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FDA Advisory Committee Meeting

Peripheral and Central Nervous System Drugs

**Design of Phase 3 Diagnostic Imaging
Studies in Alzheimer's Disease**

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Introduction and Overview

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Introduction

- A definite diagnosis of AD requires histopathology, i.e. β -amyloid plaque deposition in the brain
- There are currently no diagnostic tools widely available that permit non-invasive, *in vivo* visualization of this underlying pathology
- Bayer is developing the ^{18}F -labeled tracer BAY 94-9172 (AV1/ZK) to detect β -amyloid



Introduction

- The goal of the development is to confirm that β -amyloid can be reliably detected
- Knowledge about the presence of β -amyloid is clinically meaningful
- Proposed indication:
“BAY 94-9172 can detect β -amyloid plaque deposition in the brain, and thereby assist the physician in the diagnosis (exclusion/detection) of Alzheimer’s Disease”



Introduction

- The following aspects of the phase 3 study design to support a pathology indication will be addressed:
 - Clinical Usefulness
 - Standard of Truth
 - Study Population



Presentation Outline

- Clinical Usefulness of Imaging β -Amyloid

Kenneth Marek, M.D.

Director, Institute for Neurodegenerative Disorders, Yale University Medical School

- Clinical Program:
Standard of Truth and Phase 3 Design

Cornelia Reiningger, M.D., Ph.D.

Director, Global Clinical Development, Bayer HealthCare Pharmaceuticals



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Clinical Usefulness of β -Amyloid Imaging

Kenneth Marek, M.D.

**Director, Institute for Neurodegenerative
Disorders, Yale University Medical School**

Clinical Usefulness

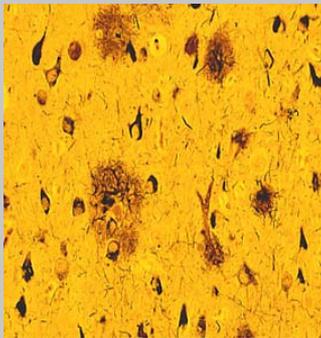
- Current clinical diagnosis of AD
- Additional diagnostic tools
- β -amyloid deposition in the brain
- Clinical implications of β -amyloid imaging



Current Clinical Diagnosis of AD

Definite diagnosis

- relies on neuro-histopathology
- requires presence of β -amyloid peptides and neurofibrillary tangles in the brain



Clinical diagnosis

- is based on comprehensive clinical and neuropsychiatric examination, medical history, laboratory, and medical imaging
- is best established using the

DSM IV-TR

Diagnostic and
Statistical Manual of
Mental Disorders IV
Edition

NINCDS-ADRDA

National Institute of
Neurological,
Communicative
Disorders and Stroke
recommended criteria

[McKhann et al, 1984]



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Current Challenges of Diagnosis

- A meta-analysis comparing the clinical diagnosis of AD versus post mortem findings reported [Knopman et al, 2001]:
 - mean sensitivity = 81% (range 49% to 100%)
 - mean specificity = 70% (range from 47% to 100%)
- Variance across centers was considerable and – in particular – specificity was marginal to suboptimal
- Dementia subjects may first be seen by a local neurologist/geriatrician and not by a specialist
- This underscores the need for tools that can increase the overall diagnostic accuracy



Additional Diagnostic Tools

- Since the NINCDS-ADRDA were originally proposed in 1984 knowledge of the biology of AD has greatly advanced
- Additional diagnostic tools now exist and are still under investigation
 - CSF biomarkers
 - Volumetric MRI
 - FDG PET
 - β -amyloid PET

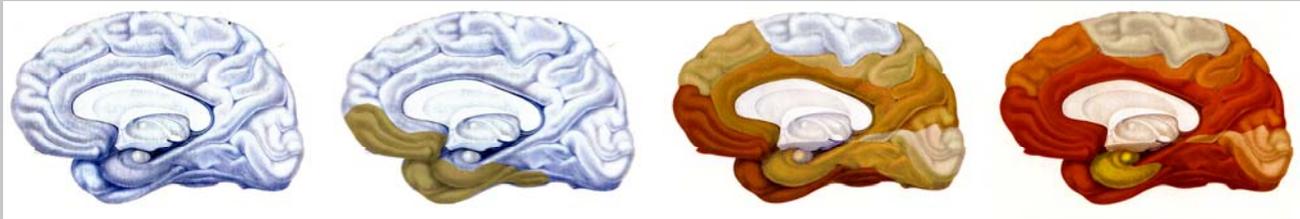


Additional Diagnostic Tools

- The NINCDS-ADRDA have fallen behind this scientific growth and revised criteria have been proposed [Dubois et al, 2007]
- Suggested revisions consider these tools to be complementary and all aimed at increasing diagnostic specificity
- Among these biomarkers, β -amyloid-targeted imaging is the only method that can delineate underlying disease pathology in AD



β -Amyloid Deposition in the Brain



Stages/Phases of β -Amyloid deposition in AD
Braak et al. 1997

- Is a hallmark of AD in all stages and an important component of the definition of AD
- Develops early on in the disease process
- Is not a typical feature in Fronto-Temporal Lobar Degeneration (FTLD)
- Sometimes detected in clinically healthy elderly individuals



Evidence that BAY 94-9172 Binds Specifically to β -Amyloid Deposits

- Preclinical data [*Zhang et al., Nucl Med Biol, 2005*]
 - High-affinity selective binding *in vitro* to β -amyloid in human post-mortem tissue
 - *Ex vivo* β -amyloid plaque labeling in a transgenic mouse model for AD
- First clinical data indicate differences in cortical uptake in subjects with AD compared to healthy subjects

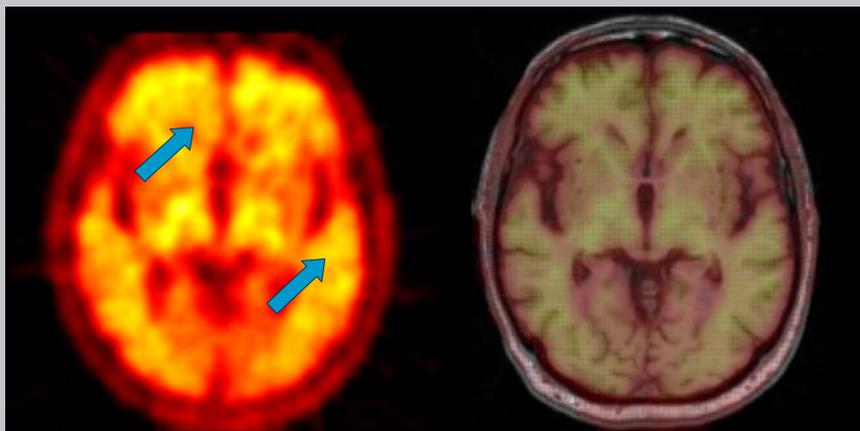
[*Rowe et al., Lancet Neurology, 2008*],
[*Barthel et al., Abstract SNM, 2008*]



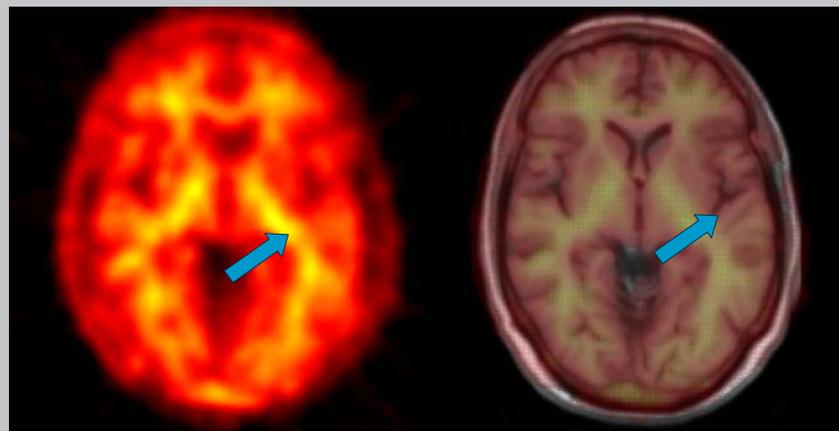
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Typical BAY 94-9172 PET Images

Alzheimer's Disease patient



Elderly control subject



100%

- Easily interpretable
- Hot-spot imaging
- Co-registration / structural correlation

%0

Barthel et al., J Nucl Med, 2008



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Clinical Usefulness: Pathology Detection

- Provides an *in vivo* detection of underlying pathology in AD – that in itself is clinically useful
- Provides valuable information that can enhance our understanding of the disease mechanism
- The absence of the pathology makes the diagnosis of AD highly unlikely



Clinical Usefulness: Pathology Detection

Example 1: Fronto-Temporal Lobar Degeneration (FTLD)

- The diagnostic process to accurately diagnose FTLD is difficult
- Clinical AD can mimic FTLD
- Treatment and prognosis of FTLD differs considerably from that of AD, diagnostic tools to assist differential diagnosis are thus of high medical need
- A negative scan can exclude AD and makes FTLD more likely



Clinical Usefulness: Pathology Detection

Example 2: Depression in the Elderly

- AD is frequently associated with depressive symptoms
- Severe depression can be associated with cognitive impairment
- Treatment and prognosis differ considerably
- Differential diagnosis can be difficult even for an experienced physician
- A negative scan can assist in the diagnosis of depression and rule out AD



Clinical Usefulness: Improved Diagnosis

- This should provide the physicians with a non-invasive imaging tool to expedite referral to specialty clinics
- Decreased time to diagnosis and treatment
 - May provide long-term reduction in disability
 - Avoid inappropriate therapy
- Provides patient and family with additional diagnostic certainty
 - Improved quality of life/anxiety reduction
 - Optimal disease management and planning



Clinical Usefulness: Future Potential

- Wide spread availability will fulfill an unmet clinical need
- Might assist prediction of patients progressing from MCI to AD
- Would support drug development of β -amyloid targeted therapies



Clinical Usefulness of β -Amyloid Imaging

- Currently around 5.0 million cases of AD in the US, this number is expected to increase to 11-16 million in 2050*
- 10-20% of all AD subjects are clinically misdiagnosed
- The potential of a PET scan to rule out AD is of major clinical value

* "Alzheimer's Disease Facts and Figures", Report Alzheimer's Association, 2008



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Clinical Development: Standard of Truth and Phase 3 Design

Cornelia Reiningger, M.D., Ph.D.

**Director, Global Clinical Development
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Phase 3 Clinical Development Proposal

- Standard of Truth
- Proposed Indication
- Phase 3 Study Design
 - Primary Efficacy Population
 - Secondary Efficacy Population
 - Methodology
 - PET Image Evaluation
 - Study Flow Chart



General Considerations for Standard of Truth

- The choice of an appropriate Standard of Truth (SOT) for the pivotal program is critical
- The following guiding principles were considered for choice of the SOT in the phase 3 trial:
 - Be prospectively validated
 - Be widely available
 - Not include any test results obtained with the medical imaging agent under investigation



Standard of Truth

- The definite diagnosis of AD requires histopathological verification
 - Post-mortem autopsy is generally not feasible in the setting of larger phase 3 clinical trials
- No other single diagnostic test meets the criteria of an ideal SOT
- Instead, an appropriate combination of validated tests may be used as a surrogate standard if known to provide a good approximation to the true disease state



Phase 3: Standard of Truth

The clinical diagnosis (i.e. the standard of truth) will be:

Based on a standardized and comprehensive clinical and neuropsychiatric examination (medical history, validated psychometric tests, laboratory values and MRI)

Based on widely accepted and validated (post-mortem) diagnostic criteria: NINCDS-ADRDA and DSM IV-TR

Established by a consensus panel of experts (adjudication committee)

- The consensus panel will be experts in the field of dementia



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Proposed Indication

- β -amyloid plaque deposition is a hallmark of AD
- Absence of β -amyloid makes AD unlikely
- The proposed indication:

The PET tracer can detect β -amyloid plaque deposition in the brain, and thereby assist the physician in the diagnosis (exclusion/detection) of Alzheimer's Disease



Phase 3 Design: Patient Population

- Open-label, multi-center, non-randomized, single dose study to determine diagnostic efficacy in approx. 450-600 subjects
- Primary efficacy population:
 - Probable AD subjects
 - Healthy volunteers
- Secondary efficacy population:
 - Other dementia subtypes like FTLD, DLB, VaD
- Tracer uptake reflects β -amyloid deposition



Primary Efficacy Population

Positive controls:

Individuals with a high probability of tracer uptake:
probable AD patients

$$\text{Sensitivity} = \frac{\text{Subjects with positive Scan}}{\text{Subjects with diagnosis of probable AD}}$$

Negative controls:

Individuals with a low probability of tracer uptake:
healthy volunteers

$$\text{Specificity} = \frac{\text{Subjects with a negative Scan}}{\text{Verified healthy volunteers}}$$



Phase 3 – Efficacy Endpoints

- **Co-primary efficacy endpoints:**

- Sensitivity and specificity of the independent visual assessment in differentiating between subjects with probable AD and healthy volunteers

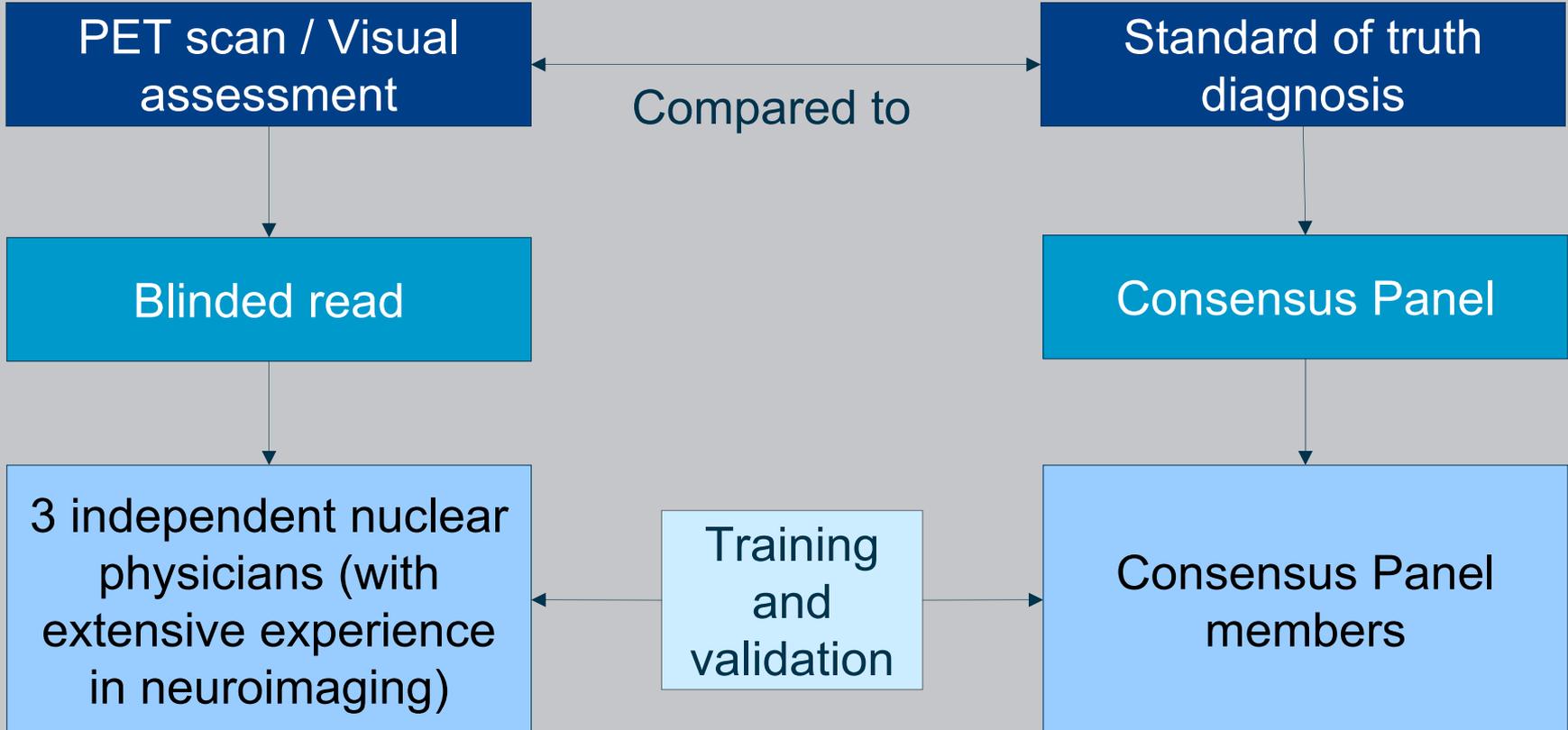
- **Major secondary endpoints:**

- Sensitivity and specificity of quantitative image analysis in differentiating between subjects with probable AD and healthy volunteers
- Descriptive analysis of tracer up-take pattern in other dementia subtypes



Efficacy Evaluation: Methodology

For determination of diagnostic efficacy the following components are compared:

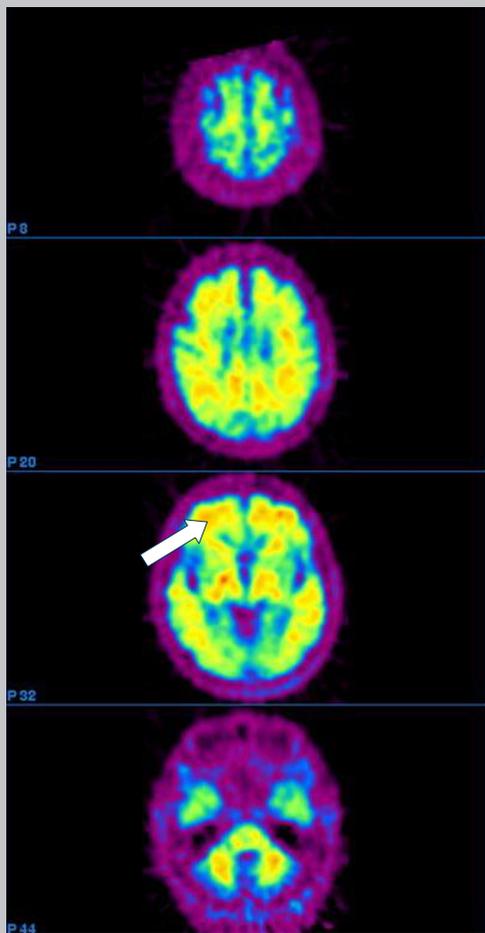


Efficacy Evaluation: Methodology

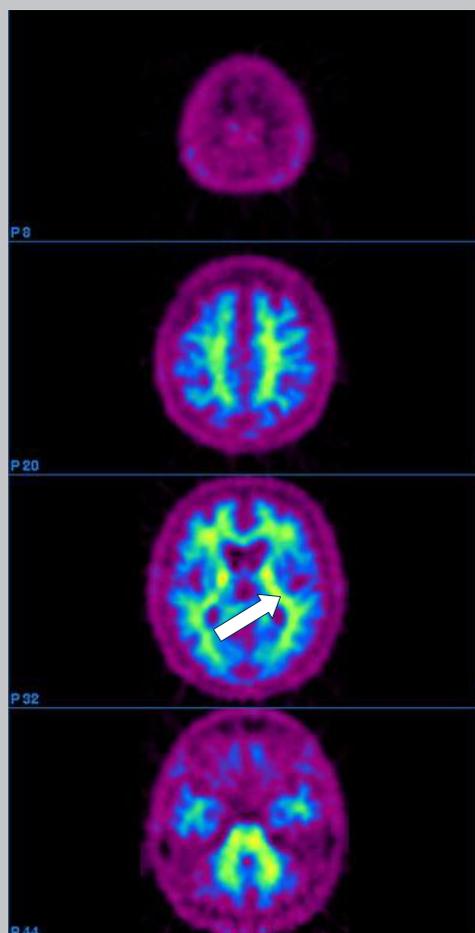
- Visual assessment of the degree of tracer uptake in pre-specified cortical brain regions
- Binary categorization of the scan:
 - based on the total regional scores
 - into positive and negative
- Evaluation of the procedure is ongoing



Example of β -Amyloid PET Scans



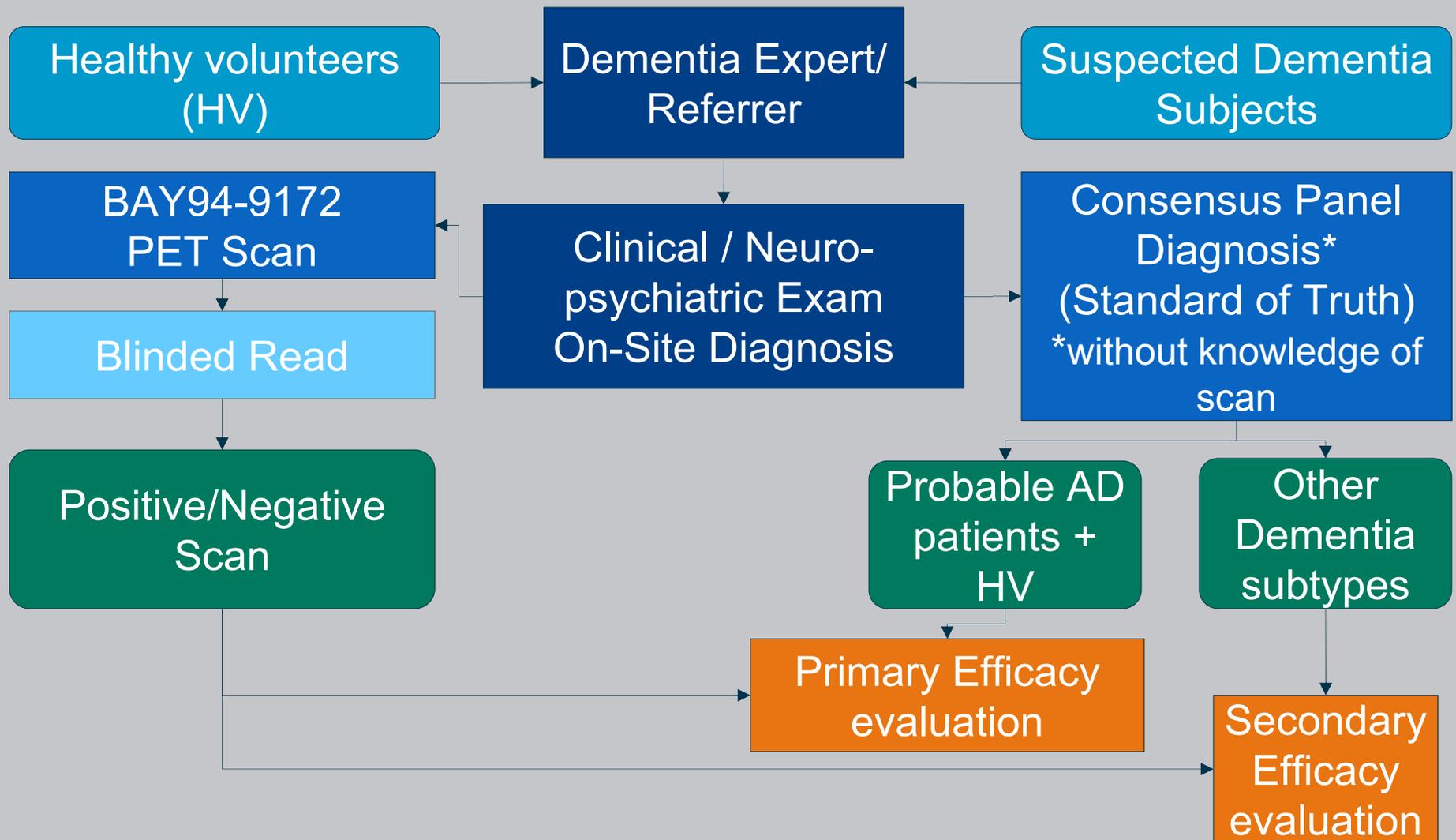
Positive Scan



Negative Scan

Barthel et al., J Nucl Med, 2008

Phase 3 Study Flow Chart



Conclusions

- β -amyloid PET imaging is a non-invasive tool for *in vivo* visualization of AD pathology – therein lies its usefulness
- The suggested SOT is a research standard that provides:
 - An appropriate surrogate for histopathology
 - The best approximation of the disease state
 - The best surrogate for β -amyloid pathology
- The phase 3 design facilitates a rigorous verification of diagnostic efficacy, thus supporting the proposed indication



Outlook

- Availability of β -amyloid PET imaging will lead to a better understanding of disease mechanisms in dementia
- In addition to the current pathology detection focus, our long-term approach includes the demonstration of efficacy for:
 - Disease prediction (i.e., conversion of MCI to AD)
 - Disease progression (i.e., for therapy monitoring)





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Thank you for your attention

