The Potential use of Biomarkers in Alzheimer's Disease in Different Stages of Drug Development

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On behalf of the EFPIA Working Group

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Declaration of Conflict of Interest

I am a full time employee Eisai Inc.

I own shares in AstraZeneca and Merck Inc.

EMA Discussion Paper#

“Qualification and/or validation of a certain biomarker as diagnostic tools or as a surrogate endpoint is out of the scope of this document”

“May be outlined in detail in separate upcoming documents after EMA qualification processes (Ref. EMA/CHMP/SAWP/72894/2008)”

“Discussion paper on the clinical investigation of medicines for the treatment of Alzheimer´s disease and other dementias”. EMA/CHMP/539931/2, 014, 23 October 2014

➢*However, a the success of a new AD guideline will be intimately linked to acceptance of biomarker context of use and approval of biomarker products*

Key considerations

- **Biomarkers have emerged as essential for defining AD and staging of the disease along its spectrum**
- **Biomarkers are critical to support AD drug development**
- **Several AD biomarkers are available - with different, but also commonly overlapping applications**
  - Alternative biomarker modalities
  - Interchangeable use of concordant biomarker modalities
- **Variable degree of assay validation & clinical qualification**
  - Which biomarker is fit for purpose in sponsor trials?
  - Which biomarkers may gain regulatory acceptance?
  - Which biomarkers will become generally used?

Early Development - Drug Mechanism Readout

Clinical Go/No-Go tests of molecules or hypotheses

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

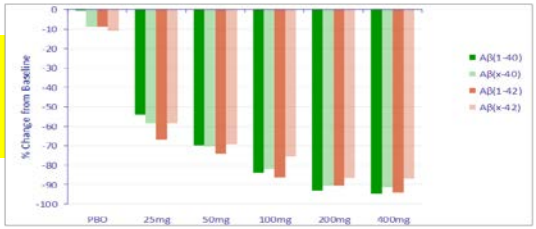
- Also called PoC Lite

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

Proof of Mechanism (PoM)
Pharmacodynamic (PD) readout

- CSF Aβ peptide species lowering

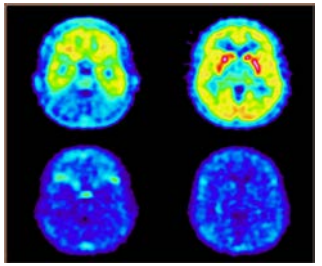
Aβ Species in CSF



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

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

Molecular Imaging - PET



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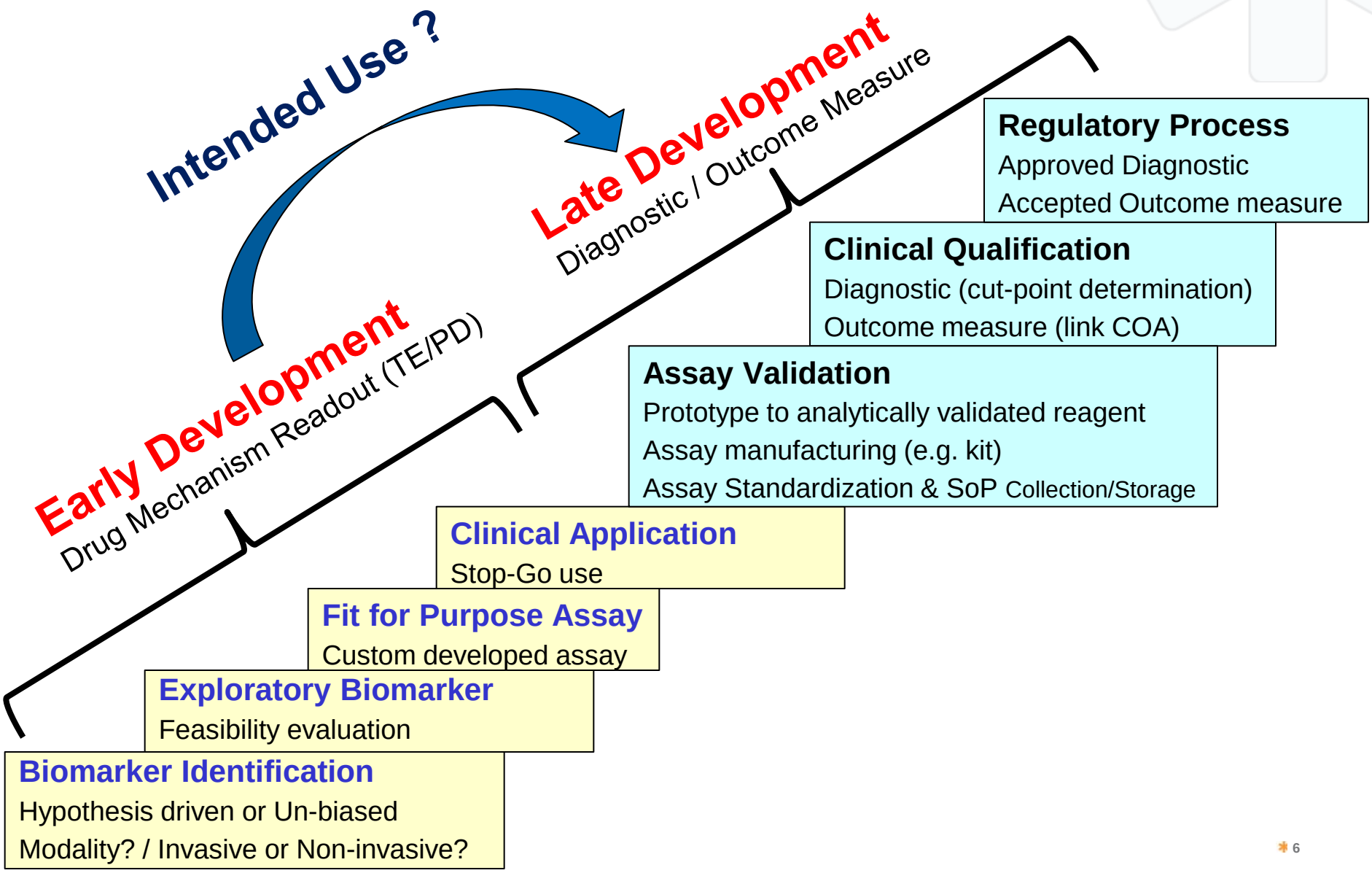
Steps from Biomarker Identification to Diagnostic/Outcome Measure



Use of AD Biomarkers

- **Diagnostic** – Determining diagnosis[#]
  - Clinically well-established - MRI, EEG etc.
  - Dominant mutations
  - Supportive/exploratory - amyloid PET, CSF measures etc.

- **Prognostic** – Determining course of illness[#]
  - Dominant mutations
  - Hippocampal atrophy - volumetric MRI
  - *Amyloid PET imaging*
  - *CSF Aβ peptides or Tau protein*

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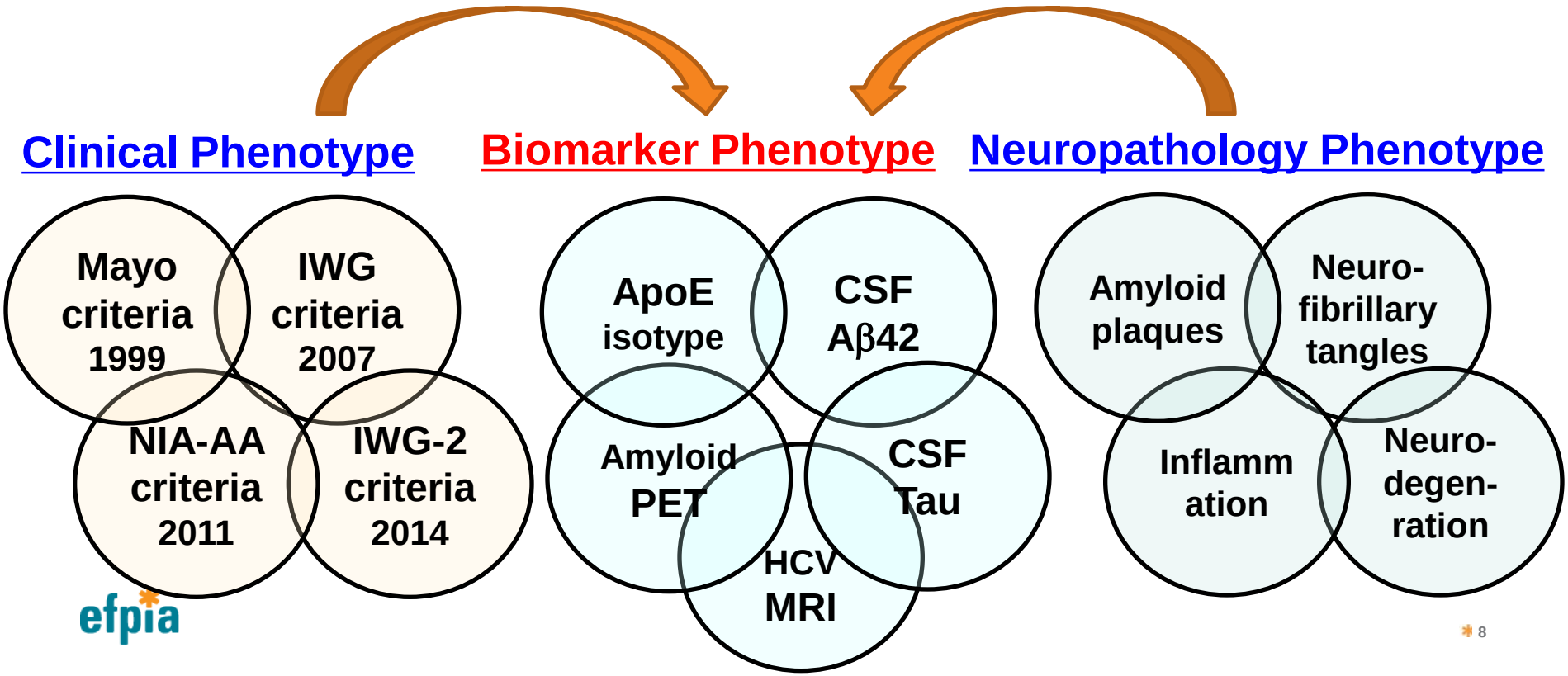
[#]*Definition according "Discussion paper on the clinical investigation of medicines for the treatment of Alzheimer´s disease and other dementias". EMA/CHMP/539931/2014,*

Role of Biomarkers in AD Diagnosis ?

- **Clinical phenotype –different diagnostic criteria**
- **Neuropathology –gold-standard in biomarker qualification**

…but obtained much later in disease and with increasing mixed pathologies

Bridging clinical & neuropathology phenotypes



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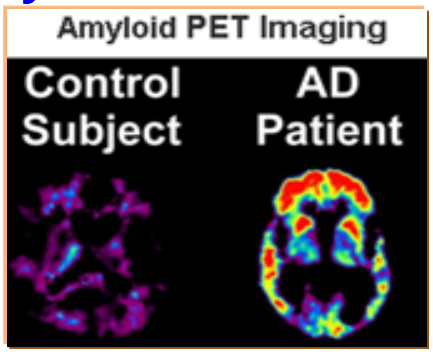
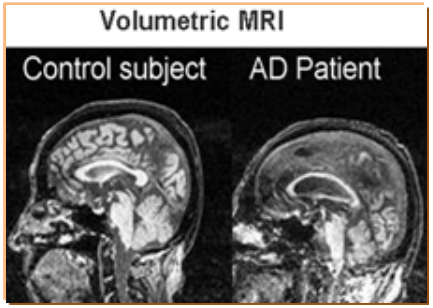
AD Biomarkers Used in Drug Development

- **Stratification** – Segmentation into predetermined categories
  - Genetic: ApoE isotype
  - *volumetric MRI – hippocampal*
- **Enrichment** (Companion Diagnostics) – Entry criteria#
  - Amyloid PET imaging
  - CSF $A\beta_{42}$ or Tau/ Aβ ratio
  - Genetic: ApoE isotype, Dominant mutations
  - *volumetric MRI – hippocampal*



- **Predictive** – Treatment effect # / Outcome measure
  - volumetric MRI – hippocampal
  - *Cerebrospinal fluid total-tau or P-tau*
  - *FTG-PET*



- **Predictive** – Safety assessment#
  - Molecule specific
  - Target class related/General measures
    - Amyloid Related Imaging Abnormalities (ARIA-E/H)
    - Skin pigmentation

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Biomarker Development

"Assay" Approval ("cleared assay")

- *Test performing measurement - "Assay Validation"*
- **Medical Device**
  - Does not work via chemical action in the body
- **IND / IMP**
  - Works via chemical action in the body, e.g. PET ligand

"Context of Use"

- *Purpose of measurement - "Clinical Qualification"*
- **Stand Alone** - Not associated with specific drug treatment
  - "Gold standard" – standard of truth comparison to judge performance
- **Companion Diagnostic** - Identifies condition of drug use
  - Enrichment biomarkers
- **Exploratory/Secondary Outcome Measure**
  - Ultimate goal is Surrogate Outcome measure

Context of Use

- **EMA - Qualification of Novel Methodologies for Drug Development**
  - **CSF Biomarkers (BMS) - Opinions April 2011 (MCI) & February 2012 (MM-AD)**
    - Need for cut-point definition
  - **vMRI/Hippocampal Volume (CAMD) - Qualification opinion October 2011**
  - **Amyloid PET (BMS) - Opinion February 2012 (PET and CSF for MM-AD)**

- **FDA - Drug Development Tools (DDT) Qualification**
  - **No AD Biomarker DDT qualification issued**
    - CSF Biomarkers submitted (CAMD) November, 2011
    - vMRI/Hippocampal volume submitted (CAMD) April 21, 2011

> **Qualification requires a reliable measurement method, but it is conceptually independent of specific test**

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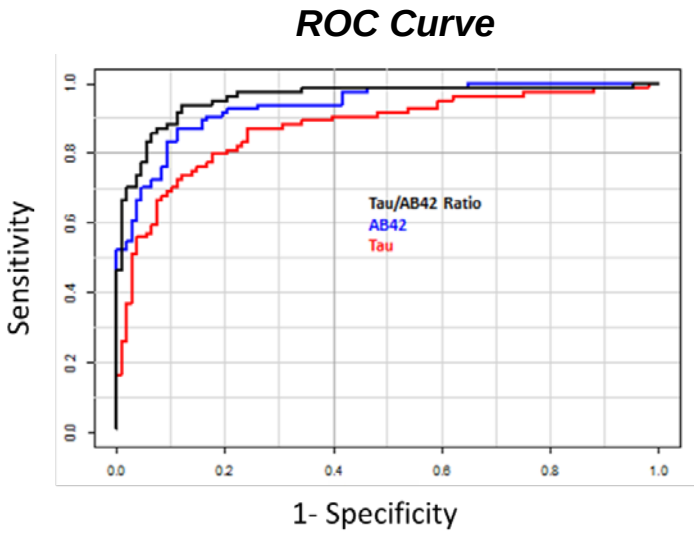
Biomarker Test Characteristics

Cut-Point (Cut-off, Threshold) Determination

- **Requires extensive assay standardization & clinical qualification**
- **Cut -points for AD biomarkers**
  - Amyloid PET – SUVR or Visual Read
  - CSF – pg/mL
  - vMRI/Hippocampal volume – cm^3



Performance Characteristics

- **Analytical performance**
  - Assay stability & precision
  - Reproducibility
- **Sensitivity & Specificity / Positive & Negative Predictive Values**
  - Receiver Operating Characteristic Curve (ROC)

“Fluid” Biomarker Assay Maturity

FDA Terminology

- **Laboratory Developed Test (LDT,** earlier called ***homebrews)***
  - Developed & used within one lab that offers testing service
- **Research Use Only (RUO)**
  - Not for diagnostic use – only for exploratory analysis
- **Investigational Use Only (IUO)**
  - Undergoing performance evaluation
    - Meet FDA criteria for Investigational Device Exemption (IDE)
- **In Vitro Diagnostic Medical Device (IVD)**
  - Diagnosis to cure, mitigate, treat, or prevent disease
    - Subject to EU IVD Director (98/79/EC)
    - Subject to FDA pre-market and post-market approval & controls

Europe – CE Mark

- **Manufacturer's self-declaration**
  - Verified by “Notified Body” (accredited to validate compliance)
  - Not linked to Intended Use
  - Permits products’ access to the market

- **Companion Diagnostic (CoDx) - viewed as low risk**
  - No need for Notified Body involvement
  - Drug approval not required for device to be CE marked
  - *FDA - High risk” device (Class III; requiring Pre-Market Approval)*

  - **Influence of <u>revision</u> of the EU regulation on In Vitro Diagnostic Medical Devices (IVD) on acceptability of stand-alone or companion AD biomarkers?**
  - Companion Diagnostic will be viewed as class C (high risk)
  - ***Target for adoption Q2/3 2015***

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Status Amyloid PET

- **Approved stand-alone ligands (FDA & EMA)**
  - Rule out presence of amyloid - not for AD “diagnosis”
  - Post mortem histopathology validation
- **Extensive use in “companion diagnostic” context**
  - Prodromal AD, Mild AD, Pre-symptomatic AD
  - Ongoing Reference standard project - the “Centiloid project”
- **Hampered by high entry barriers**
  - High costs & Reimbursement challenges
  - Complex infrastructure (cyclotron, distribution networks, PET centers)
  - Injection radioactivity – approval issues (German BfS)

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Status CSF Biomarkers

- **No approved Stand alone or Companion IVD**
  - Commercialized RUO assays for Aβ42, Tau & P-tau (some CE marked)
  - Progression of Precision-based IVDs
  - Ongoing standardization
    - Reference Material and Methods (Accuracy-based assays)
      - "Global Consortium for the Standardization of CSF Biomarkers"
      - Initial focus on Aβ42 peptide

- **Companion Diagnostic use in AD drug trials**
  - Alone, or in sub-groups (supplement to Amyloid PET), using CE Mark / RUO assays

- **Cultural/medical barriers for lumbar puncture**
  - High acceptance Europe / Lower acceptance North America & Asia

- **Supportive biomarker for disease modification claims**
  - Tau or P-Tau –further clinical qualification needed

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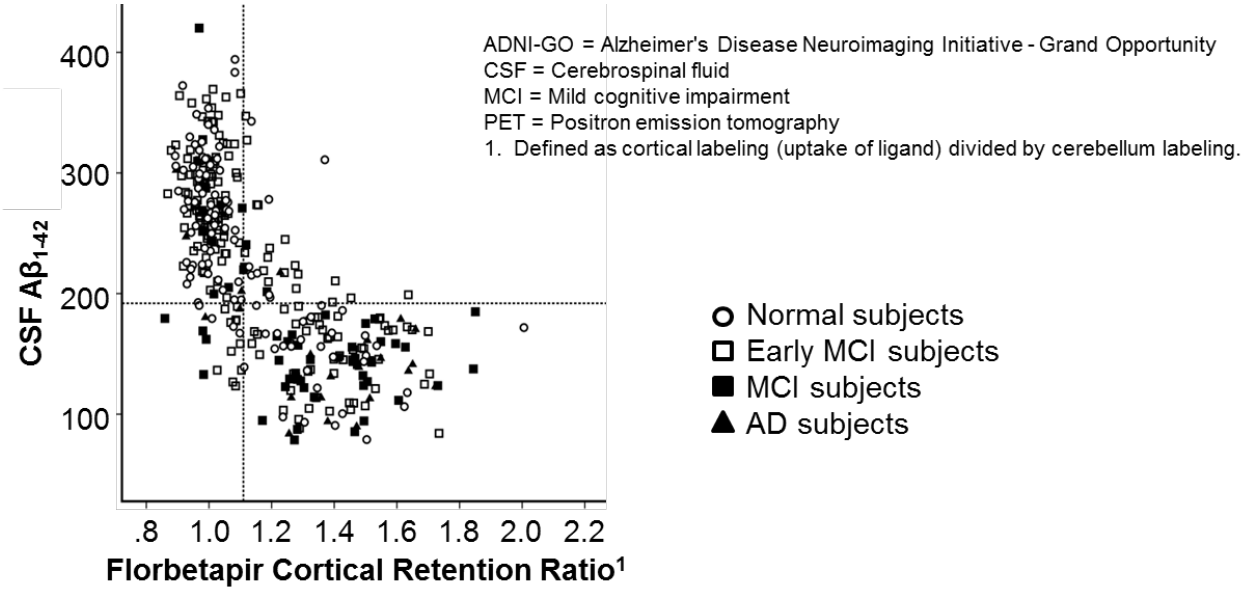
Inter-changeable Use of CSF Biomarkers & Amyloid PET for Enrichment

EMA Discussion Paper: "For the time being it's not clear whether CSF and PET amyloid biomarkers are interchangeable……"

Florbetapir Amyloid PET & CSF $A\beta_{42}$ relationship

374 recently-recruited ADNI-GO/2 subjects

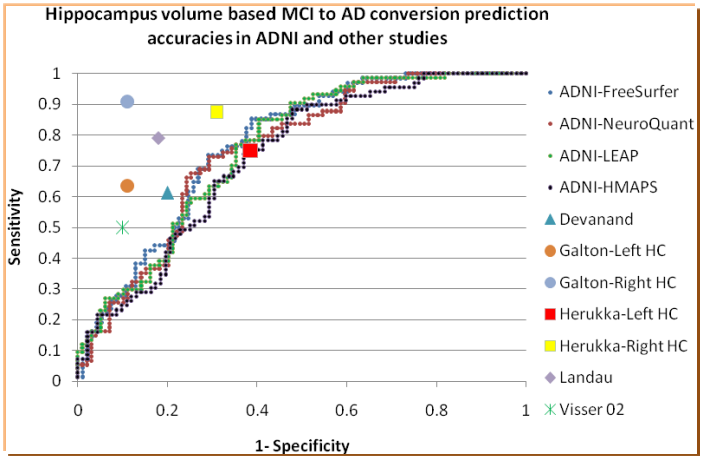


ADNI-2 data kindly provided by Susan Landau, Les Shaw and Bill Jagust.

- ***Concordance CSF/PET has consistently been shown to be >85%***
  - ***Key comparison Visual Read on Amyloid PET & CSF assay cut point***

Hippocampal Volumetric (HCV) MRI as Diagnostic for MCI to AD Conversion

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



EMA/CHMP/SAWP/809208/2011H, 17 November 2011
Hill et al., Alzheimer's & Dementia 10 (2014) 421–429

- **Lower entry barriers c.f. CSF/Amyloid PET**
  - High availability of clinical MRI, reasonable cost
- **Low uptake for primary enrichment**
  - Anti-amyloid therapy trials favor Amyloid PET or CSF $A\beta_{42}$
  - vMRI concordance with other Biomarkers?
  - Stacking of biomarkers - further screening failure?
- **High uptake as supportive Outcome measure (Disease Modification)**
  - HCV remains to show effect in the "right" direction

Other Emerging "Diagnostic" Biomarkers

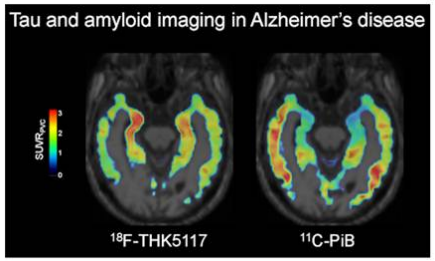


Image courtesy of SNMMI.

- **Tau PET Imaging**
  - Ligands in development (patient studies)
  - Potential to refine disease staging (Braak stages)
  - Potential to re-define role of tau in early stage disease
  - Potential to support clinical diagnosis (differential diagnosis)
- **CSF Biomarkers** (beyond Aβ and tau)
  - Oligomeric Aβ, TDP-43, VILIP1, NFL, α-synuclein (differential diagnosis).. etc.
- **Blood Biomarkers** (beyond genetics/ApoE)
  - High potential, possible use as tier 1 profile biomarker
  - Many kinds of analytes – single of multiplex
  - Commonly high sensitivity, while challenges with specificity
- **Retinal imaging**
  - Development of high resolution/sensitive techniques - Optical Coherence tomography etc.
  - Fluorescence imaging of amyloid
- **Physiological tests**
  - Olfactory function (hyposmia), pupillary diameter etc.

Key regulatory questions (1/3)

- **Is the agency accepting that well established Research Use Only (RUO) CSF $A\beta_{42}$ assays can be used for "enrichment" in trials?**

EFPIA believes that

- **established RUO assays of $A\beta_{42}$ (Innotest $A\beta_{1\text{-}42}$ and Inno-BIA AlzBio3) have sufficient performance characteristics and adequately established cut points**
  - Using centralized lab analysis
- **established RUO $A\beta_{42}$, assays permit bridging to emerging Accuracy-based and IUO / IVD Precision-based assays**

- *EMA Discussion paper: ".it is strongly advised to measure not only Aβ1-42 but also T-Tau or P-Tau levels…"*
  - EFPIA agrees that measuring Tau & p-tau is important as supportive predictive biomarkers
  - Measurements of Tau species should not form the basis for trial enrichment until Accuracy-based or IUO assays are available for those analytes

Key regulatory questions (2/3)

EMA Discussion Paper: "For the time being it's not clear whether CSF and PET amyloid biomarkers are interchangeable ……"

- **Could the agency revise its position and accept inter-changeable use of biomarker products and modalities for "enrichment" of trial subjects?**

EFPIA's believes that

- **amyloid biomarkers do no need additional within trial validation**
  - **available data support interchangeable use of approved Amyloid PET products**
  - **Amyloid PET and CSF Biomarkers show sufficient concordance for either/or enrichment**
    - **without need for using PET and CSF in largely overlapping populations**

➢*EFPIA also proposes that the drug product Labeling language should reflect the pathology identified (evidence of amyloid pathology) rather than the specific biomarker modality used (e.g. Amyloid PET)*

Key regulatory questions (3/3)

- **Is the agency accepting bridging strategies for Standard of Truth validation of further "stand alone" diagnostics that identify a specific molecular pathology (e.g. amyloid pathology)?**

EFPIA proposes that

- **clinical and biomarker phenotypes are better suited as Standard of Truth for new biomarkers, if a high level of concordance is found between the new biomarker compared to an "established" biomarker** (previously characterized using neuropathology data)
- **sufficient data are available permitting using Amyloid PET as "standard of truth" for validation of CSF$A\beta_{42}$ emerging CSF IVD products**

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