

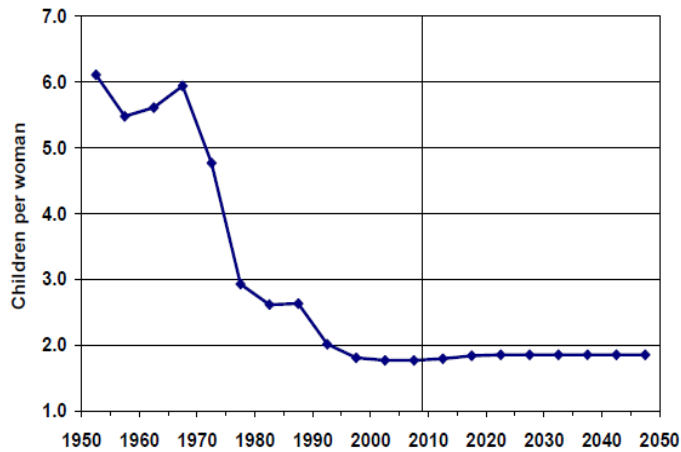


Advances in Investigation and Management of Neurodegenerative Diseases in Aging

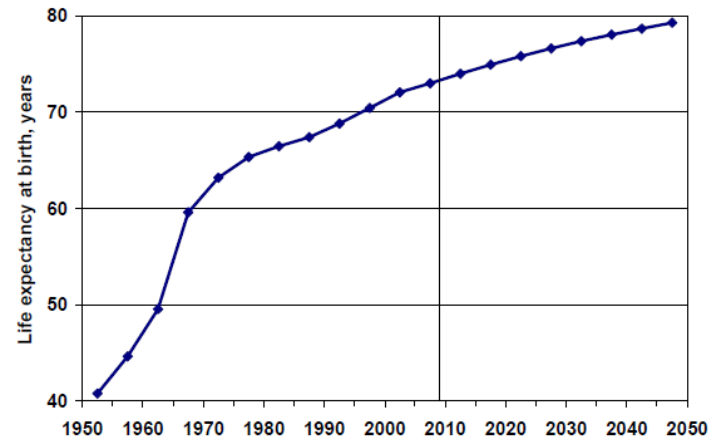
**Piu Chan, MD PhD
Beijing Institute of Geriatrics
Xuanwu Hospital of Capital Medical
University**

人口老龄化是世界发展的必然 (UN 2009 data)

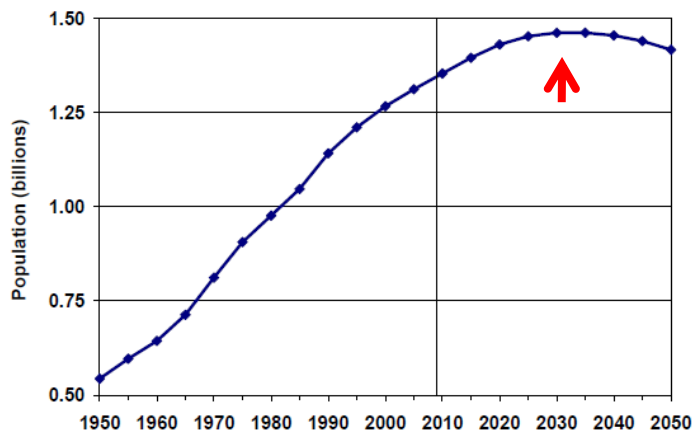
China's Total Fertility Rate



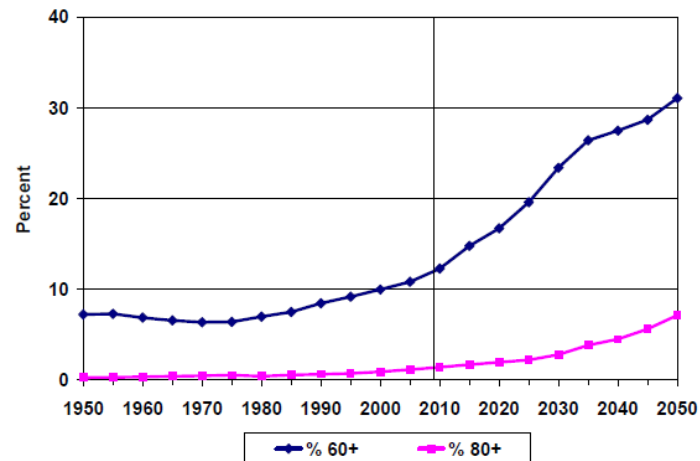
China's Life Expectancy



China's Population Size



China Population Aging



生命的第三阶段

生命第一阶段(0~15)
以学习为目的

生命第二阶段(15~50)
以生育为目的

生命第三阶段(50~90?)
以适应和自由为目的





Neurodegenerative Disorders

Dementia disorders

Alzheimer's Disease
Pick's Disease

All share
common
characteristics

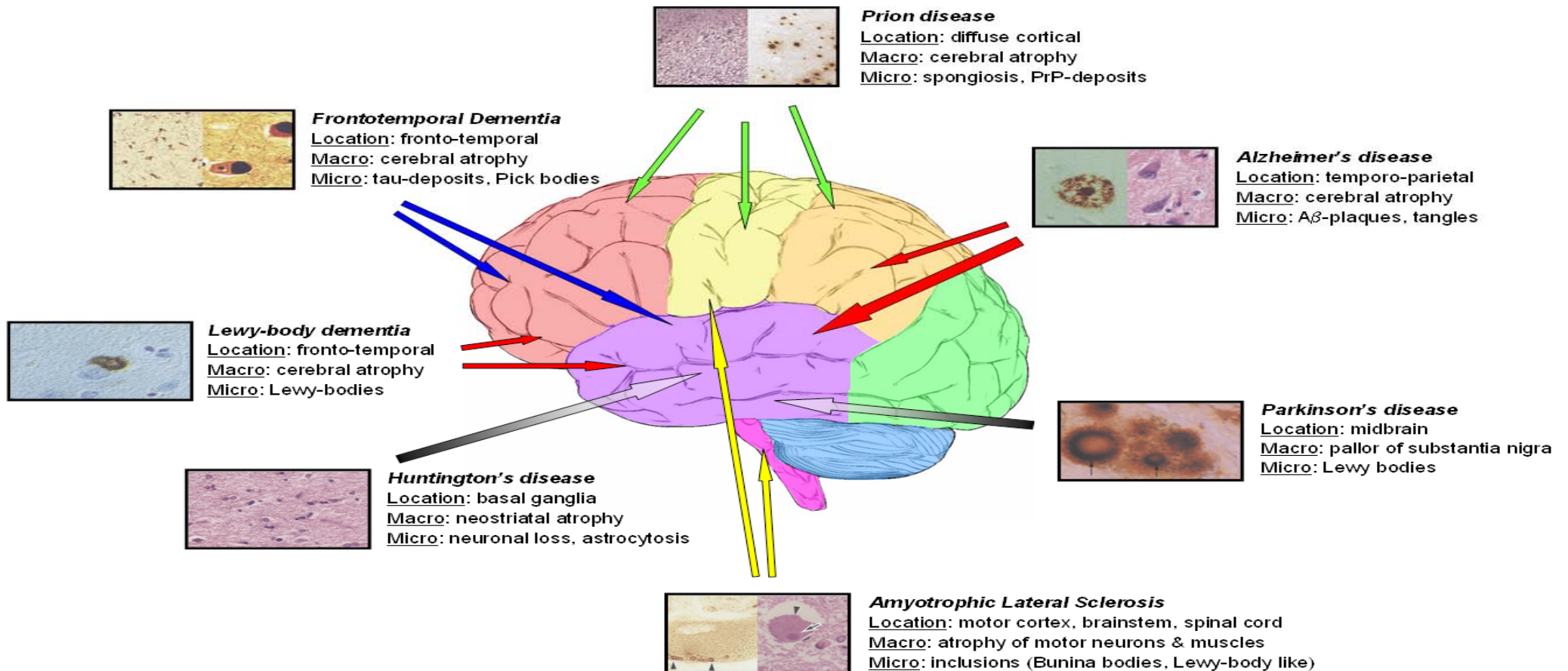
Dementia + Movement disorders

Diffuse Lewy Body Disease
Alzheimer's Disease Lewy Body variant
Huntington's Disease

Movement disorders

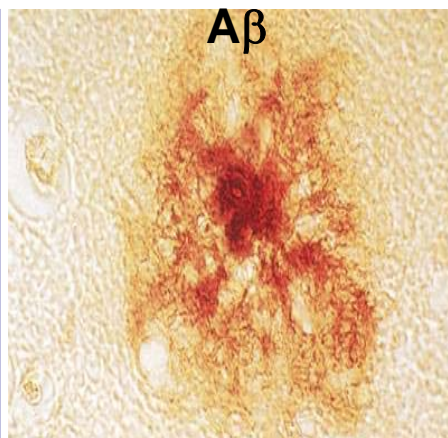
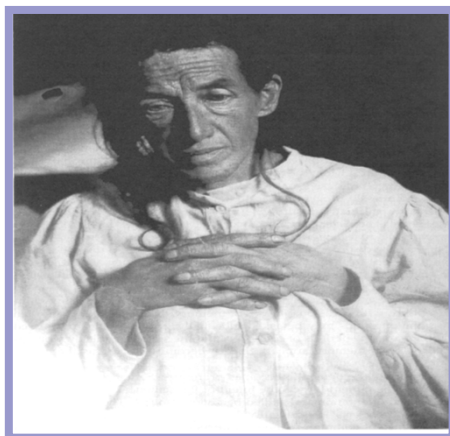
Parkinson's Disease
Motor Neurone Disease
Multiple System Atrophy

Pathological Features of Neurodegenerative Disorders

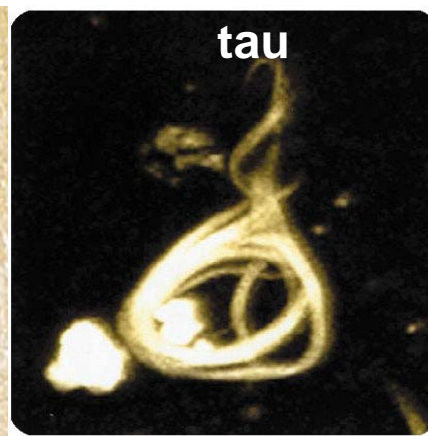


AD/PD的共同病理特征

AD



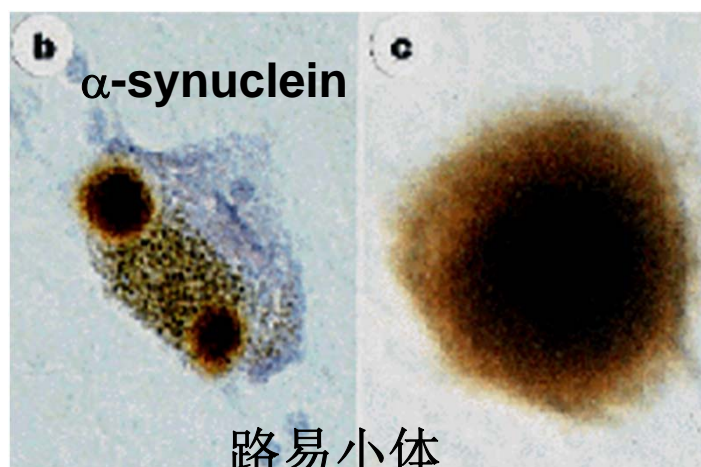
SP



NFT

- 近记忆力减退
认知功能障碍
- 乙酰胆碱能神经元丢失
- 老年斑(SP)形成和神经元纤维缠结(NFT)

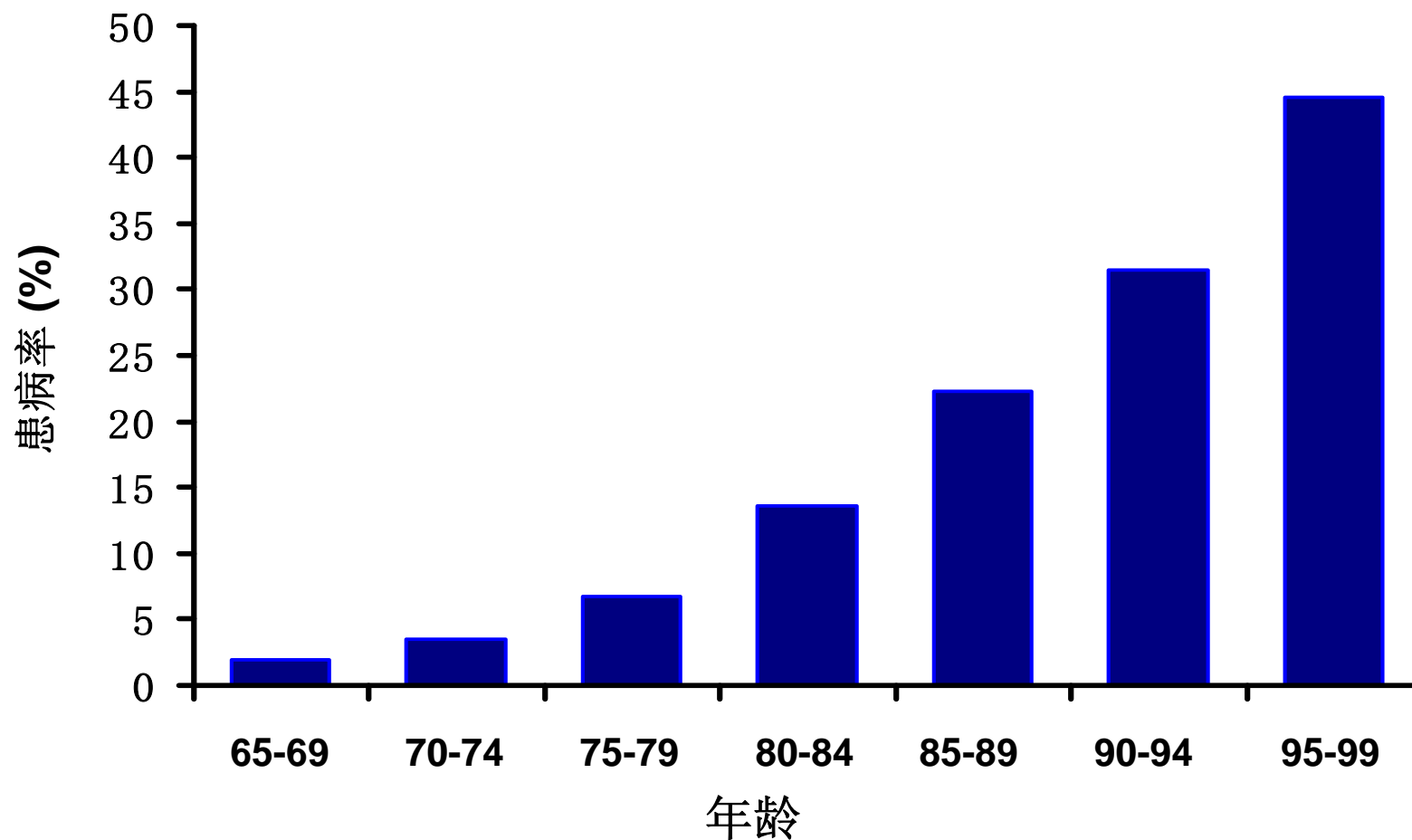
PD



路易小体

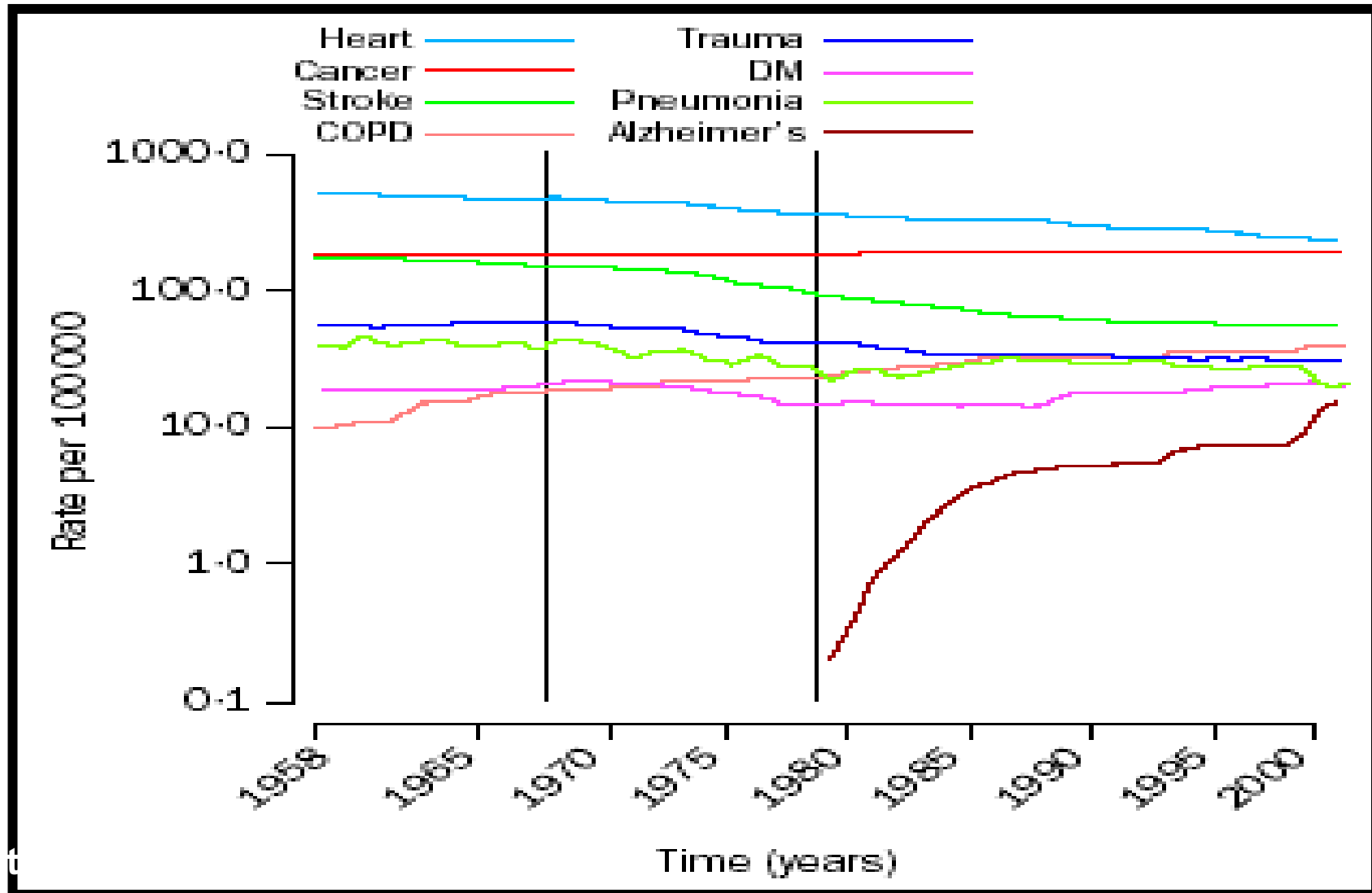
- 静止震颤、运动迟缓
姿势不稳
- 多巴胺能神经元丢失
- 路易小体形成

AD Prevalence in China

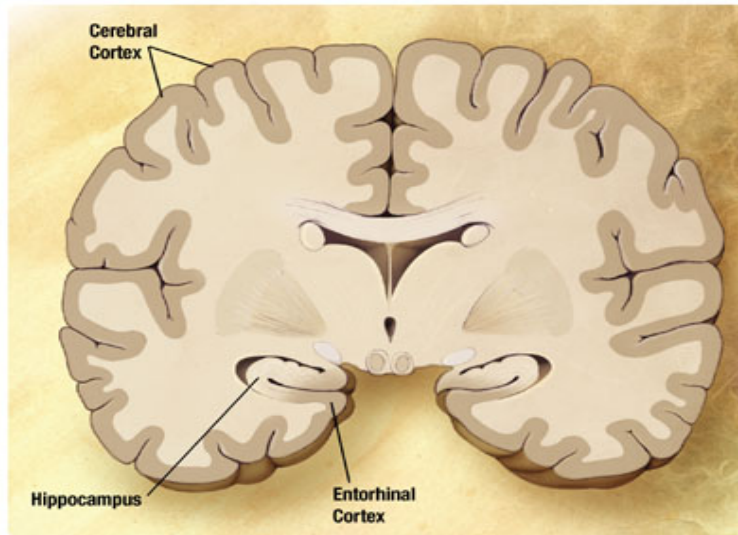


1990年流行病学调查（张明园等，1990，中华医学杂志）
我国>60岁患病率为3.46%-6.41%。患者人数>800万。

Change of Prevalence of Major Diseases

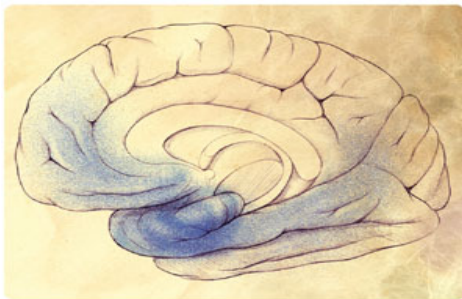
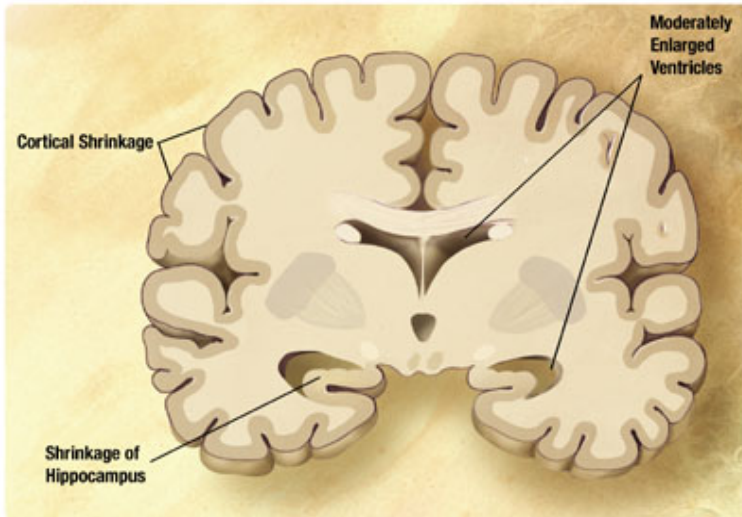


Preclinical AD



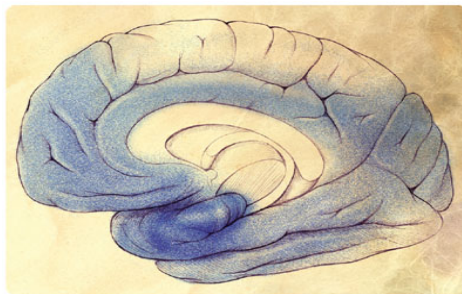
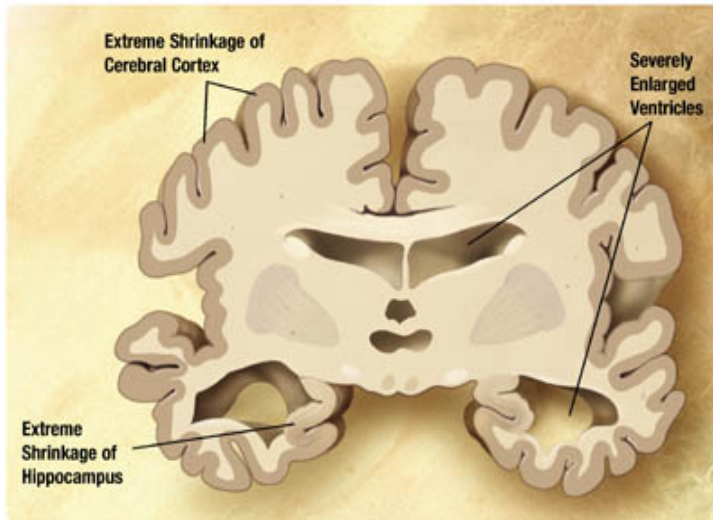
- Signs of AD are first noticed in the entorhinal cortex, then proceed to the hippocampus.
- Affected regions begin to shrink as nerve cells die.
- Memory loss is the first sign of AD.

Mild to Moderate AD



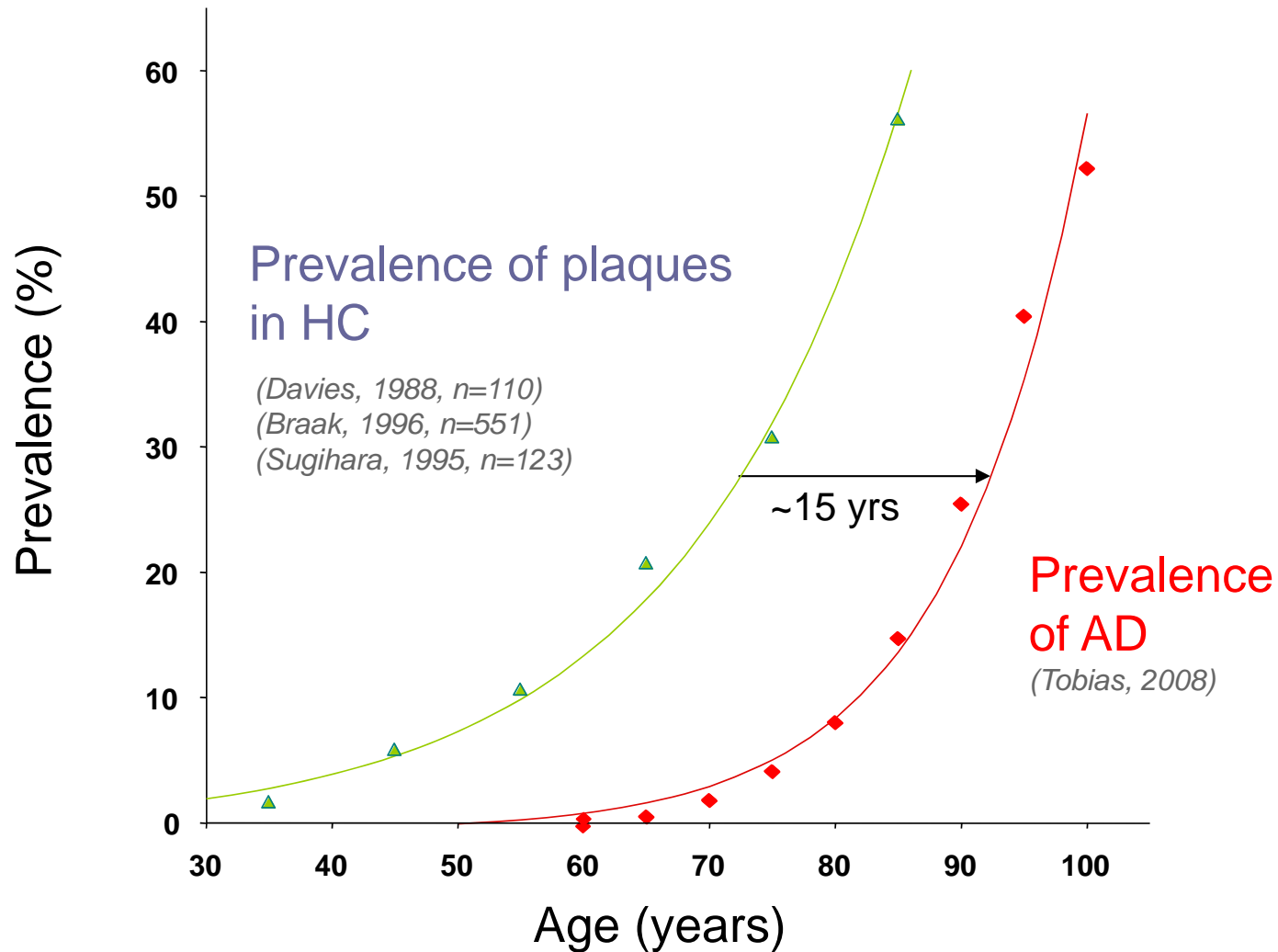
- The cerebral cortex begins to shrink as more and more neurons stop working and die.
- *Mild AD signs* can include memory loss, confusion, trouble handling money, poor judgment, mood changes, and increased anxiety.
- *Moderate AD signs* can include problems recognizing people, difficulty with language and thoughts, restlessness, agitation, wandering, and repetitive statements.

Severe AD

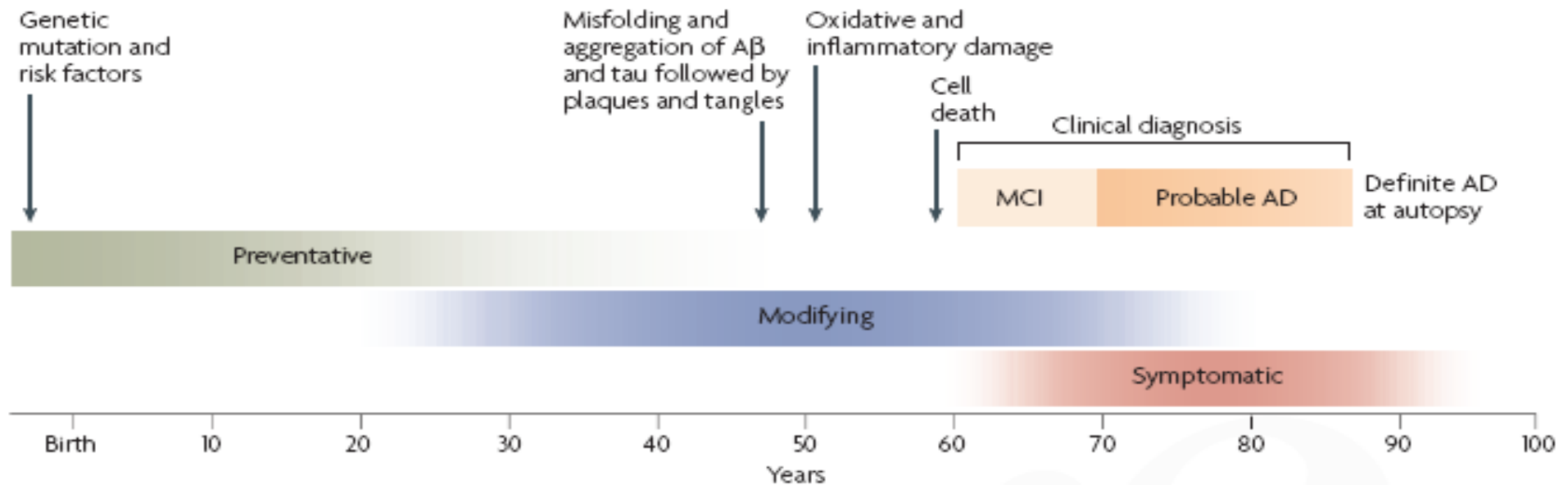


- In severe AD, extreme shrinkage occurs in the brain. Patients are completely dependent on others for care.
- Symptoms can include weight loss, seizures, skin infections, groaning, moaning, or grunting, increased sleeping, loss of bladder and bowel control.
- Death usually occurs from aspiration pneumonia or other infections. Caregivers can turn to a hospice for help and palliative care.

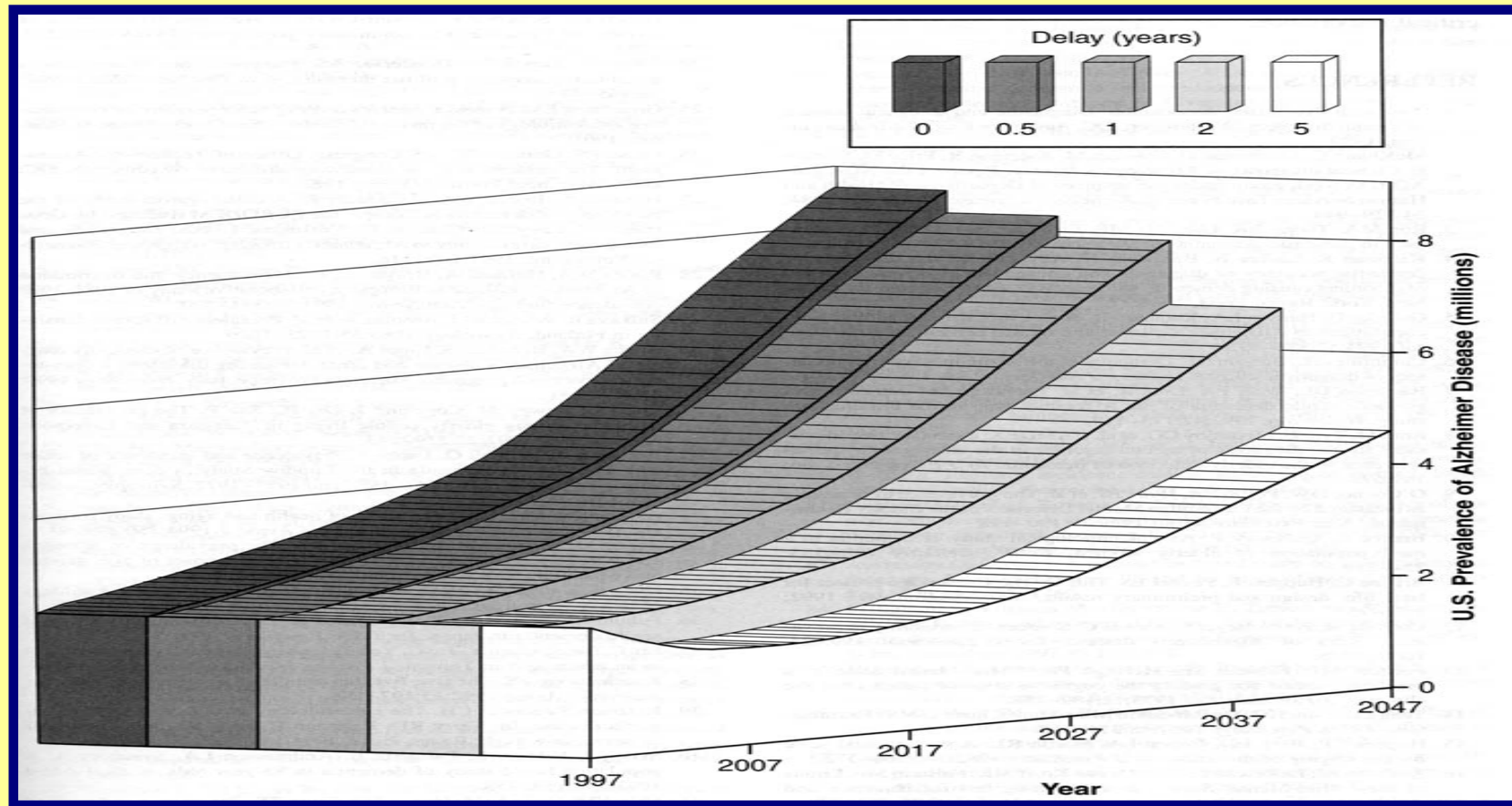
Preclinical Alzheimer's Disease?



Hypothetical timeline for the onset and progression of AD

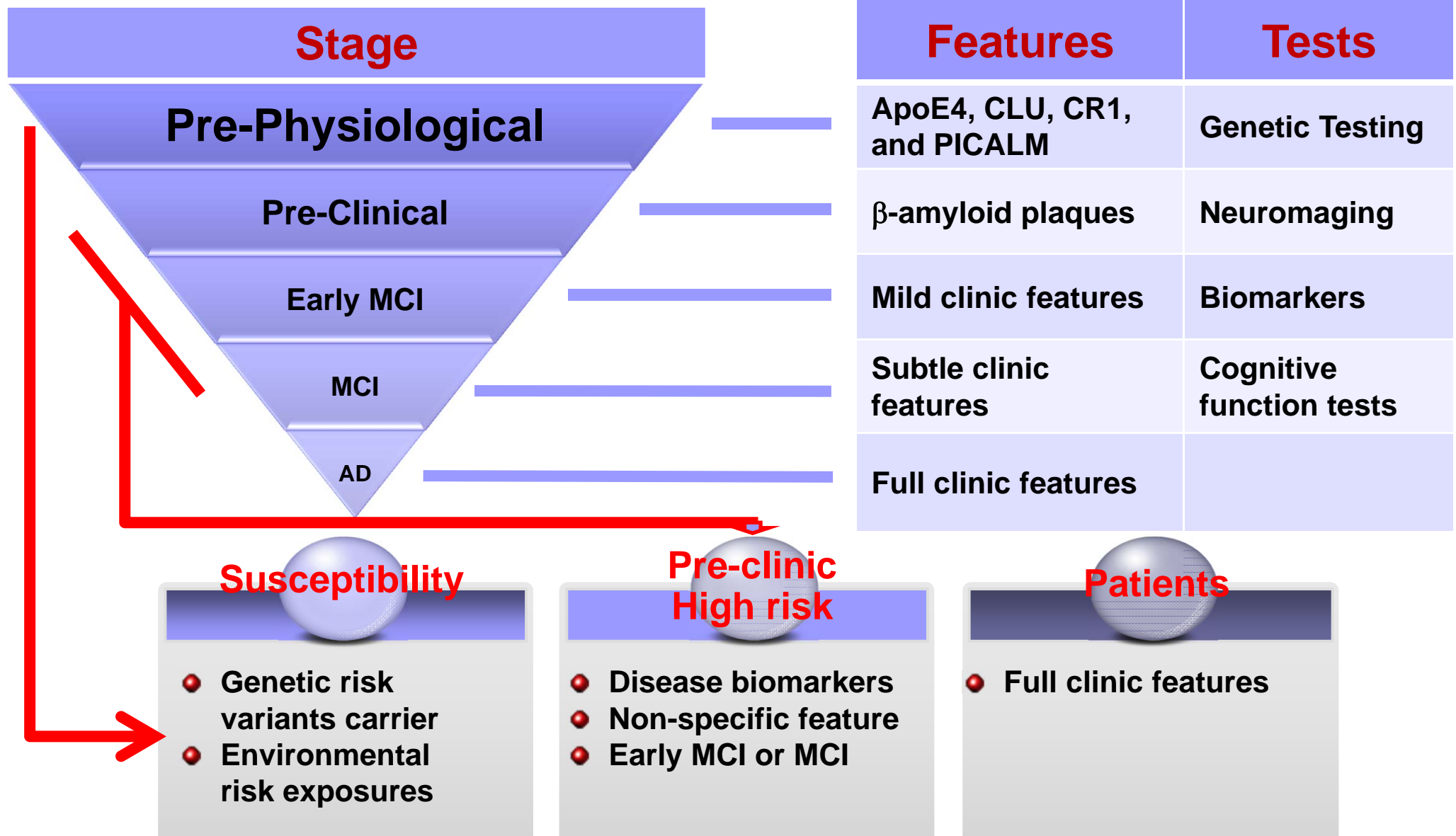


Five Year Delay in AD Onset *Halves* Prevalence & Incidence



From Claudia Kawas

Molecular Classification of AD





Identifying Individuals at-Risk

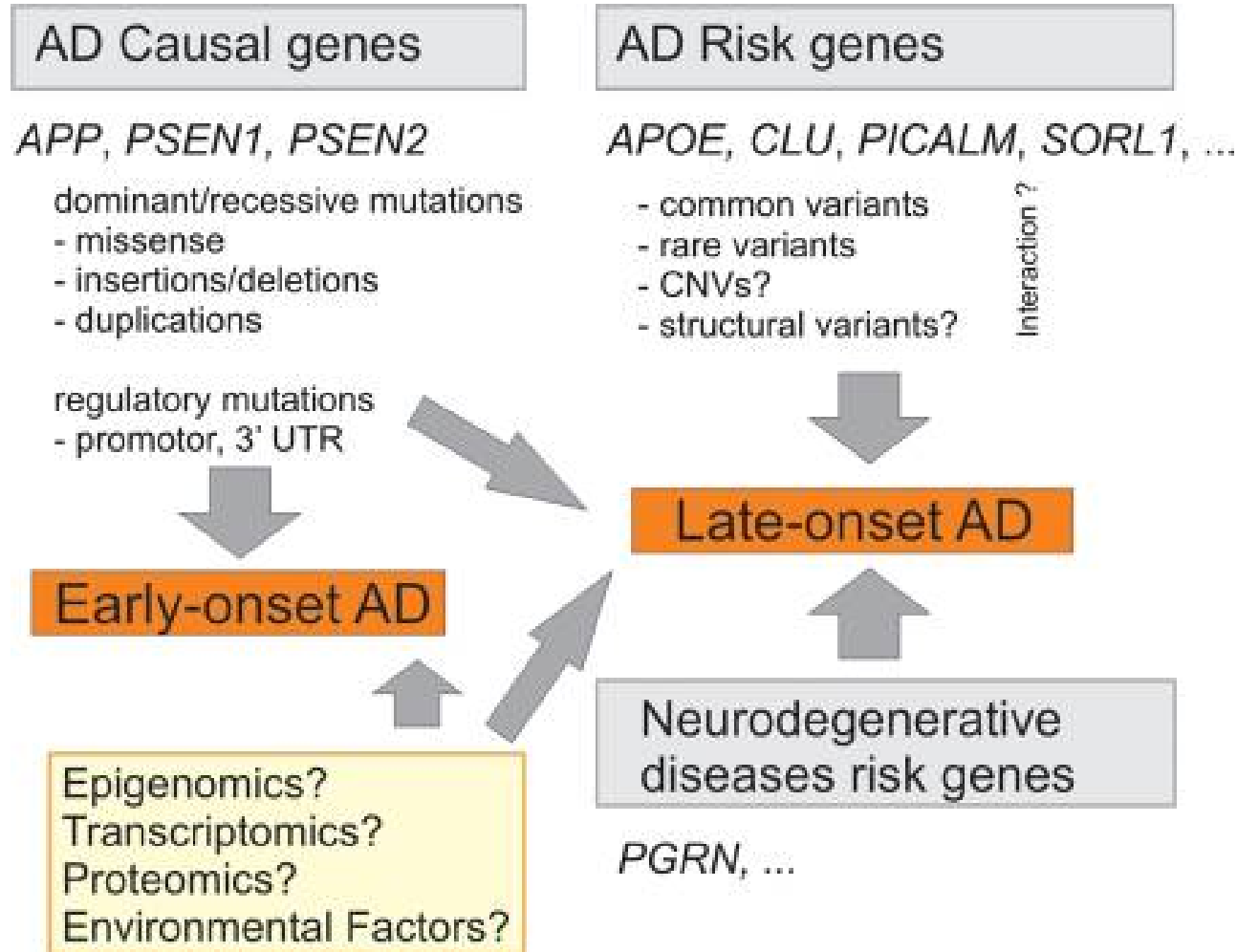
- Susceptible:

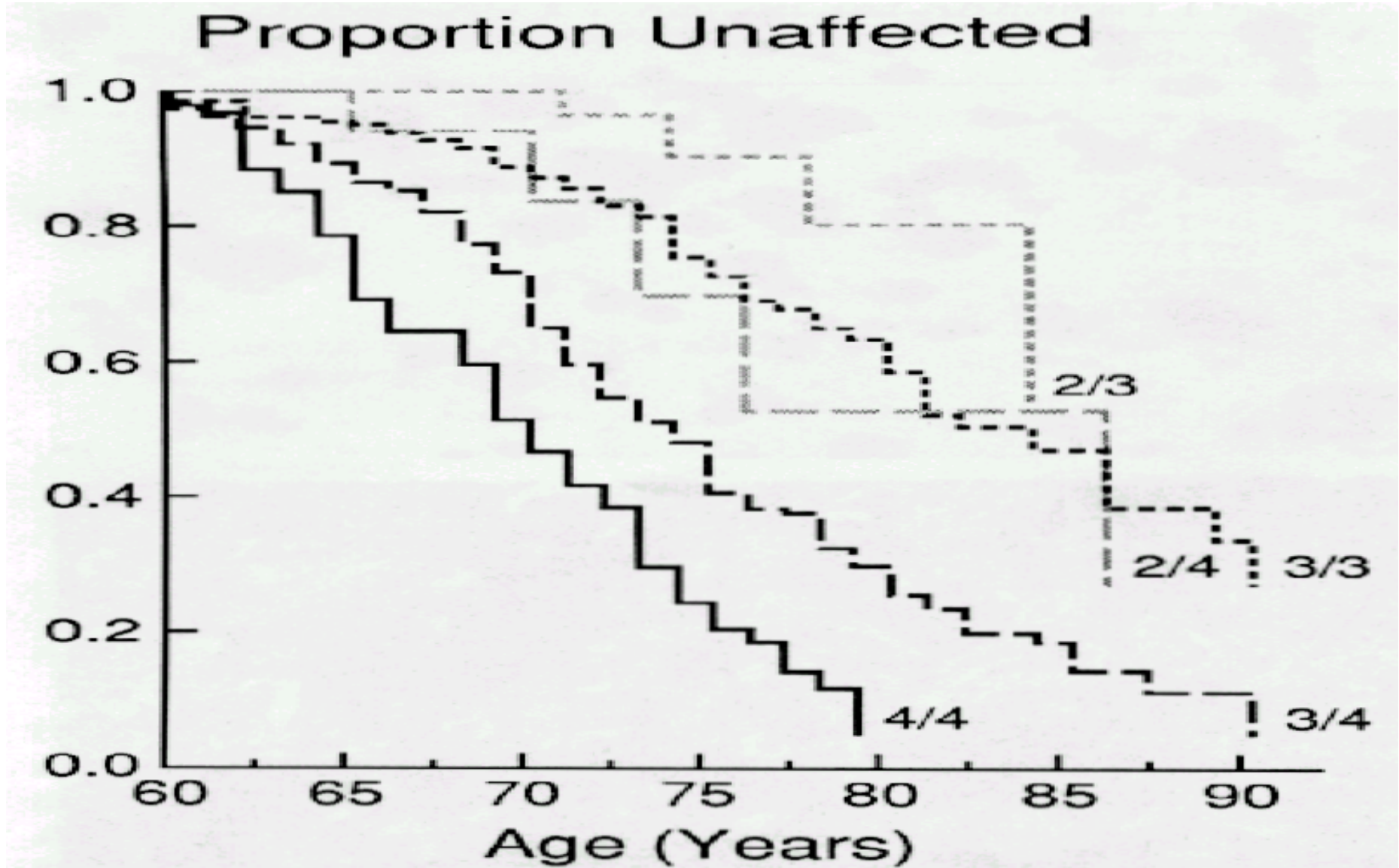
- carry a mutation that causes disease or have positive family history or genetic and environmental risk factors

- At-Risk:

- Pre-symptomatic: with profile of risk biomarkers.
- Asymptomatic: with prodromal risk features-MCI

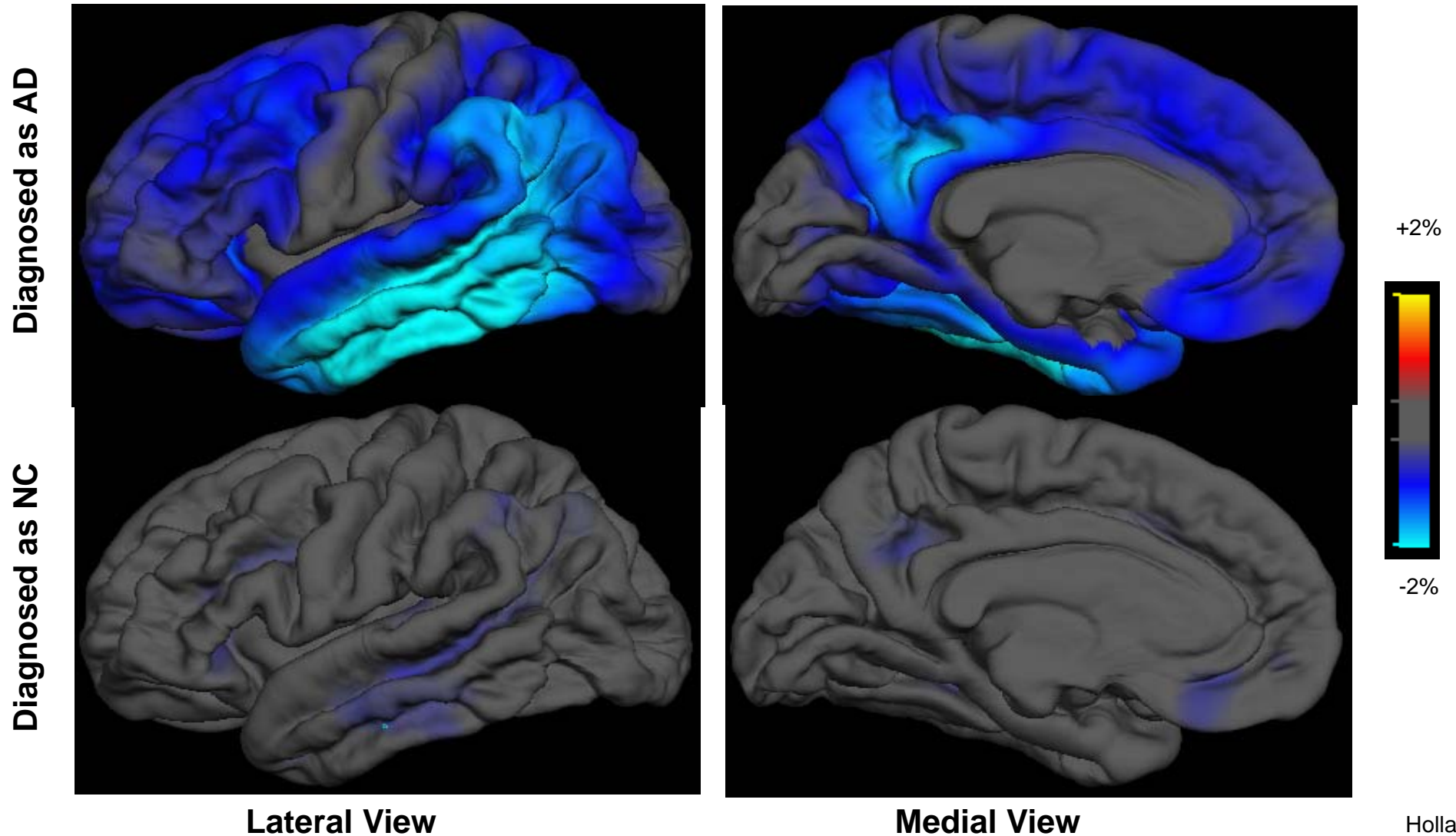
Genes Associated with AD





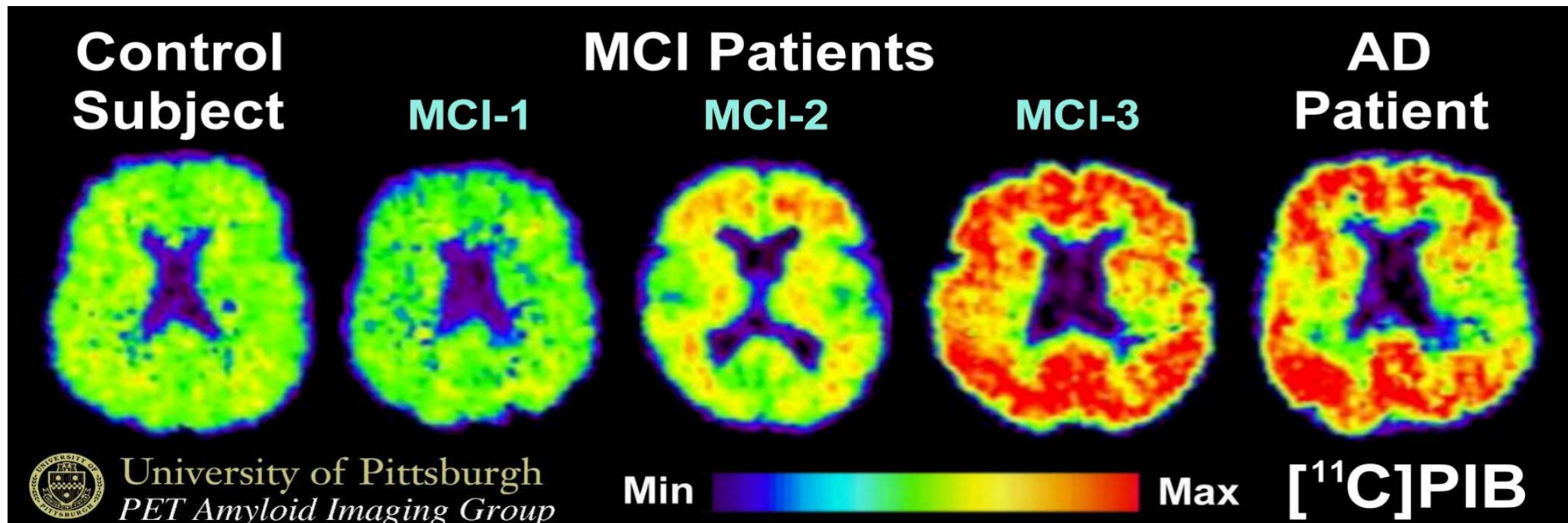
APOE genotype-specific risk of remaining unaffected

Mean Cortical Thickness Change over 12 Months



PIB in Controls, MCI, AD

Chet Mathis, U Pittsburgh



Some MCI's have control-like PIB retention, some have AD-like retention, and some have intermediate retention

Price et al., JCBFM 2005

Lopresti et al., J Nucl Med, in press



PiB-Positivity in Predicting Clinical Conversion in MCI

Melbourne Cohort
N=28, 21 mo. follow-up

PiB(-)	13
Converters to AD	1

PiB(+)	15
Converters to AD	12

Villemagne et al., SNM 2008

Pittsburgh Cohort
N=23, 24 mo. follow-up

PiB(-)	10
Converters to AD	0

PiB(+)	13
Converters to AD	5

Wolk et al., AAN 2008
Neurology, in press

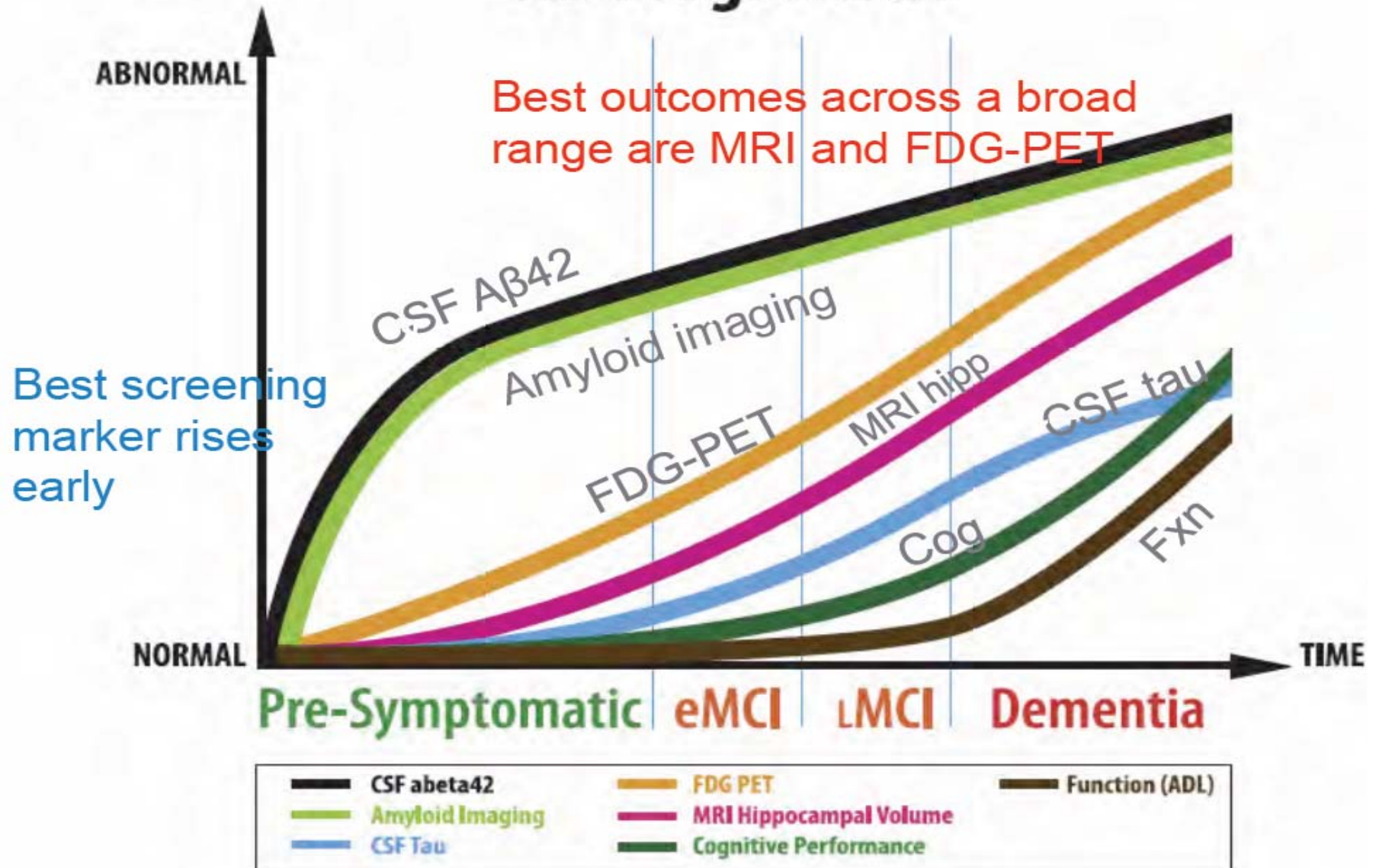
Predictors of Longitudinal Change in Hippocampal Volume - AD

Predictor of change/yr	Univariate Model	Multivariate Model*	
	p-value	Coefficient	p-value
Apoe4+	0.087	-29	0.18
Yrs of education	0.79	-3.4	0.18
CSF A β	0.002	-1.3	0.92
CSF tau	0.031	-8.7	0.046
FDG-PET ROI-avg (UCB)	0.73	10.2	0.75

* Sample size is very small for multivariate models (1/4 of overall sample)

ADNI Study

AD Progression



New Criteria for Pre-clinical AD

Staging categories for preclinical AD research

Stage	Description	A β (PET or CSF)	Markers of neuronal injury (tau, FDG, sMRI)	Evidence of subtle cognitive change
Stage 1	Asymptomatic cerebral amyloidosis	Positive	Negative	Negative
Stage 2	Asymptomatic amyloidosis + "downstream" neurodegeneration	Positive	Positive	Negative
Stage 3	Amyloidosis + neuronal injury + subtle cognitive/behavioral decline	Positive	Positive	Positive

Stage 1

Asymptomatic amyloidosis

- High PET amyloid tracer retention
- Low CSF A β_{1-42}

Stage 2

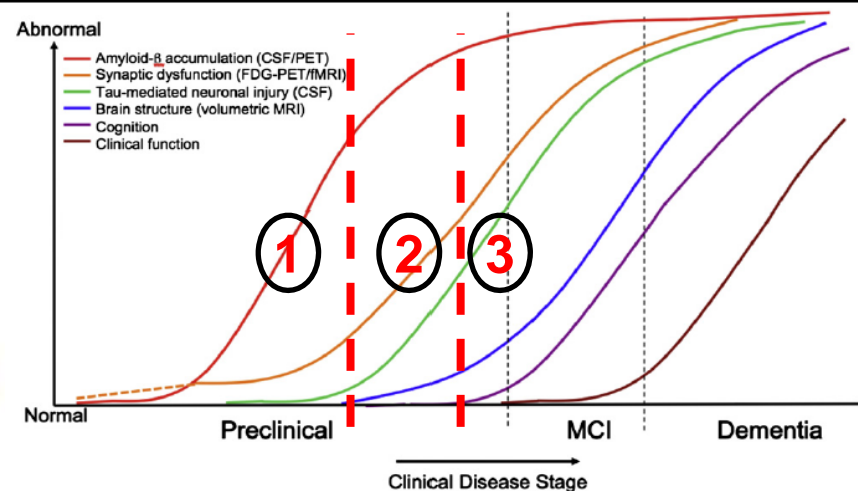
Amyloidosis + Neurodegeneration

- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

Stage 3

Amyloidosis + Neurodegeneration + Subtle Cognitive Decline

- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI



MCI → AD dementia



Evolving therapeutic areas

- New symptomatic therapies
- Treatment of prodromal/mild AD
- Disease modification
- Treatment of advanced dementia



Disease Modification

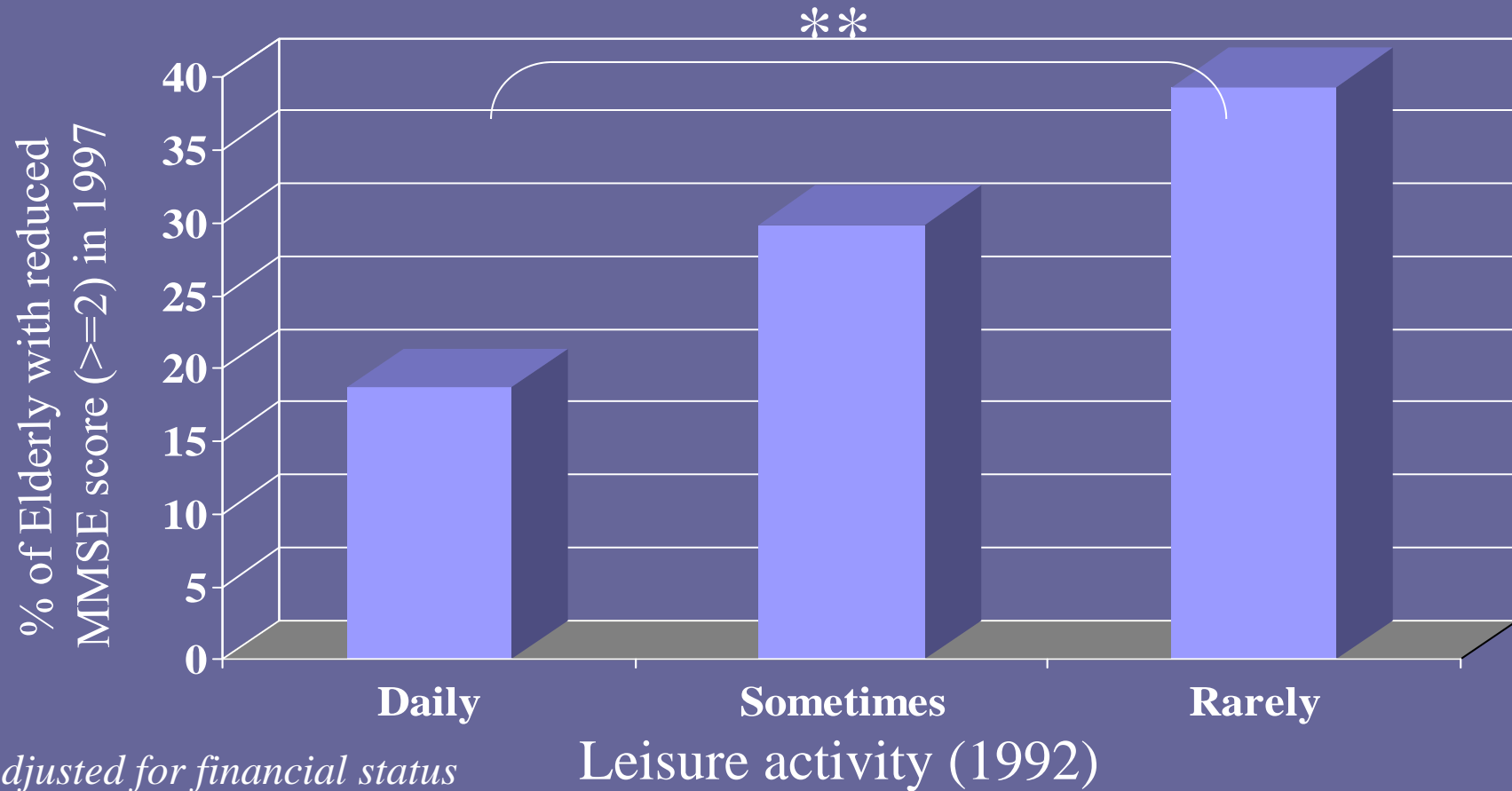
- Targeting amyloid
- Targeting tau
- Combined approaches
- Others
 - Mitochondria



Biomarkers for Selection of the Target Population for Clinical Trial

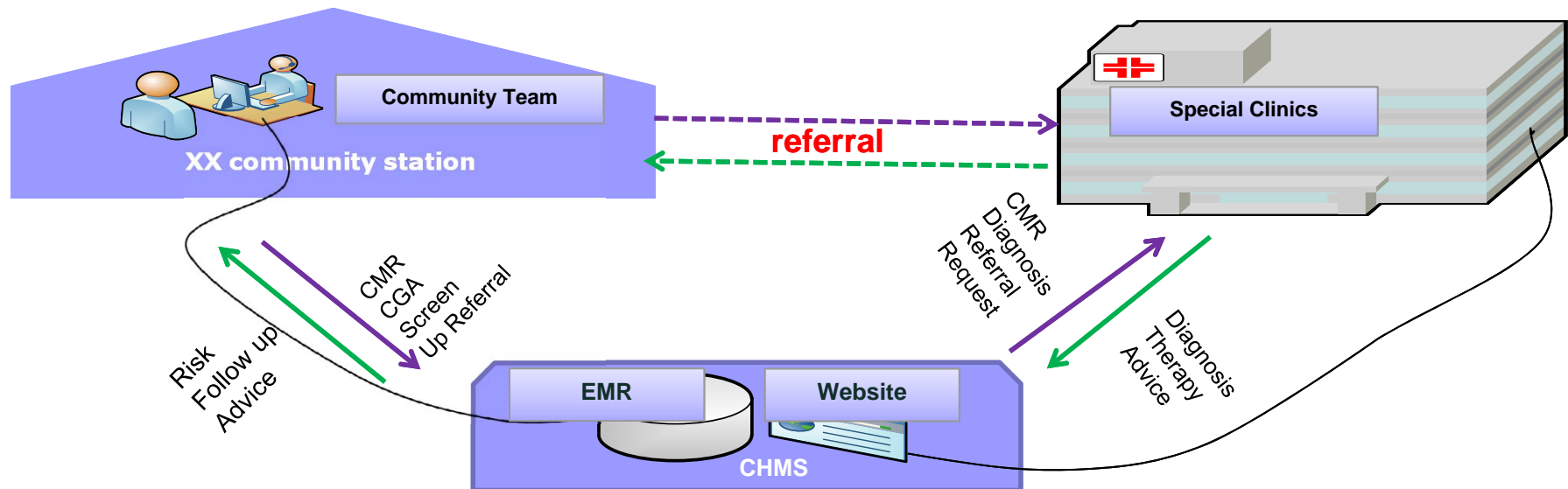
- Disease modifying therapies may be most effective in the earlier stages of the disease
- Recent MCI disease-modifying trials have failed because
 - the disease was too advanced
 - study population (defined by clinical criteria) was too heterogeneous
- Future development of clinical trial for AD
 - before onset of clinical symptoms
 - New criteria for prodromal AD as a continuum to AD with biomarkers as the new measures of disease modification
 - drug-target specific population

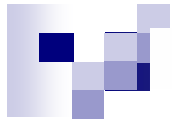
Elderly with Less Leisure Activity Tend to Have a Decreased Cognitive Function (MMSE)



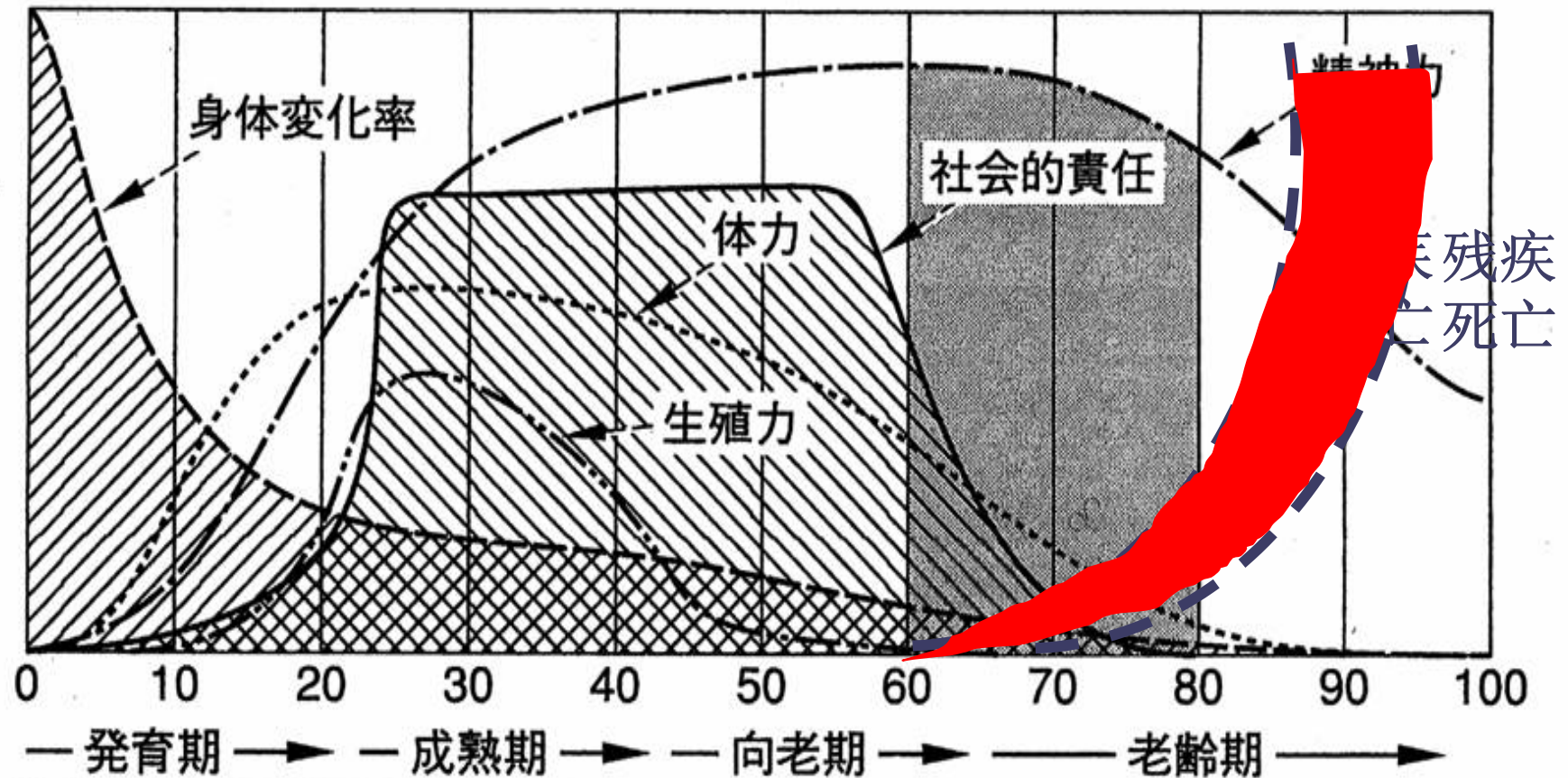
Integrated Geriatric Service Network

- ◆ **“Gate Keeper”**: Establishing and train community clinic professional team (including social worker, nurses and doctors) and medical care registry for the community elderly
- ◆ **“Referral”**: Establishing referral system between “gate keeper” and specialists at hospitals
- ◆ **“Web-based EMR”**: Establishing web-based Community Health Management System (CHMS) that aids collection of medical records, comprehensive assessments, disease screening and management





人一生中的生理功能和社会能力变化



(吉田寿三郎：1981. を一部改変)



创新是解决人口老龄化所带来问题的
关键！

转化医学和新技术



Thanks!