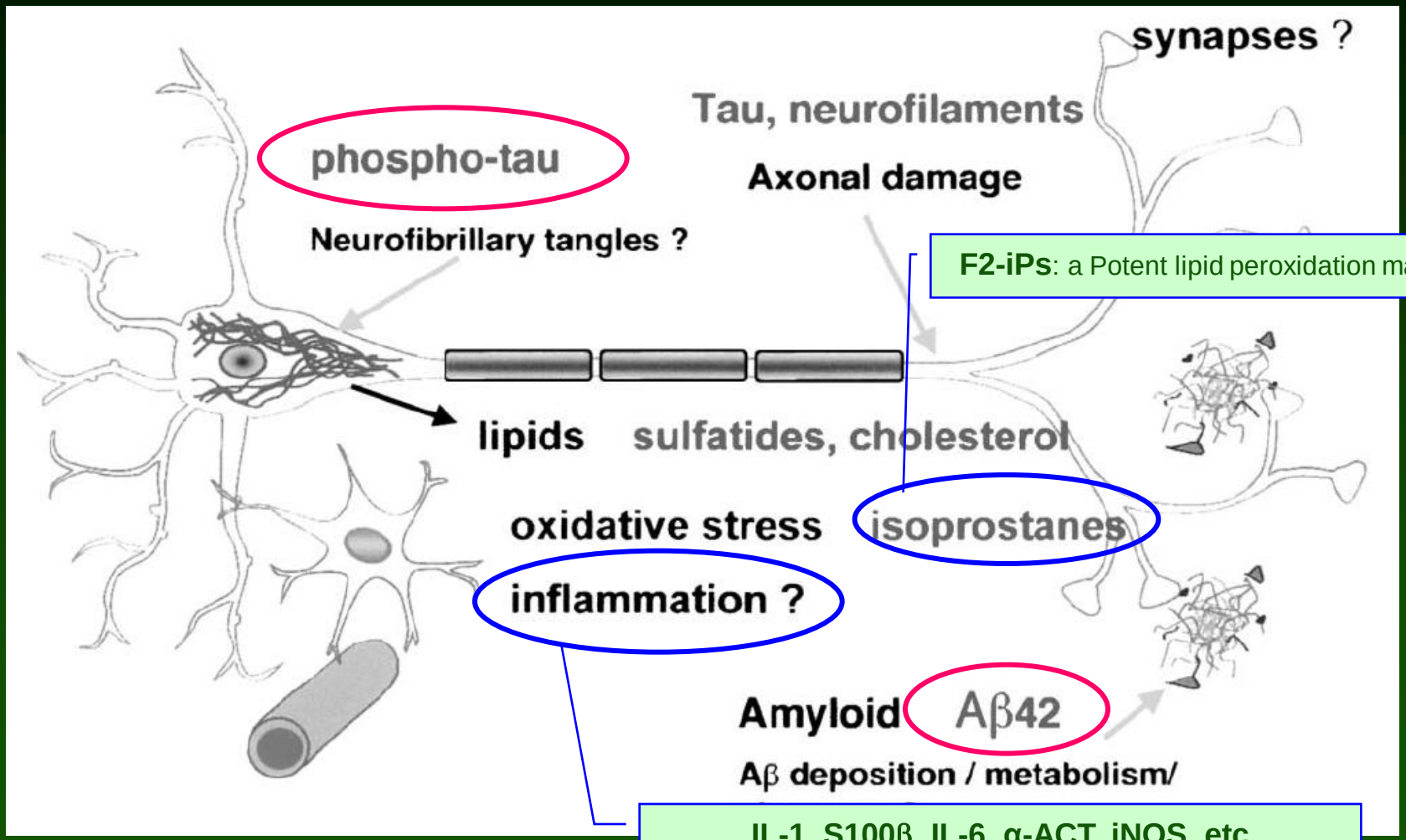
Thal et al (2007) ADAD

Sample size calculations based on $A\beta_{42}$, tau and p-tau

Marker	Study	Number of Subjects Needed Per Group
CSF total tau in AD	Andreasen et al, 1999 Moriearty et al, 1999	40
CSF Aβ42 in controls	Andreasen et al, 1999 Galasko et al, 1998 Prince et al, 2004	16
CSF Aβ42 in AD	Andreasen et al, 1999 Moriearty et al, 1999 Simons et al, 2002	36

- Comparable with imaging measures and smaller than size based on clinical measures
- However, more longitudinal studies are needed!

AD pathology and potential biomarkers

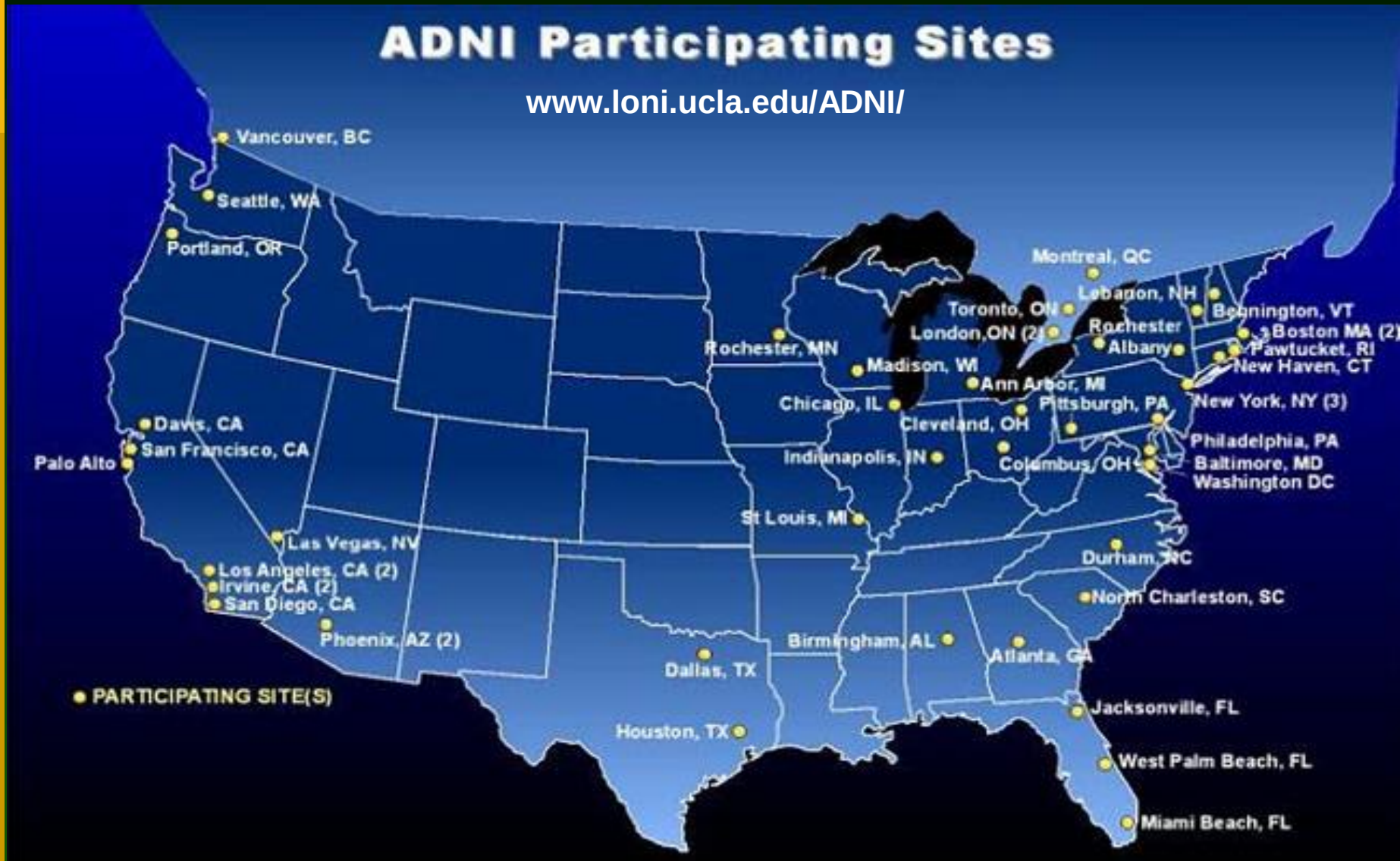


Current status and future perspectives

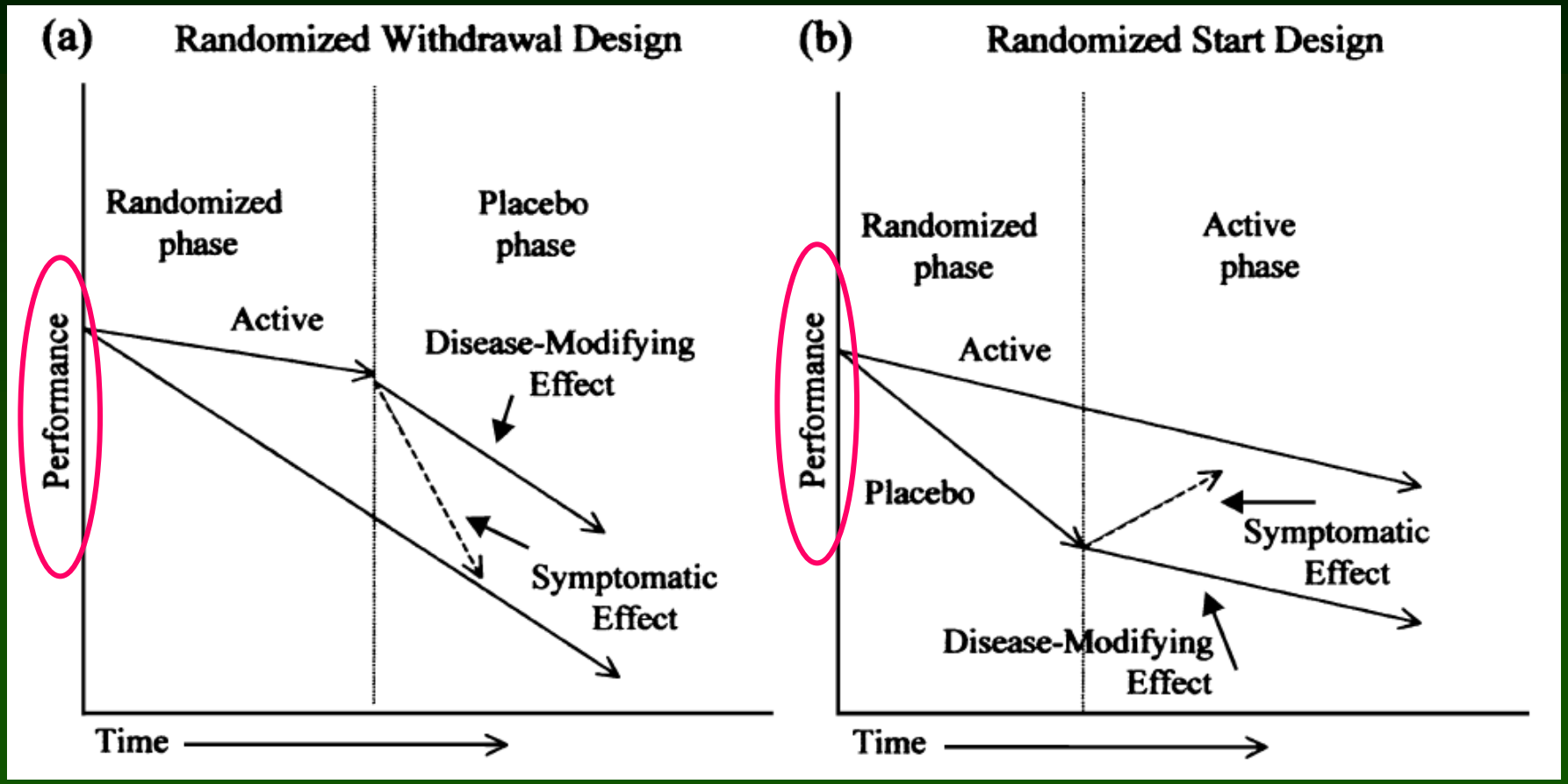
- Imaging biomarkers have greater face validity and are more well developed than biochemical biomarker.
- Effects of putative ds-modifying drugs could be determined with fewer subjects using biomarkers than by using cognitive measures.
- Additional longitudinal multi-site studies of these biomarkers (esp., FDG-PET, PIB-PET, CSF biomarkers) would aid greatly in their application to clinical trials.

ADNI (Alzheimer's Disease Neuroimaging Initiative)

: NIA-initiated, large observational study of AD, MCI and elderly controls to assess longitudinal changes in AD biomarkers (obtaining vMRI, FDG-PET, biochemical biomarkers, and clinical data ; since 2005)



*Design-based methods
to demonstrate Ds-modifying effect vs. Sx effect



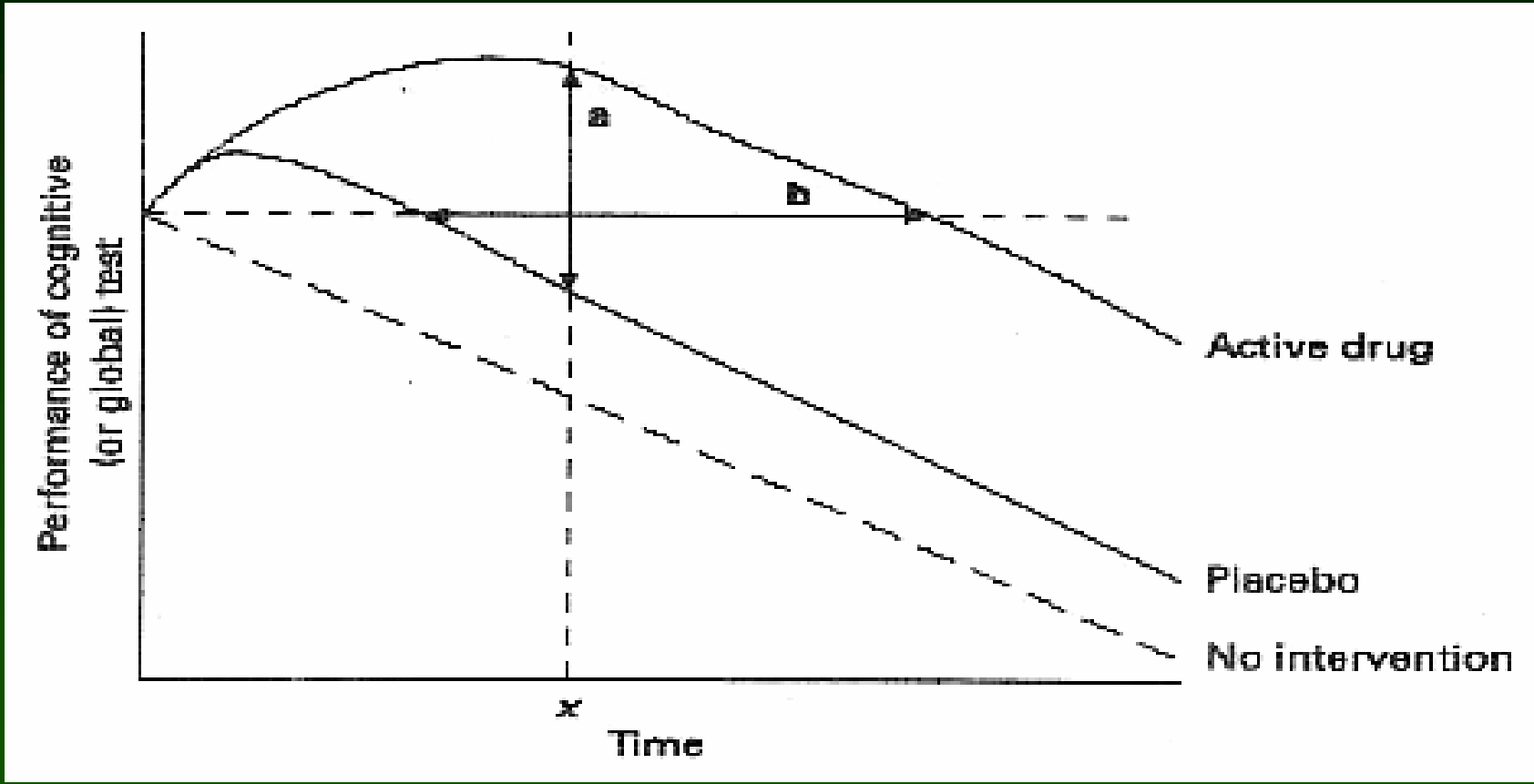
Performance :cognition and function

Typical AD drug trial designs

Stage	Trial Design	Primary Outcome
Presymptomatic	Survival over 5 years	Incident dementia
Prodromal	Survival over 3 years	Conversion to dementia
Mild to moderate	Six months parallel groups	Cognition and global impression of change
Moderate to severe	Six months parallel groups	Cognition and ADL, behaviour or global impression of change
Severe behavior	Six months parallel groups	Cognition and behavior

Typical AD drug trial design (1)

A parallel-group, placebo-controlled randomized trial, typically lasting 6 months



a : Symptomatic improvement

b : Delay of symptomatic decline

Typical AD drug trial design (2)

Time-to-event design (survival design)

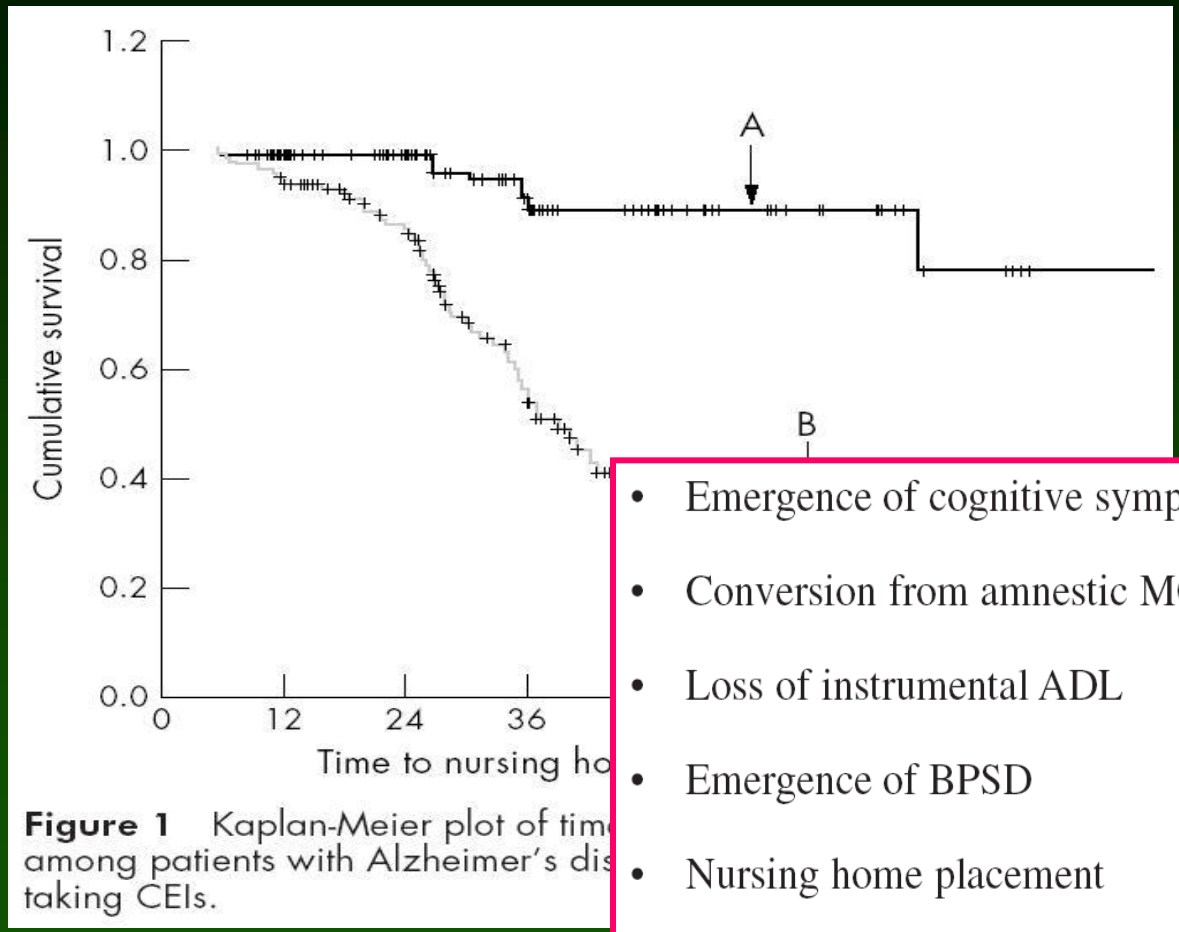


Figure 1 Kaplan-Meier plot of tim among patients with Alzheimer's dis taking CEIs.

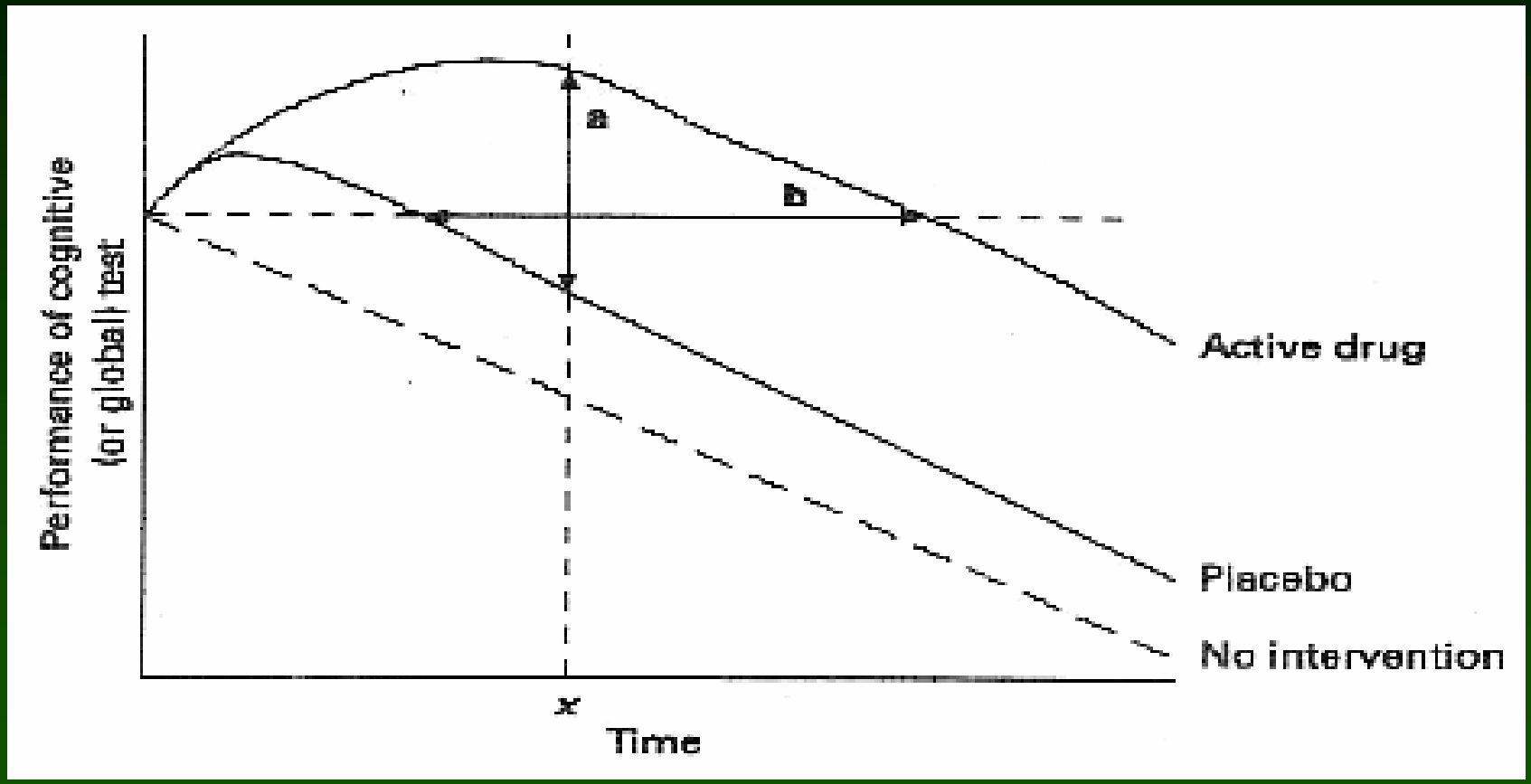
J Neurol Neurosurg Psychiatry 2002;72

- Emergence of cognitive symptoms
- Conversion from amnestic MCI to diagnosable dementia
- Loss of instrumental ADL
- Emergence of BPSD
- Nursing home placement
- Loss of self-care ADL
- Death

How to differentiate disease modifying effect with symptomatic effect?

- Design-based methods
  - Randomized withdrawal design
  - Randomized start design
- Using biomarkers
  - Neuroimaging markers
  - Other biomarkers

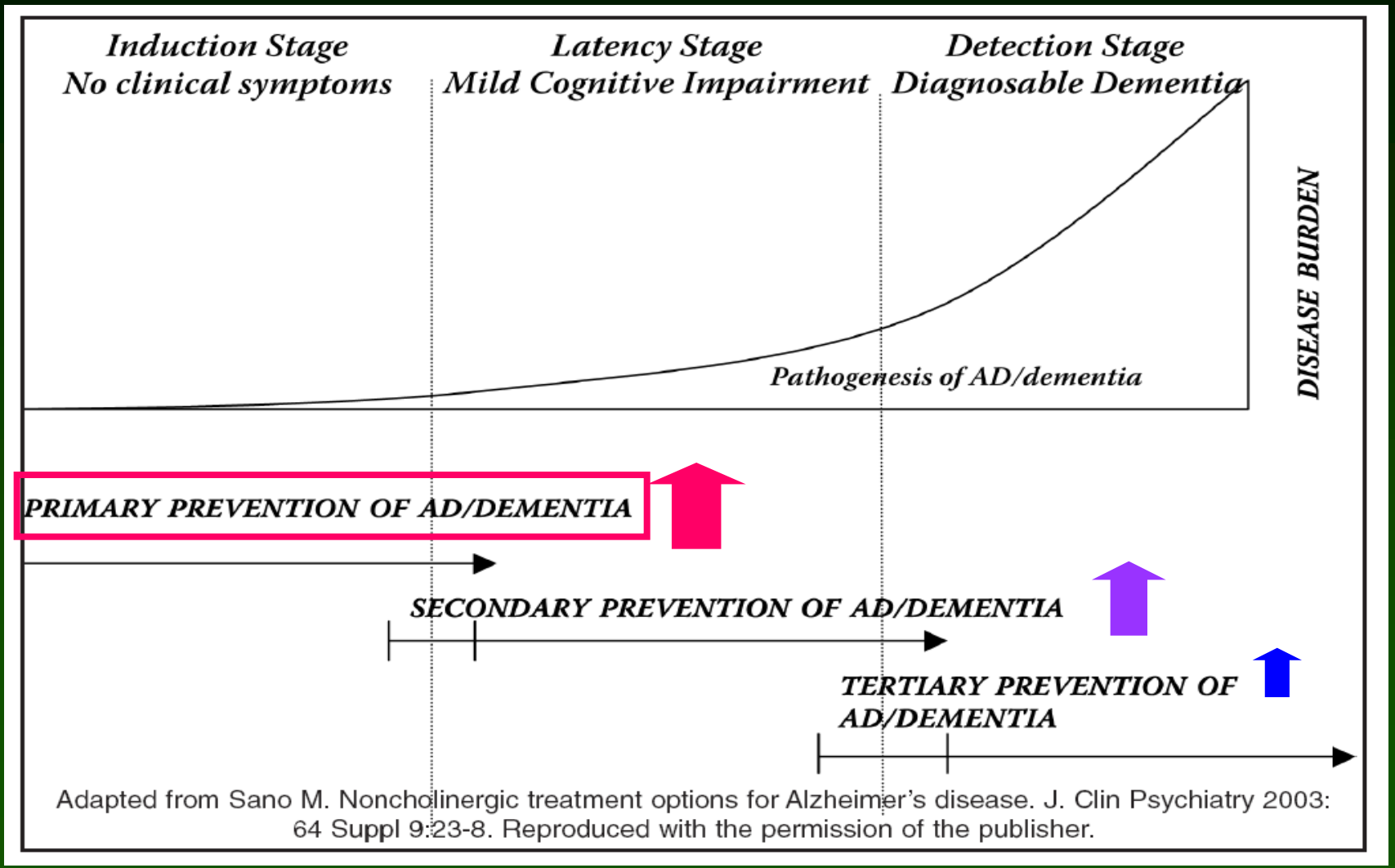
Symptomatic Treatment



a : Symptomatic improvement

b : Delay of symptomatic decline

Concept of Prevention in AD / dementia



Adapted from Sano M. Noncholinergic treatment options for Alzheimer's disease. J. Clin Psychiatry 2003: 64 Suppl 9:23-8. Reproduced with the permission of the publisher.

Placebo-controlled AD/dementia 1º prevention RCTs (ongoing and completed)

Trial (Acronym)	Status	Intervention	Subject selection criteria	Duration (years)	Overall estimated incidence rate (% per year	Planned sample size
PREPARE	Discontinued	Conjugated equine estrogen alone Conj. equ. estrogen + medroxyprogesterone acetate	Female sex Family history of AD Age ≥ 65	3	5	900
ADAPT	Discontinued	Naproxen or Celecoxib	Family history of dementia Age ≥ 70	5 – 7	3 - 3.4	2,800
SYST-EUR	Completed	Nitrendipine and/or Enalapril and/or Hydrochlorothiazide	Systolic hypertension Age ≥ 60	5	1.6	3,000
SCOPE	Completed	Candesartan cilexetil	Systolic hypertension Age 70 to 89	3 - 5	2.4	4,000
GEMS	Ongoing extended	Ginkgo biloba	Age ≥ 75 (≥ 71 if of African ancestry)	5	4	3,000
GUIDAGE	Ongoing	Ginkgo biloba	Age ≥ 70 Memory complaints	5	Not available	2,800
WHIMS	Discontinued	Conjugated equine estrogen alone Conj. equ. estrogen + medroxyprogesterone acetate	Female sex Age ≥ 65	6	2	8,300
PREADVISE	Ongoing	Vitamin E or Selenium or Both	Age ≥ 62 (≥ 60 if of African or Hispanic ancestry)	9-12	1	10,700

Feldman et al. (2007) Can J Neurol Sci

Unique methodological challenges for AD/dementia prevention RCTs

- Sample size and study length
  - Recruitment Issue (Health Cohort Effect)
  - Retention Issue
  - Enrichment technique
- Timing to interventions
- Limitations of clinically defined endpoints

Sample size and study length

- Require very large sample size
  : 1,000 ~ 20,000 (ave 4,500)
- Require very long F/U period
  : 3 to 12 years (ave 6 years)

➔ Resulting in formidable cost

Typical ChEI trials require:
300 subjects (ave) &
3~6 month study period

Duet to modest therapeutic efficacy of currently available agents

Due to very low progression rate from normal to AD
(1~3% per year in longitudinal studies)

Recruitment issue: "Health Cohort Effect"

- Characteristics of subjects who volunteer for multiyear intervention trials
  - More educated
  - More health-oriented
  - Greater than average motivation and initiative

- Could skew the trial population toward lower risk of AD
- Lead to slower progression than expected from incidence studies

Retention Issues

: given very long F/U period

- Loss of F/U
  - Drop-outs
  - Deaths
  - Unexpected S/E
  - Appearance of competing treatments
- Non-adherence
  - Non-protocols use of the study drugs (if OTC)

► may need more sample size to preserve adequate power

► may use F/U strategies without on-site visit (ex: telephone interviews) or conduct within usual care setting (ex: GP offices)

“Enrichment techniques”

: General approaches to enrich populations for primary prevention trials

- Inclusion of persons with an elevated risk profile based on epidemiological risk factors for AD
  - Old age, FHx, memory complaint, vascular history, etc
- Inclusion of at-risk-individuals through the use of biomarkers that change in anticipation of clinical decline
  - Genetic (apoE e4), neuroimaging (PIB), CSF Aβ, Tau, etc

► Limitation in generalization of results

► Useful to establish “proof-of-concept” as a prelude to larger-scale study

Timing to interventions : Biological "window of opportunity"

- Demonstrating positive effect through prevention trial may depends on the timing of intervention
  - Target age range
  - Target stage among disease process

Limitations of clinically defined endpoints

- The validity of clinical states [normal, MCI, dementia] and state transitions is limited by the absence of conclusively established biological markers within a continuous disease process
- Rater and center biases can be anticipated in multi-center trials.
- Biological markers may assist, or even become surrogate outcome measures.