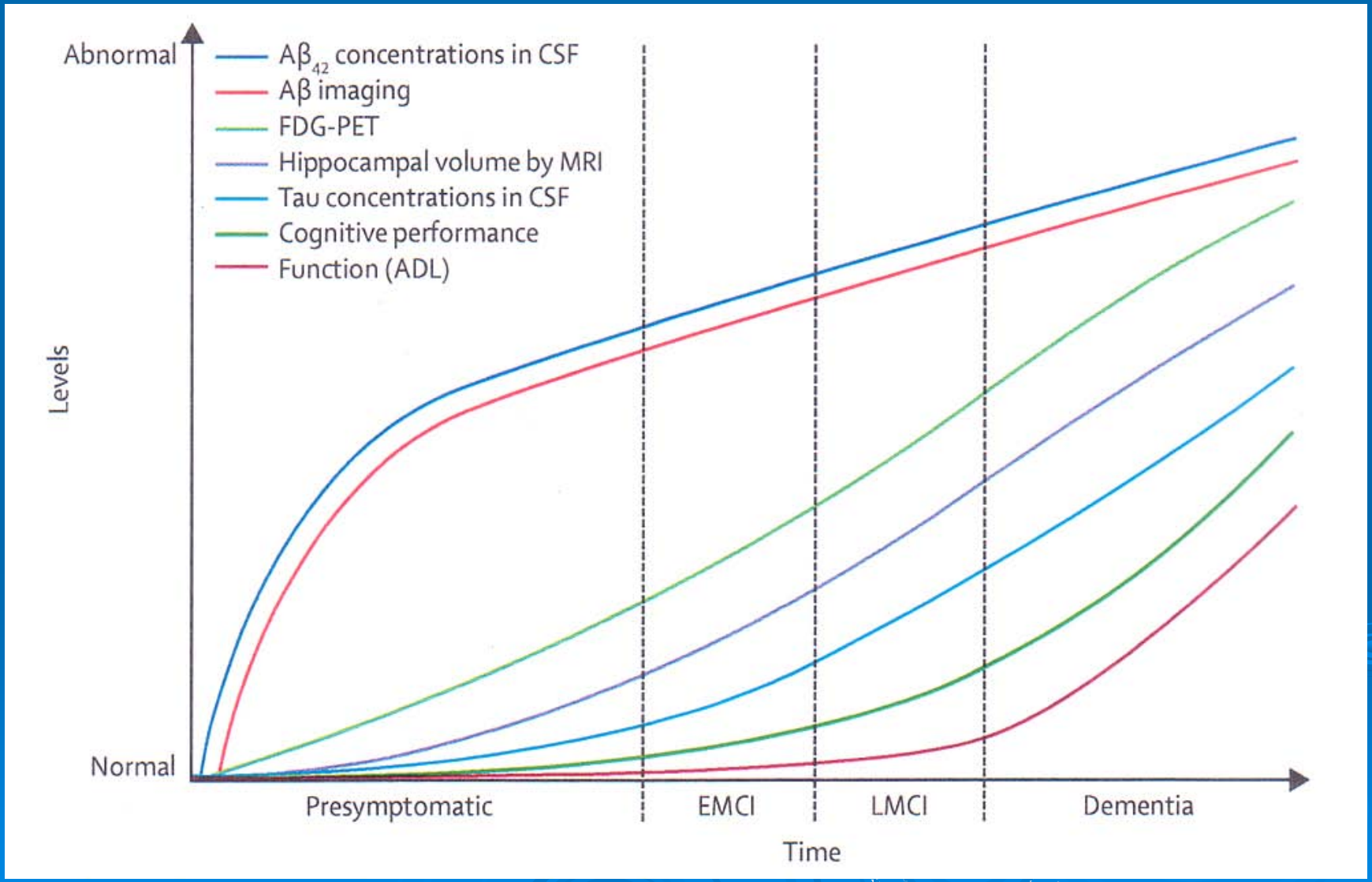
Clinical profile of high risk for AD

- Advanced age
- Family history of a known AD-causative gene mutation
- APOE ε4 genotype
- Family history of AD in 1st degree relatives
- History of repeated head injuries with loss of consciousness
- Diagnosis of MCI
- Reluctance to drink Bordeaux wine

Biologic measures to detect pre-symptomatic AD

- CSF signature of low $A\beta_{1-42}$, high total tau and high phosphotau
- MR brain scan – hippocampal atrophy
- fMRI – changes in the default network
- PET FDG scan – hypometabolism in temporal & parietal regions
- PET amyloid scans – increased uptake, but some unsolved issues regarding predictive value in normal individuals

Hypothetical progression of events in the course of aging to AD, and the imaging techniques, functional measures & biomarkers to detect them



Petersen RC. Lancet Neurology 2010;9:4-5

Pre-symptomatic screening for disease is a common practice in medicine

- Predicated on there being a treatment for the detected condition
- Many screening tests are simple; some are more elaborate
- Examples:
- Hypertension – blood pressure cuff

  Diabetes – blood sugar, A_{1c}

  Hypercholesterol – blood lipid profile

Challenges for AD pre-symptomatic screening

- Currently available symptomatic treatments are weak, and we lack curative or even neuroprotective therapies; and
- The potential screening measures identified this morning are more elaborate and costly than a simple blood test.

The tools are at hand to implement the screening measures if we can develop therapies that delay or retard onset of AD and its subsequent course.

An analogy to colon cancer and a proposal for screening AD

- Many individuals harboring colon cancer are asymptomatic
- Millions of adults – some with risk factors for cancer
  - undergo colon endoscopies every 5-10 years
- The procedure takes two days, is unpleasant and costly
- Procedure is accepted because….
- Pre-cancerous adenomas are removed before cancer invades and spreads

- Most individuals entering the age danger zone for AD are asymptomatic/presymptomatic
- CSF Aβ & tau characteristic alterations, and PET amyloid uptake identify individuals destined to develop AD
- Lumbar puncture takes <1 hour, is not that unpleasant, and costs a fraction of what an endoscopic exam or a PET brain scan costs

- A routine LP every ___ years would be accepted if preventive treatments were available for pre-symptomatic AD.