Update on amyloid and p-tau tests for dementia diagnosis

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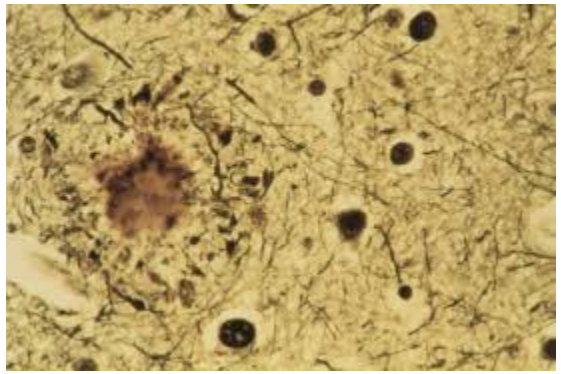
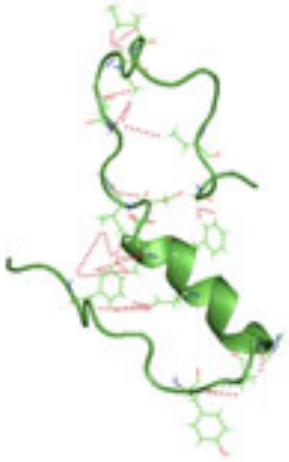
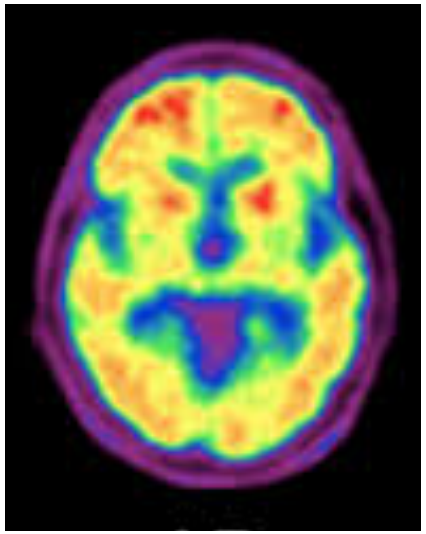
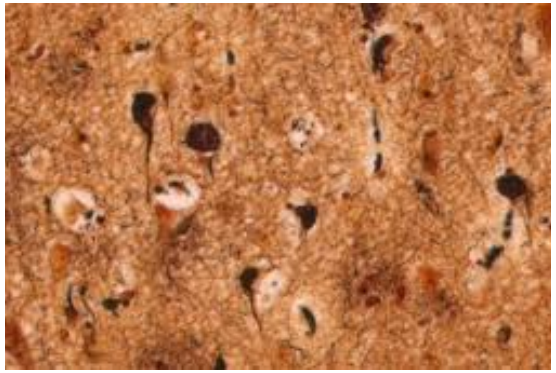
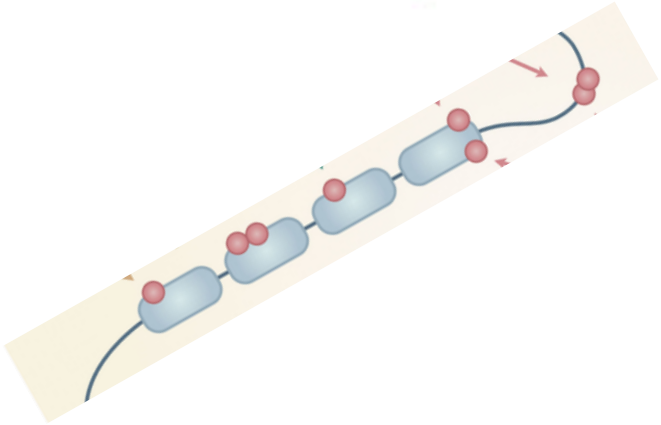
Alzheimer’s disease: biology and biomarkers





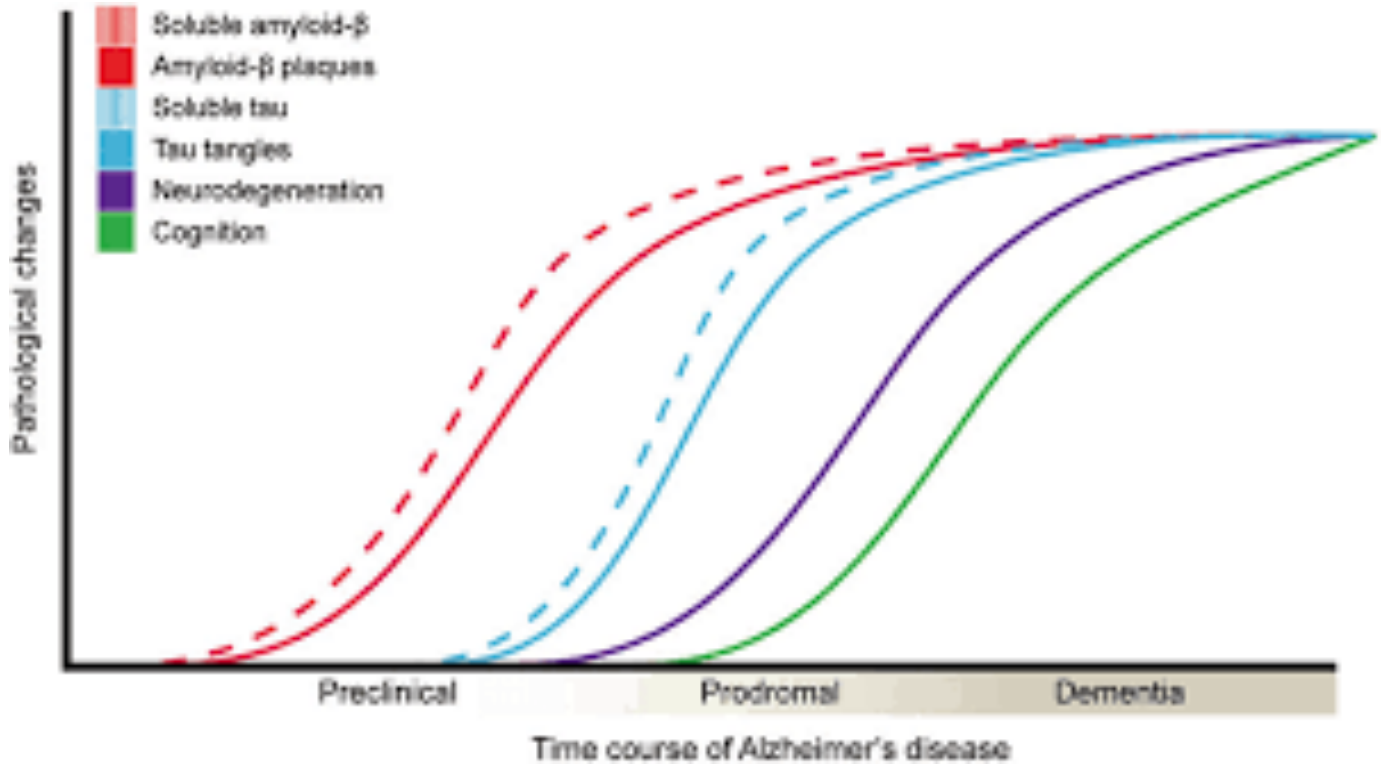






ASSAY	ACCURACY
p-tau:t-tau	~90%
Abeta42:40	~90%

Changes occur sequentially

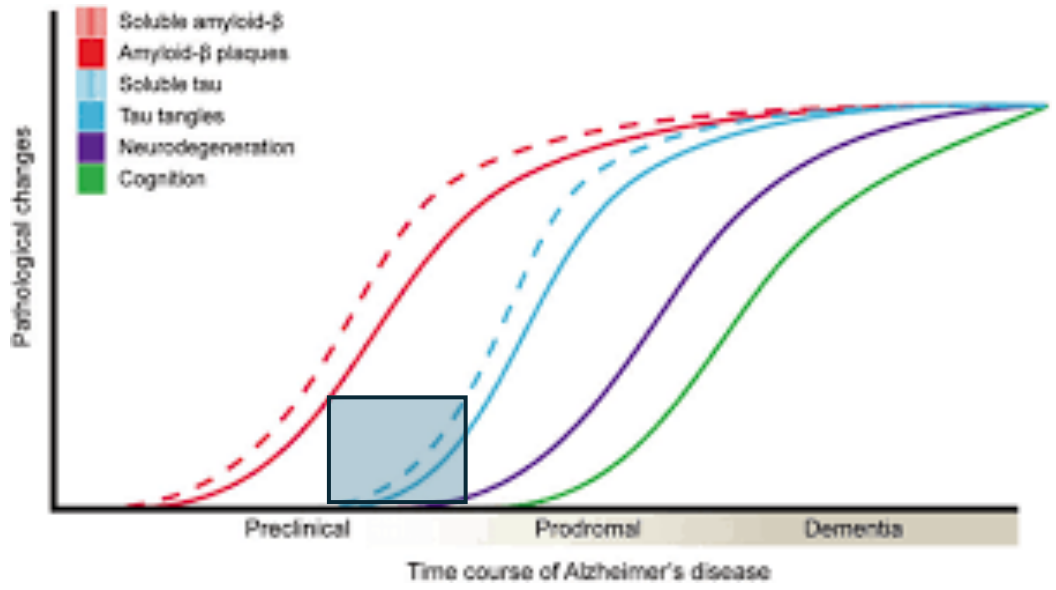


Development of blood biomarkers

- Technical breakthroughs occurred between 2018 and 2022
- Highly sensitive plasma assays for:
  - p-tau181
  - **p-tau217**
  - Abeta42
- Diagnostic accuracy found to correlate well with PET and CSF
- Regulatory approval secured in USA in 2025
- Still under consideration in UK with large scale prospective trials still recruiting

Predicting clinical onset

- Elevation of plasma p-tau217 can be detected in the pre-symptomatic period
- Can predict cognitive symptom onset 3 – 4 years later



Estimating time to symptom onset

- p-tau217 informs the ‘Alzheimer’s clock’ model
- Rate of change depends on age
- Currently used to inform clinical trials:
  - Stratification of recruitment
  - New outcome measures
- Potential utility in clinical practice

Amyloid biomarkers

- Aβ40 vs Aβ42
- Measures of Aβ42 and Aβ42: Aβ40 ratios used
- Deviations from normal emerge early
- Correlate strongly with Amyloid PET and CSF measures
- Potentially useful for screening
- Most informative when combined with plasma p-tau markers

Markers of neurodegeneration

- Not pathologically specific
- Important as measures of the downstream effects of AD pathology
- **Neurofilament light chain (NfL)**
  - Increases after any form of axonal injury
- **Glial fibrillary acidic protein (GFAP)**
  - Marker of astrocytic activation

Potential utility of blood biomarkers

- **Ruling out AD in primary care**
  - Absence of pTau181 can reduce the need for PET scanning and CSF
  - Supports reassurance or accelerates investigation for other pathologies
- **Earlier and simpler triage**
  - Expand access to diagnostic assessment beyond specialist services
  - Support earlier recognition of disease states
  - Possibly improve outcomes from novel therapies
- **Importance of clinical context**
  - Must be accompanied by proper clinical and cognitive assessment
  - AD is not the only cause of dementia!

Key points

- **Plasma p-tau (especially p-tau217) plus Aβ42/40 enable biologically grounded detection of AD in blood.**
- ↓ **Aβ42/40 ratio**: reflects cerebral amyloid deposition; correlates with amyloid PET
- ↑ **Phosphorylated tau (p-tau181, p-tau217, p-tau231)**: highly specific for AD; tracks both amyloid and tau pathology and disease stage
- **Clinical utility:** Remains subject to extensive ongoing research, **but** non-invasive, scalable, disease monitoring, potential for population screening;
- **Research utility:** screening, risk stratification, trial enrichment