From Biomarkers to Diagnostics: Applications from Target Engagement to Patient Stratification

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Steps from Biomarker to Diagnostic

Biomarker Identification
- Hypothesis driven or Un-biased
- Modality? / Invasive or Non-invasive?

Early Development
- Drug Mechanism Readout (TE/PD)

Late Development
- Diagnostic (stand alone or companion)

Intended use?

Regulatory Process
- Approved Diagnostic
- Accepted Outcome measure

Clinical Qualification
- Diagnostic
- Outcome measure (surrogate)

Assay Validation
- Prototype assay to Assay “lock down”
- Assay manufacturing (e.g. kit)
- Assay standardization

Clinical Application
- “Fit for purpose”

Fit for Purpose Assay
- Custom developed assay

Exploratory Biomarker
- Exploration of candidate biomarker

Biomarker Identification
- Hypothesis driven or Un-biased
- Modality? / Invasive or Non-invasive?
Drug Mechanism Readout

**Proof of Concept (PoC)**
Effect on disease

- Requires large studies using **clinical outcome measures**
- No surrogate outcome biomarkers

**Proof of Principle (PoP)**
PD effect on pathophysiology
- Also called PoC Lite

- Brain Amyloid lowering (amyloid mAb)
- Brain Tau lowering (tau therapies)

**Proof of Mechanism (PoM)**
Pharmacodynamic (PD) readout

- CSF Aβ peptide species lowering

**Proof of Presence**
Drug reaches target organ and/or shows Target Engagement (TE)

- Molecular PET for TE
- Micro-dosing (AMS)

**Molecular Imaging - PET**

Aβ Species in CSF
Valid PoC requires adequate receptor occupancy
  – Can sufficient occupancy be achieved at well tolerated doses?
  – Is it worthwhile testing efficacy?

- No occupancy - no efficacy – not surprising
  - New molecule needed

- Full occupancy – no efficacy – concept flawed
  - Do something else

Biomarker Supported Early Development

- **Go/No-Go tests of molecules & hypotheses**
  - Target interaction, Dose guiding & Safety margin

- **Internal decision-making**
  - Standards & criteria defined internally

- **Development tools**
  - Rarely commercialization of biomarker itself
  - But maybe commercialized technology platforms
Intended use of Biomarkers in Late Drug Development

- **Disease Diagnosis**
  - Supportive in clinical diagnosis
  - Early diagnosis – at risk diagnosis (antecedent biomarkers)

- **Prognostic (Predictive) – Disease progression**
  - Diagnosis of disease aggressiveness

- **Prognostic (Predictive) – Treatment effect**
  - Outcome measure in trials
  - Ultimate goal surrogate outcome measure
    - *Surrogacy qualification time-consuming & costly*

- **Drug safety assessment**

- **Stratification**
  - Segmentation into predetermined categories

- **Enrichment**
  - Inclusion criteria in trials
  - Companion Diagnostics
AD Biomarkers Applications in Ph 2/3 Trials

• **Stratification – Segmentation in predetermined categories**
  - Genetic: ApoE isotype
  - *volumetric MRI* – hippocampal (*not applied yet in trials*)

• **Enrichment (Companion Diagnostics) – Entry criteria**
  - Amyloid PET imaging
  - CSF Aβ_{42} or Tau/ Aβ ratio
  - Genetic: ApoE isotype, Dominant mutations
  - *volumetric MRI* – hippocampal (*not applied yet in trials*)

• **Predictive – Treatment effect / Outcome measure**
  - *volumetric MRI* – hippocampal
  - Amyloid & Tau-PET
  - Cerebrospinal fluid total-tau or P-tau
  - *FDG-PET* (*not applied yet in trials*)

• **Predictive – Safety assessment**
  - Molecule specific
  - Target class related/General measures
    - Amyloid Related Imaging Abnormalities (ARIA-E/H)
    - Skin pigmentation, Notch signaling in hair follicles, etc.
Impact of Availability of Patient Stratification Biomarkers

512 (5%) of 9,985 clinical/regulatory transitions with stratification biomarkers

Clinical Development Success Rates 2006-2015
BIO, Biomedtracker & AMPLION
Conceptual Shift of AD Diagnosis Based on Biomarkers

1984 NINCDS-ADRDA

Clinical

Post-Mortem

Alzheimer’s Disease

MCI

dementia
probable/possible

neuropathology

2007 IWG

Clinical

Biological

Alzheimer’s Disease

typical / atypical

biomarkers

Role of Diagnostic Biomarkers

- **Clinical phenotype – Different diagnostic criteria**
- **Histopathology gold-standard** in biomarker qualification
  - Complicated by Mixed Pathologies

*Bridging clinical & histopathology phenotypes*

**Clinical Phenotype**
- Mayo criteria 1999
- IWG criteria 2007
- NIA-AA criteria 2011
- IWG-2 criteria 2014

**Biomarker Phenotype**
- ApoE isotype
- Amyloid PET
- CSF Aβ42
- CSF Tau
- HCV MRI

**Histopathology Phenotype**
- Amyloid plaques
- Neurofibrillary tangles
- Inflammation
- Neurodegeneration
Regulatory Process
Biomarkers to Diagnostics

 “Context of Use” Acceptance
  ➢ Purpose of the measurement ("Clinical Qualification")
    – Stand Alone or Companion Diagnostic
    – Outcome Measure - Surrogate Outcome Measure

 “Assay” Approval
  ➢ Test performing the measurement ("Assay Validation")
    – Medical Device
      • In Vivo, Ex Vivo or In Vitro application
      • Do not work via chemical action in the body
    – IND / IMP
      • In Vivo application
      • Work via chemical action in the body, e.g. PET ligand
Assay Approval
“Fluid” Biomarker (FDA Terminology)

• **Research Use Only (RUO)**
  – Not for diagnostic use
  – Evaluate design & performance
  – Developing knowledge related to human disease

• **Investigational Use Only (IUO)**
  – Undergoing performance evaluation
  – Used for diagnosis or treatment decisions or used as part of a drug trial to determine which arm of the trial subjects will be placed in
  – Meet criteria for Investigational Device Exemption (IDE)
    • Pre-IDE consultations and IDE submission

• **In Vitro Diagnostic (IVD) Medical Device (kit)**
  – For diagnosis - to cure, mitigate, treat, or prevent disease
  – FDA - CDRH (Center for Devices & Radiologic Health)
    • Pre-market and post-market controls
    • Commercialized to CLIA certified labs
Pathways to Diagnostic Approval

- **Stand-Alone Diagnostic**
  - Not associated with specific drug treatment
  - "Gold standard" against which to judge performance
    - Other established diagnostic
    - Post mortem histopathology

- **Companion Diagnostic**
  - Context of Use established by drug treatment effect
  - Identifies condition for safe & effective use of a therapeutic product
  - No "gold standard" requirement to judge performance
  - Collaboration between Center for Drug Evaluation and Research (CDER) and CDRH (Center for Devices & Radiologic Health)
Status Amyloid PET

**Approved stand-alone ligands (FDA & EMA) device (PMDA)**
- Rule out presence of amyloid - not for AD “diagnosis”
- Post mortem histopathology validation required as gold standard
- No clinically meaningful differentiation between tracers

**Extensive use in “companion diagnostic” context**
- Pre-symptomatic AD, Prodromal AD, Mild AD (“Early AD”) drug trials
- Ongoing Reference standard project - the “Centiloid project” – interchangeable use of tracers

**Hampered by high entry barriers**
- High costs & Reimbursement challenges
- Injection radioactivity – limited possibilities for repeat measures as well as approval issues (e.g. German BfS etc)
- Complex infrastructure (cyclotron, distribution networks, PET centers)
Emerging Biochemical Assay
Alternatives to Amyloid PET

- The best substitute is sampling of cerebrospinal fluid (CSF) and measurements of Aβ peptide and Tau protein.

Graphs showing sensitivity and specificity of CSF Aβ42 predictions for sporadic Mild Cognitive Impairment or AD at least 9 years before symptoms.
Status CSF Biomarkers

🌟 No approved Stand alone or Companion IVD yet
• Commercialized RUO/IUO/CE Mark assays for Ab42, Tau & P-tau

🌟 Limited Companion Diagnostic use in AD drug trials
• Supplement to Amyloid PET, CE Mark/RUO or IUO assays

🌟 Rapid progression of Precision-based assays to IVDs
• Several Diagnostics companies in late stage development of Stand alone IVDs
• Standardization: Reference Material & Methods (Accuracy-based assays)
  ✴ “Global Consortium for the Standardization of CSF Biomarkers”
  ✴ Initial focus on Aβ42 peptide

🌟 Cultural/medical barriers for lumbar puncture
• High acceptance Europe / Lower acceptance North America & Asia (Japan increasing acceptance)

🌟 Supportive biomarker for disease modification claims
• Tau or P-Tau – further clinical qualification needed
Hippocampal Volumetric (HCV) MRI as Diagnostic for MCI to AD Conversion

- Well established and early Qualification (EMA) for HCV-vMRI
  - Reasonable sensitivity / specificity

Lower entry barriers c.f. CSF/Amyloid PET
  - High availability of clinical MRI, reasonable cost – will it take over PET/CSF on market?

Low uptake for primary enrichment
  - Anti-amyloid therapy trials favor Amyloid PET or CSF Aβ42
  - vMRI concordance with other Biomarkers?
  - Stacking of biomarkers - further screening failure?

Used as supportive Outcome measure (Disease Modification)
  - HCV remains to show effect in the “right” direction

Hill et al., Alzheimer’s & Dementia 10 (2014) 421–429
MRI Safety Biomarkers
Amyloid Related Imaging Abnormalities (ARIA)

• ARIA with vasogenic edema (ARIA-E) straight-forward to diagnose
  - Rare event (incidence rate AD ~0.2%)
  - Primarily associated with anti-amyloid mAbs
    - Can be associated with clinical symptoms of concern
  - Diagnosed with MRI (T2; fluid attenuation inversion recovery/FLAIR)
    - Signal intensity on FLAIR or other T2-weighted sequences
    - Parenchyma and/or leptomeninges
      o parietal, occipital, and frontal lobes

• ARIA Incidence much higher in ApoE4 + subjects (higher amyloid load)
  - ApoE stratification strategies in anti-amyloid mAbs trials
Several ligands in clinical development

- Lilly/Avid (\(^{18}\)F-Flortaucipir/AV4051/T807; previously Siemens) in Phase 2/3 trials, ADNI-3
- Cerveau (\(^{18}\)F-MK6240), Piramal (new leads; AC Immune), Aprinoia (\(^{18}\)F PM PBB3), Genentech (\(^{18}\)F-GTP1), GE (THK5351; Tohoku), Roche

Commercial uncertainties: development costs & commercial opportunity (reimbursement?)

Clear differentiation between the ligands

- Tau subtype selectivity (R3/R4), PSP/FTD binding (?), off target binding
- Kinetics/time activity curves, defluoridation etc.

Potential for more detailed disease staging (Braak-Braak staging)

- Tau PET changes seem to align well with symptomatic progression
Other Emerging “Diagnostic” Biomarkers

**CSF Biomarkers** (beyond Aβ and tau)
- Neurodegeneration markers: Neurogranin, NFL, etc
- Differential diagnosis markers: α-synuclein, TDP-43, VILIP1 etc.

**Blood tests**

**Physiological tests**
- Olfactory function (hyposmia), pupillary diameter etc.
  - Pre-symptomatic/early stage AD sensitivity/specificity?

**Retinal, lens, or corneal imaging**
- Development of high resolution/sensitive techniques - Optical Coherence tomography (OCT) etc.
- Fluorescence imaging of amyloid

**Cognitive (computerized) tests**
Considerations AD Blood Biomarkers

- **Routine use of ApoE genotyping**
  - ARIA-E safety stratification in Phase 2&3 trials

- **Diverse context of use possible for Blood Dx**
  - Detection of AD pathology in pre-symptomatic or MCI subjects
    - Prescreen before amyloid PET or CSF measures
  - Replacement amyloid PET or CSF measures for enrichment

- **Very low barriers**
  - Blood sampling universally acceptable and common practice

- **Expected very low cost**
  - Most analytical approaches/technology platforms very affordable

- **High volume analysis possible**
  - Possibility to screen 1000’s of samples
Challenges AD Blood Biomarkers

• No breakthrough in spite of several years of dedicated efforts
  – Analyte selection challenges (single or multiplex, relevance AD pathology)
  – Sensitivity challenges (most interesting analytes have very low blood levels)
  – Clinical specificity challenges (vs other chronic neurodegenerative diseases)
  – Only RUO (or CE Mark) assays available, no apparent dedicated IVD program
  – Small samples sizes – need replication in large cohorts

➢ Ongoing critical clinical qualification – large longitudinal data sets from consortia (ADNI, IMI-EPAD, AIBL)
Eye Scanning Test for Early Detection & Diagnosis of AD

Eye scanned by the SAPPHIRE instrument to detect a specific fluorescent signature of ligand-marked Aβ in the supra-nucleus region of the human lens

- Sensitivity of 85% / specificity of 95%
- 20 patients diagnosed with probable AD from 20 age-matched healthy volunteers
- Excellent correlation to amyloid PET

Fluorescent Ligand Scanning (FLS) of amyloid aggregates in the lens

- Aβ-specific small molecules dropped into a patient’s eye - absorbed into the lens to bind amyloid
- FLS system excites the fluorescent ligands to quantitatively measure emission
- If binding increases over time, a positive diagnosis can be made
Cognivue –
1st FDA Cleared (June, 2015) Cognitive test Device

- Fully automated cognition assessment device (De Novo 510k) for neurology & primary care clinics
  - Adjunctive tool evaluating perceptual and memory function in individuals aged 55-95 years old
  - Individual scores on a battery of cognitive tasks: 10 Tests in 10 minutes