ETHICAL ISSUES IN THE USE OF NEW DIAGNOSTIC BIOMARKERS AND FUTURE COMBINATION THERAPIES FOR AD

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Conflict of interest

- Clinical trial support from Lilly and Roche in DIAN-TU, TauRx, Lundbeck
- DSMB member of ADCS, ATRI, API,Eisai
- Scientific advisor to Affiris, Boehringer-Ingelheim, Lilly, Servier, Sanofi, Schwabe, Takeda, TauRx, Roche

OUTLINE

- Who is at risk of progression to AD?
- Biomarkers allow for risk assessment for progression to AD
- Biomarkers allow for enrolment in clinical trials
- Possible combination therapies
- Ethical considerations

STAGING OF AD: THE GLOBAL DETERIORATION SCALE (Reisberg)

1 no complaints no impairment

2 complaints but no impairment (SCI)

3 early cognitive impairment (MCI)

4, 5 mild to moderate dementia

6, 7 severe dementia

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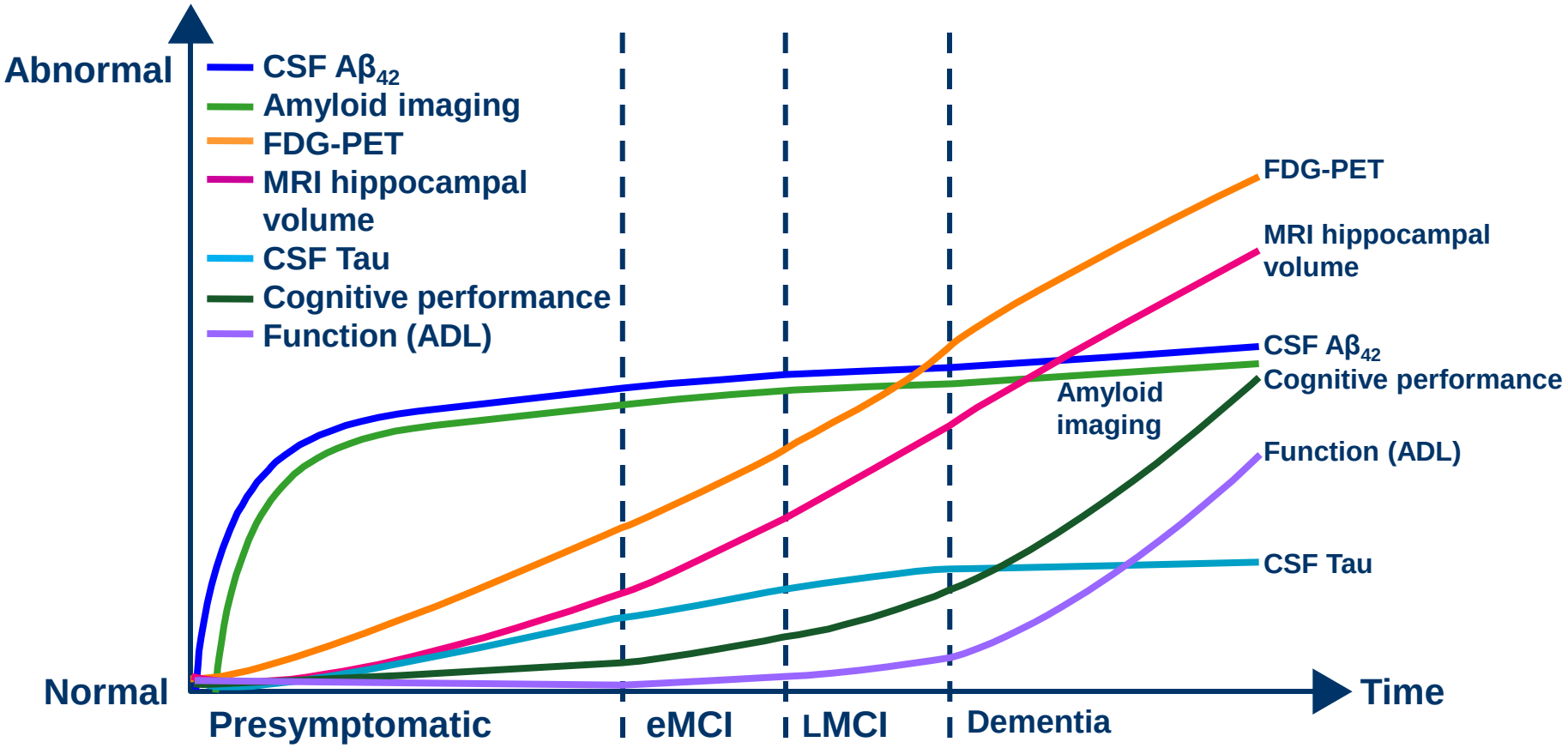
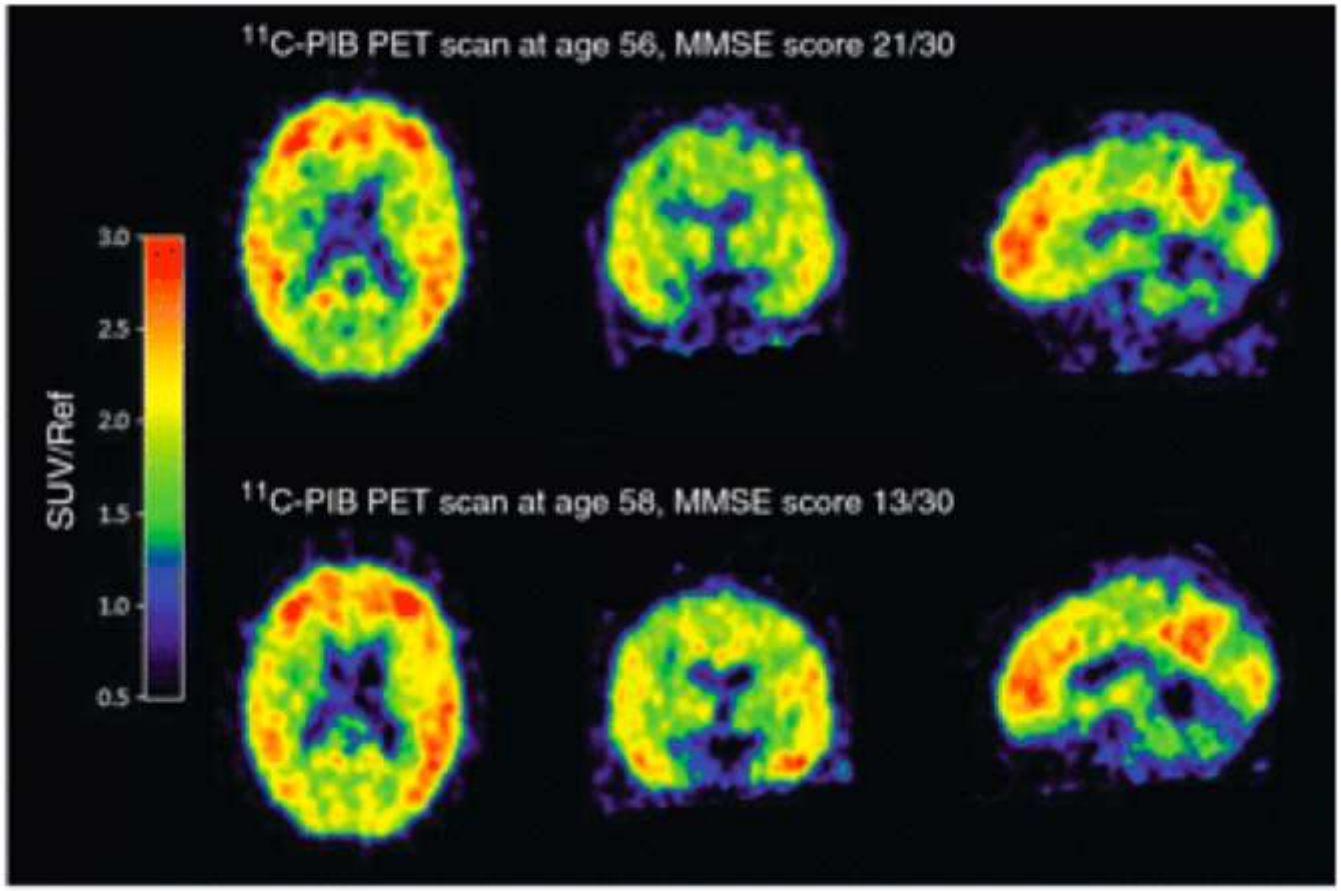
AD Progression



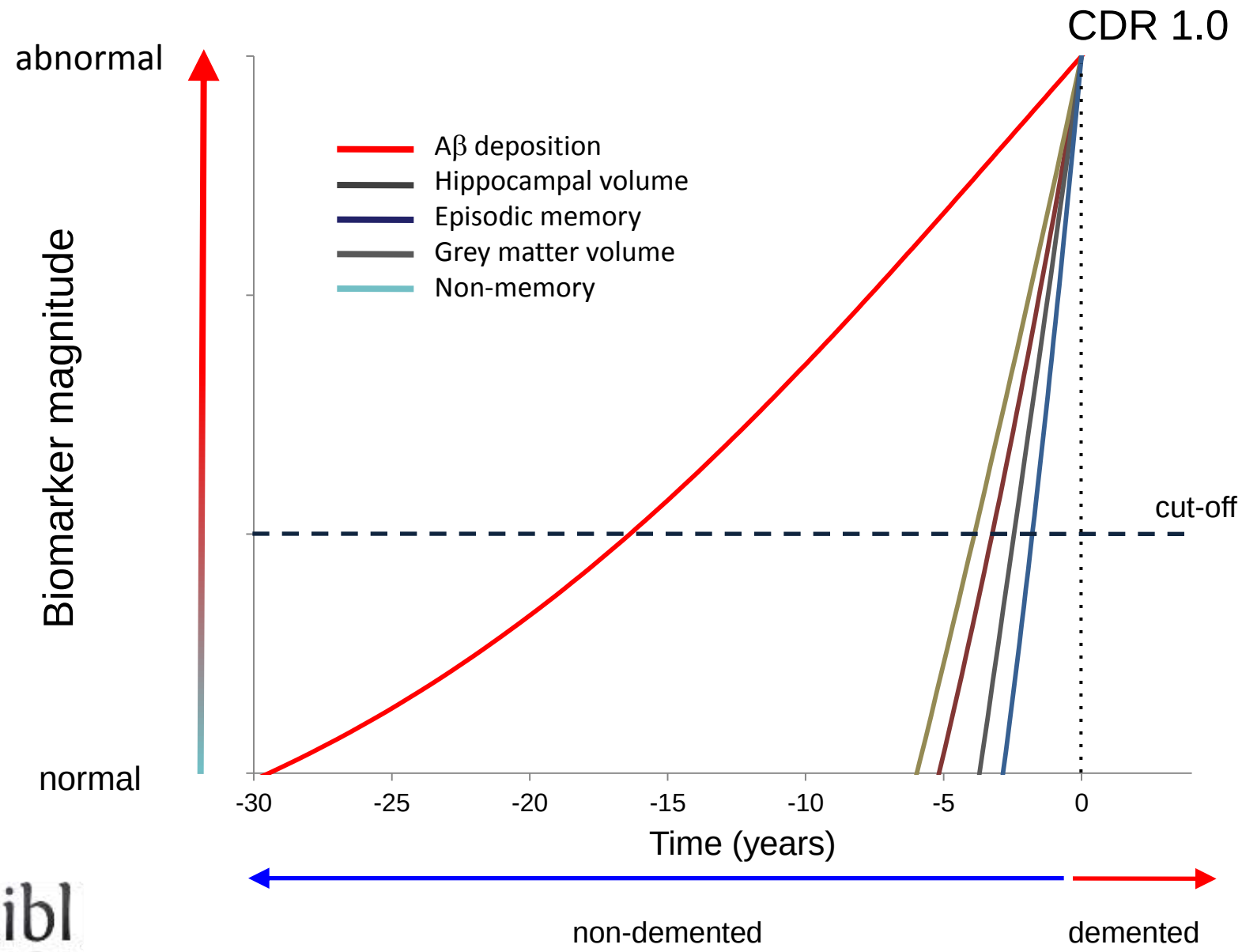
Aisen PS, Petersen RC, Donohue MC, et al. *Alzheimers Dement.* 2010;6:239-246.



Kadir, Marutle et al Brain 2010

Relationship between “abnormality” and CDR of 1.0

Villemagne VL, et al. Lancet Neurology 2013



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DIAGNOSTIC CRITERIA FOR PRECLINICAL AD USING BIOMARKERS

(Modified from Sperling et al, 2011)

	Aß	Neuronal injury	Symptoms
• Asymptomatic cerebral amyloidosis (ACA)	+	-	-
• ACA + evidence of neuronal injury (NI)	+	+	-
• ACA + NI + subtle cognitive decline	+	+	+

MOVING TOWARDS EARLY CLINICAL TRIALS FOR AMYLOID-TARGETED THERAPY IN AD

Aisen, Vellas, Hampel. Nature Reviews/Drug Discovery
doi:10.1038/nrd3842-cl

- “The concept of a biomarker-defined pre-symptomatic stage of AD provides a foundation for early-stage clinical trials”
- “Asymptomatic individuals with amyloid-ß accumulation in the brain show faster cognitive decline than similar individuals without amyloidosis”

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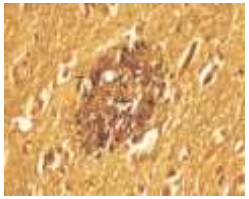
PATHOLOGIES ASSOCIATED WITH AD

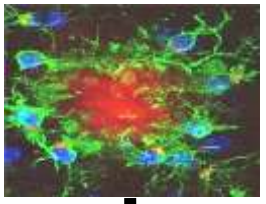
AGE

30
40
50
60
70
80
90
100

β-amyloid deposition



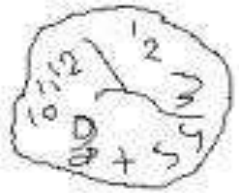
Microglial activation



NFTs

Neuronal loss

Symptoms



COMBINATION Rx IN AD

- So far anti-amyloid monotherapy has not helped in a clinically meaning way
- Combination of anti-amyloid drugs are being considered (ex. BACE inhibitor and antibodies)
- Combinations of an anti-amyloid drug and an anti-tau phosphorylation drug should be considered

Socio-economic considerations of combination Rx in AD

Tomaszewski et al, JPAD 2015

- Tuberculosis, HIV/AIDS and breast cancer are useful models to work out the costs of combination therapies in common diseases
- WHO's Access Framework facilitates assess to essential medicines: rational selection, affordable prices, sustainable financing, reliable health & supply systems

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Currently unresolved issues with very early diagnosis of AD

- Risk of false positive diagnosis
- Social stigma
- Risk of catastrophic reaction
- No proven long-term treatments
- Additional costs for tests
- Burden on memory clinics

POSSIBLE FUTURE SCENARIO 1

- An anti-amyloid drug is effective in 35% of patients in prodromal AD before age 80
- A positive amyloid biomarker is required for Rx coverage (CSF or PET)
- Safety MRIs are needed for the first three months of Rx
- The Rx is stopped when patients reach CDR1.

POSSIBLE FUTURE SCENARIO 2

- A combination of anti-amyloid and anti-tau drugs is effective in 50% of patients with prodromal or mild dementia due to AD, all ages
- Same biomarker restrictions and monitoring
- The Rx is stopped when patients reach CDR2

CONCLUSION

- Caution in knowledge transfer between exploratory biomarkers of AD and clinical testing, diagnosis and treatment
- Particularly true in asymptomatic persons
- Disclosure of individual tests results for research participants should be restricted to clinically relevant information
- Optimism for the near future!