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La Cité-Nantes

3es JFMN
Journées
Francophones de
Médecine Nucléaire

Impact de la TEP au Florbetaben sur le diagnostic et la prise en charge de patients éligibles à une analyse du LCR pour une suspicion de maladie d'Alzheimer

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F. Pasquier, F. Semah, B. Dubois, M.-O. Habert, D. Hannequin, M. Chastan,
NEUUS in AD study group, A. Stephens, M. Ceccaldi

Service de Biophysique et Médecine Nucléaire & DHU-Imaging, CHU Timone, Marseille

…

FCMRR

DHU Imaging

neuus in AD

Neuraceq Utility Study in Alzheimer Disease

Piramal
knowledge action care

Disclosure

Consultant: *GE Healthcare, Lilly, **Piramal***

Research & clinical trials: *Eisaï, Pfizer, Sanofi, Lilly, Novartis, Roche, MSD, Biogen*

Introduction

- In daily practice Alzheimer's disease (AD) is not easily diagnosed in patients presenting with **complex clinical presentations** (atypical clinical profiles, eg non amnestic – aphasic, visual… – profiles, early onset dementia…)

- **AD-specific biomarkers** can be measured:
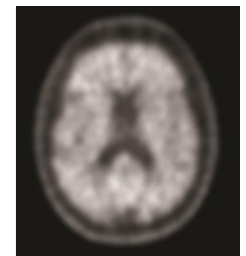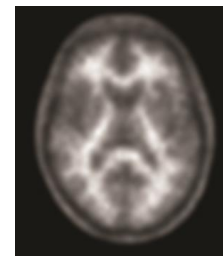 - indirectly by assessing Aβ42, T tau and PH tau levels in cerebrospinal fluid (CSF)
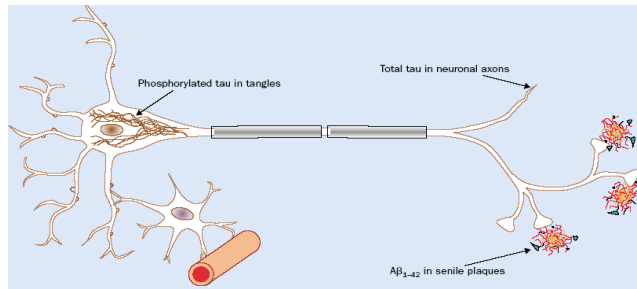
  T-tau ⬆

  P-tau ⬆

  Aß1-42 ⬇

  from Blennow & Hampel, Lancet Neurol. 2003 Oct;2(10):605-13.

  - directly through positron emission tomography (PET) using amyloid-specific ligands

  Florbetaben (18F) / NeuraCeq™

The French Clinical Practice

HAS
HAUTE AUTORITÉ DE SANTÉ

Maladie d'Alzheimer
et maladies apparentées :
diagnostic et prise en charge

- **HAS recommends the use of LP in clinical practice in complex or atypical clinical presentations** http://www.has-sante.fr
- **Measuring CSF biomarkers of AD** is recommended in case of **diagnostic uncertainty**, particularly in young patients

Who Needs Cerebrospinal Biomarkers?
A National Survey in Clinical Practice

Anne Cécile Troussière[a,1], David Wallon[b,1], François Mouton-Liger[c,d,e,1], Rachida Yatimi[f], Philippe Robert[f], Jacques Hugon[c,d,g], Didier Hannequin[b], Florence Pasquier[a] and Claire Paquet[c,d,g,*]
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[c]INSERM U942, Paris, France
[d]Department of Histology, Lariboisière Fernand Widal Saint Louis Hospital, APHP, University of Paris Diderot, Paris, France
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[g]Research Memory Center, Lariboisière FW Saint-Louis Hospital, APHP, University of Paris Diderot, Paris, France

Indications of CSF AD biomarker prescriptions, n (%)	Research memory center n = 65
Atypical dementia	63 (96.9)
Doubtful cases	59 (90.7)
MCI	42 (64.6)
Systematically for AD	5 (0.07)
Systematically for MCI	11 (16.9)
At the request of the patient	9 (13.8)
Clinical Research	49 (75.3)
Others	26 (40)
Referred by a colleague for CSF AD biomarkers	13 (20)

Journal of Alzheimer's Disease 40 (2014) 857–861

- **The use of CSF biomarkers has long been part of routine clinical practice of French CMRR to differentiate AD from non-AD aetiologies in atypical dementia and doubtful cases**

The French Clinical Practice

- **In few cases CSF analysis**
  - **may be uninterpretable for technical reasons**
  - **may not be feasible**
    - refusal
    - contraindications
  - **may be considered as "non-contributory" by the clinician**
    - ambiguous CSF result
      - values close to threshold
      - or only one or two abnormal biomarkers out of three
    - CSF result inconsistent with clinical information

  ➤ **a collaborative work**

- implemented in the **French clinical practice setting**
- between **French tertiary memory clinics** (FCMRR), **Nuc Med Dpts** and **Piramal**
- in order to investigate the **impact of florbetaben amyloid PET on diagnosis and management** in these patients

neuus in AD

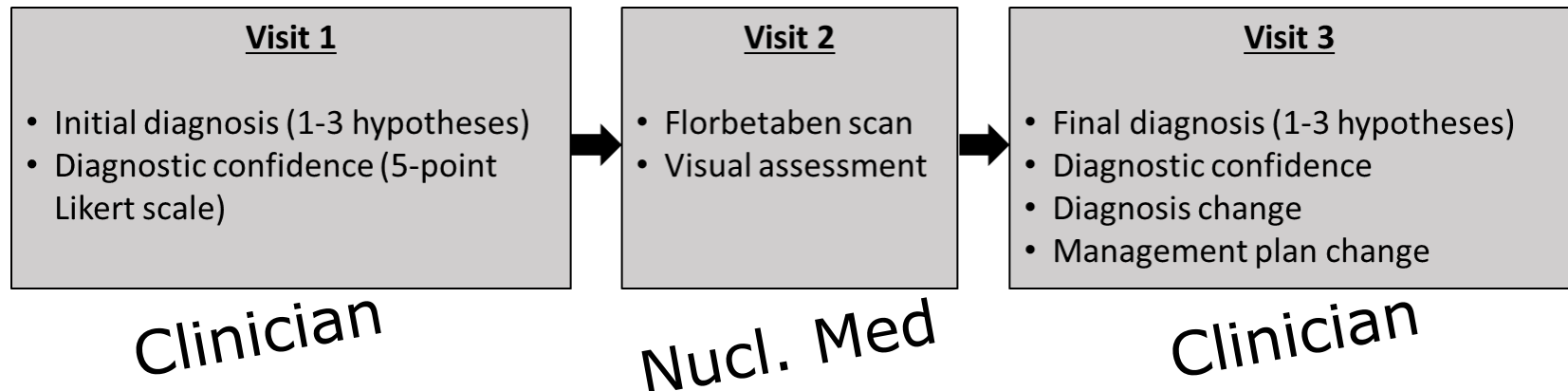## Neuraceq Utility Study in Alzheimer Disease

- Phase 4 multicentre open-label study (ClinicalTrials.gov: NCT02681172)
- conducted in the outpatient setting of 19 CMRR
  - approval from Institutional Review Boards or Independent Ethics Committees
  - in accordance with the Declaration of Helsinki and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines

Objective

- This study was designed to **evaluate the potential impact of use of Florbetaben PET scan in diagnosis and management of patients for whom CSF examination was planned _but_ was not performed or was considered as non-contributory:**
  - **change in clinical diagnosis** made by clinicians in patients in whom a Florbetaben PET scan was performed
  - **increase in clinician diagnosis confidence** for these patients after use of Florbetaben PET scan
  - **change in management of the patient**

Methods

- Population
  - Patients being evaluated for AD, but aetiology of symptoms unexplained after a complete diagnostic work up
  - Patients were eligible if lumbar puncture (LP) and CSF examination were planned but
    1. results of CSF analysis were considered as non-contributory; or
    2. LP was refused by the patient; or
    3. LP was not feasible for medical reasons
- Outpatient setting of 19 centres of the network of French tertiary memory clinics (CMRR)

Visit 1	Visit 2	Visit 3
• Initial diagnosis (1-3 hypotheses) • Diagnostic confidence (5-point Likert scale)	• Florbetaben scan • Visual assessment	• Final diagnosis (1-3 hypotheses) • Diagnostic confidence • Diagnosis change • Management plan change
Clinician	Nucl. Med	Clinician

Population

{Neuus in AD

Neuraceq Utility Study in Alzheimer Disease}

Patient demographics	n=205
Age (years), mean ± SD (median)	70.9 ± 9.7 (71.0)
Gender, n (%)	
Male	103 (50.2)
Female	102 (49.8)
MMSE score, mean ± SD (median)	22.1 ± 5.1 (23.0)
Underwent lumbar puncture, n (%)	**87** (42.4)
Ambiguous CSF result	71 (34.6)
CSF result inconsistent with clinical information	16 (7.8)
Uninterpretable CSF result for technical reasons	4 (2.0)
Did not undergo lumbar puncture, n (%)	**118** (57.6)
Patient refusal	75 (36.6)
Contraindicated or failed	45 (22.0)

The full study cohort included 205 patients, of whom 42.4% (n=87) underwent LP, but results were considered as "not contributory" by the expert clinician.

Diagnosis prior scan

| Diagnosis (probability level 1),* n (%)	Prior scan n=205[†]
AD dementia	**148 (72.2)**
Sporadic AD, atypical form	67 (32.7)
Early-onset AD	50 (24.4)
Sporadic AD, typical form	27 (13.2)
Rapid progressive AD (CJD excluded)	4 (2.0)
Non-AD dementia (neurodegenerative)	**32 (15.6)**
Fronto-temporal lobar dementia	14 (6.8)
Primary progressive aphasia	8 (3.9)
Lewy body disease	7 (3.4)
Cortico-basal dementia	2 (1.0)
Semantic dementia	1 (0.5)
Parkinson's disease	-
Mixed dementia	**17 (8.3)**
Non-neurodegenerative dementia	**10 (4.9)**
Psychiatric disorders	3 (1.5)
Vascular dementia	2 (1.0)
Other	5 (2.4)

*Clinicians could report up to three possible diagnoses for each patient and indicate the probability by rank order. Level 1 was defined as the most probable of up to three potential hypotheses; [†]Two patients had two level 1 diagnoses with equal probability
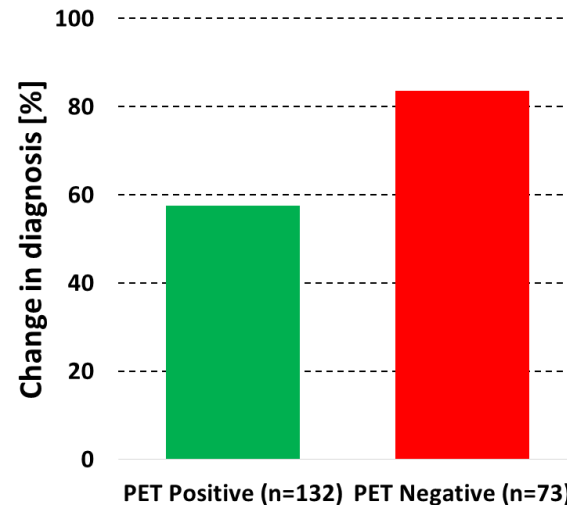
Change in diagnosis

- **Florbetaben-PET status**
  - PET negative n=73
  - PET positive n=132

- **Change of diagnosis** after florbetaben imaging reported in:
  - 67% (137/205) of cases, independently of amyloid status
  - 58% (76/132) of positive amyloid cases
  - 84% (61/73) of negative amyloid cases
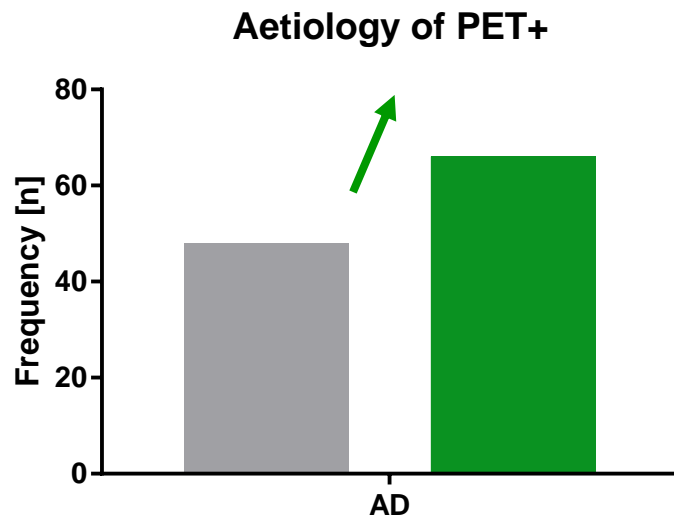
Florbetaben PET status

Negative (n=73) 36%

Positive (n=132) 64%

Diagnosis Change

Change in diagnosis [%]

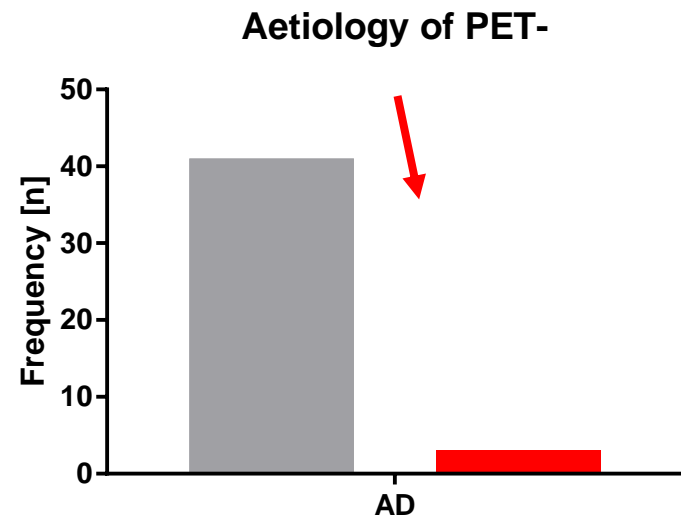PET Positive (n=132)   PET Negative (n=73)
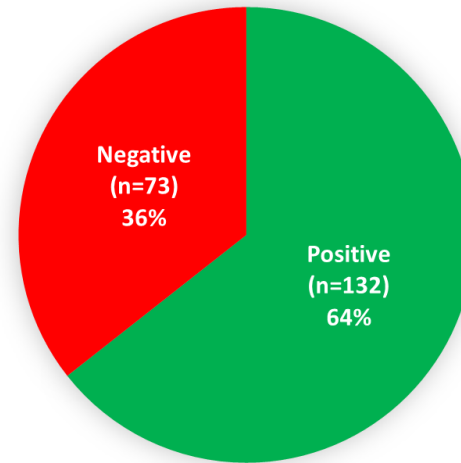
Aetiology of patients with a changed diagnosis

- Of 67% (137/205) patients with a changed diagnosis:
  76 PET+ and 61 PET-

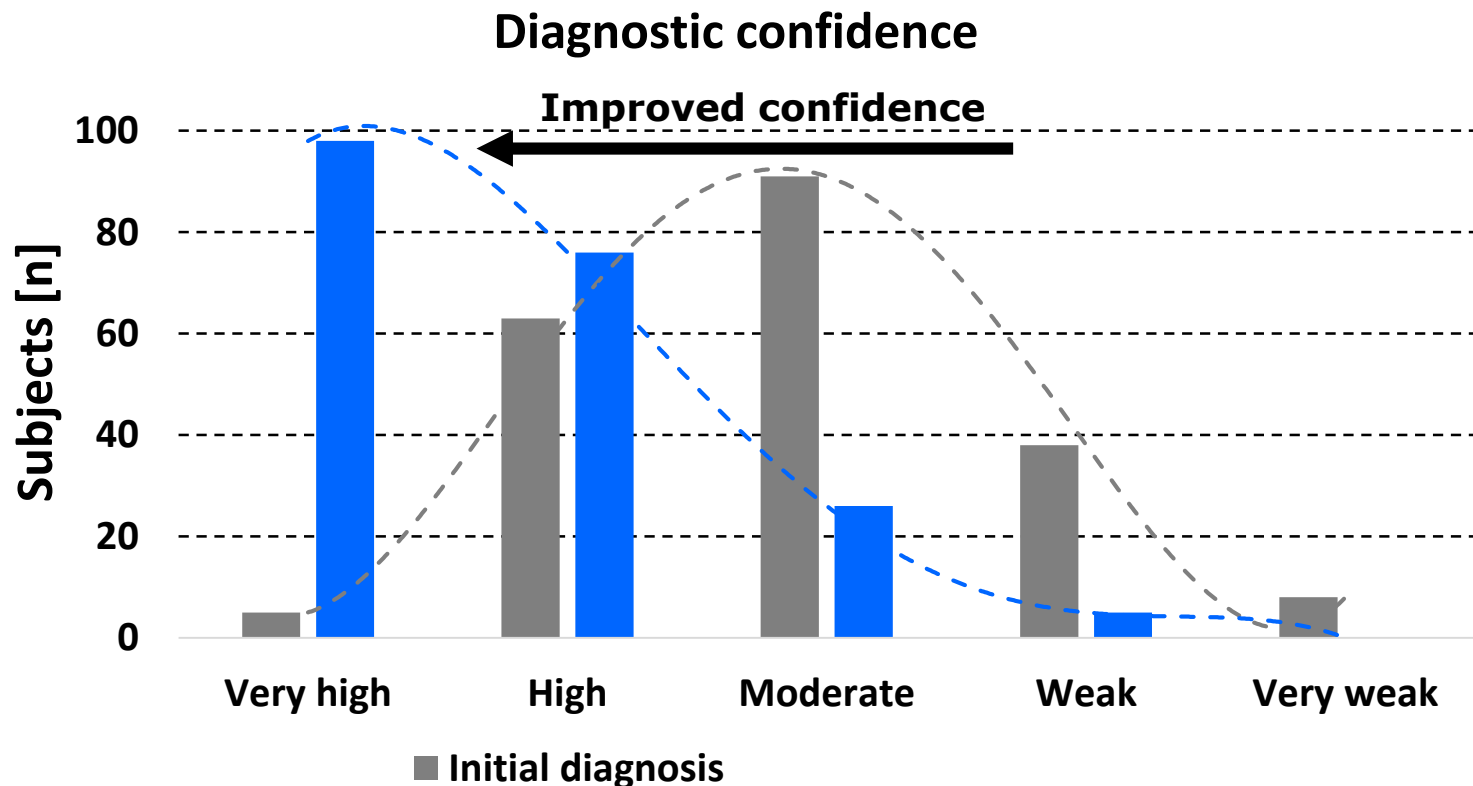Prior florbetaben: 63% (48/76) AD
Post florbetaben: 87% (66/76) AD

Prior florbetaben: 67% (41/61) AD
Post florbetaben: 5% (3/61) AD

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Florbetaben improved diagnostic confidence

- Confidence at initial diagnosis was moderate
- Improved confidence reported for 81% (167/205) of patients after disclosure of florbetaben results and re-assessment

Diagnostic confidence

Improved confidence

Subjects [n] (y-axis: 0, 20, 40, 60, 80, 100)

Categories: Very high, High, Moderate, Weak, Very weak

■ Initial diagnosis

Change in Management

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Neuraceq Utility Study in Alzheimer Disease

- <u>Change of management</u> after florbetaben imaging reported in:
  - 80% (164/205), independently of amyloid status
    - o 80% (106/132) of positive amyloid cases
    - o 80% (58/73) of negative amyloid cases
    - o 51% (104/205) of patients had initiation or withdrawal of medication, additional diagnostic tests, or referral to another specialist

Management Changes by PET result
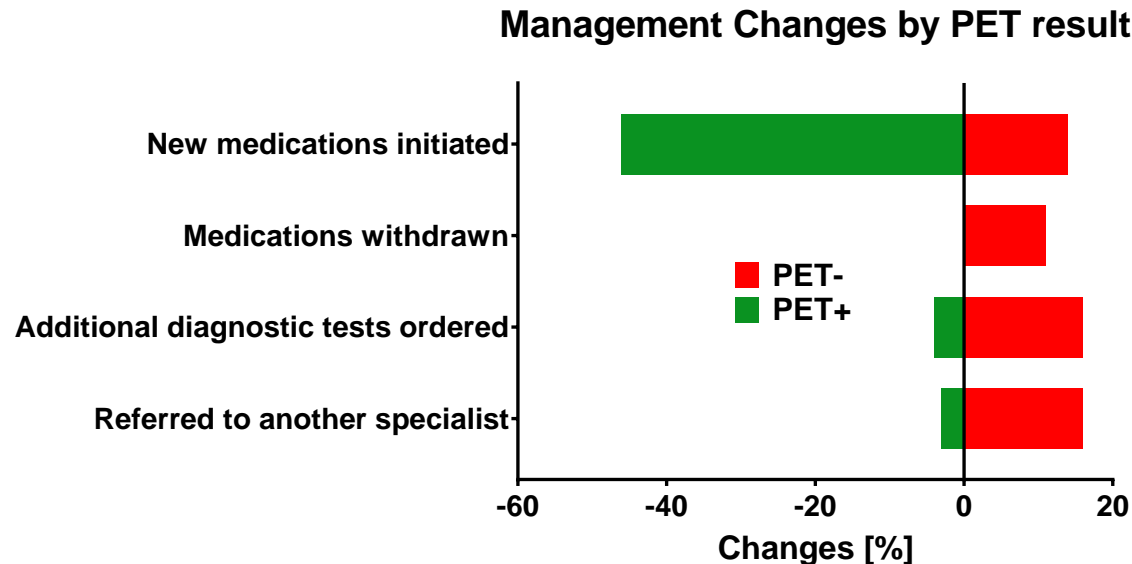
Assessment of the Incremental Diagnostic Value of Florbetapir F 18 Imaging in Patients With Cognitive Impairment
## The Incremental Diagnostic Value of Amyloid PET With [18F]-Florbetapir (INDIA-FBP) Study

Marina Boccardi, PhD; Daniele Altomare, MS; Clarissa Ferrari, PhD; Cristina Festari, MS; Ugo Paolo Guerra, MD; Barbara Paghera, MD;
Claudio Pizzocaro, MD; Giulia Lussignoli, MD; Cristina Geroldi, MD; Orazio Zanetti, MD; Maria Sofia Cotelli, MD; Marinella Turla, MD; Barbara Borroni, MD;
Luca Rozzini, MD; Dario Mirabile, MD; Carlo Defanti, MD; Michele Gennuso, MD; Alessandro Prelle, MD; Simona Gentile, MD; Alessandro Morandi, MD;
Stefano Vollaro, MD; Giorgio Dalla Volta, MD; Angelo Bianchetti, MD; Marta Zaffira Conti, MD; Melania Cappuccio, MD; Pasqualina Carbone, MD;
Daniele Bellandi, MD; Luciano Abruzzi, MD; Luigi Bettoni, MD; Daniele Villani, MD; Maria Clara Raimondi, MD; Alessia Lanari, MD; Alfonso Ciccone, MD;
Emanuela Facchi, MD; Ignazio Di Fazio, MD; Renzo Rozzini, MD; Stefano Boffelli, MD; Laura Manzoni, MD; Giovanni Pietro Salvi, MD;
Sabina Cavaliere, MD; Gloria Belotti, MD; Stefano Avanzi, MD; Patrizio Pasqualetti, MS; Cristina Muscio, PhD; Alessandro Padovani, MD;
Giovanni B. Frisoni, MD; for the Incremental Diagnostic Value of Amyloid PET With [18F]-Florbetapir (INDIA-FBP) Working Group

Participants were consecutive patients receiving care at AD evaluation units for diagnosis of cognitive abnormalities and suspicion of AD. Inclusion criteria were cognitive abnormality, age between 50 and 85 years, availability of an informant (spouse, adult child, or other knowledgeable informant), and a prescan diagnostic confidence of AD between 15% and 85%.

Figure 2. Amyloid Positron Emission Tomography Result and Diagnostic Change by Prescan Diagnosis
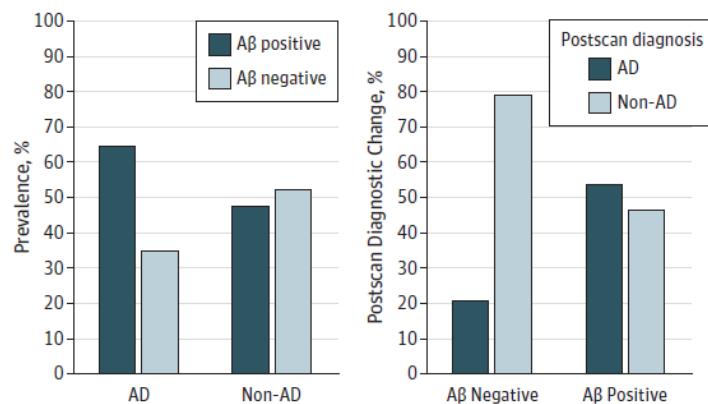
Postscan diagnostic changes occurred only in the Alzheimer disease (AD)-negative and in non-AD-positive groups.

Figure 4. Cognition-Specific and Non–Cognition-Specific Medication Prescriptions After Amyloid Positron Emission Tomography (PET)
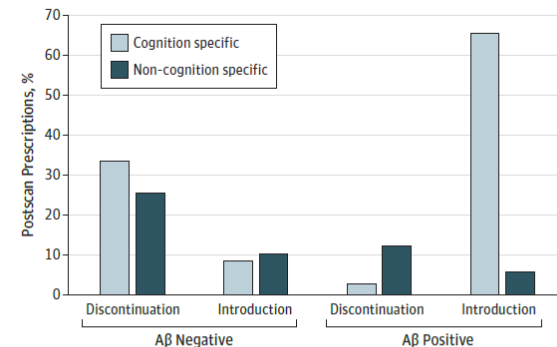
Prescriptions for cognition-specific medications (acetylcholinesterase inhibitors and memantine hydrochloride) and non–cognition-specific medications (anxiolytics, hypnotics, antidepressants, antipsychotics, and anticonvulsants) that were introduced after amyloid PET in patients who were previously not receiving the same medication or discontinued after amyloid PET in patients who were previously receiving it. All changes were significant at $P < .001$ in a 1-sample proportions test.

Alzheimer's
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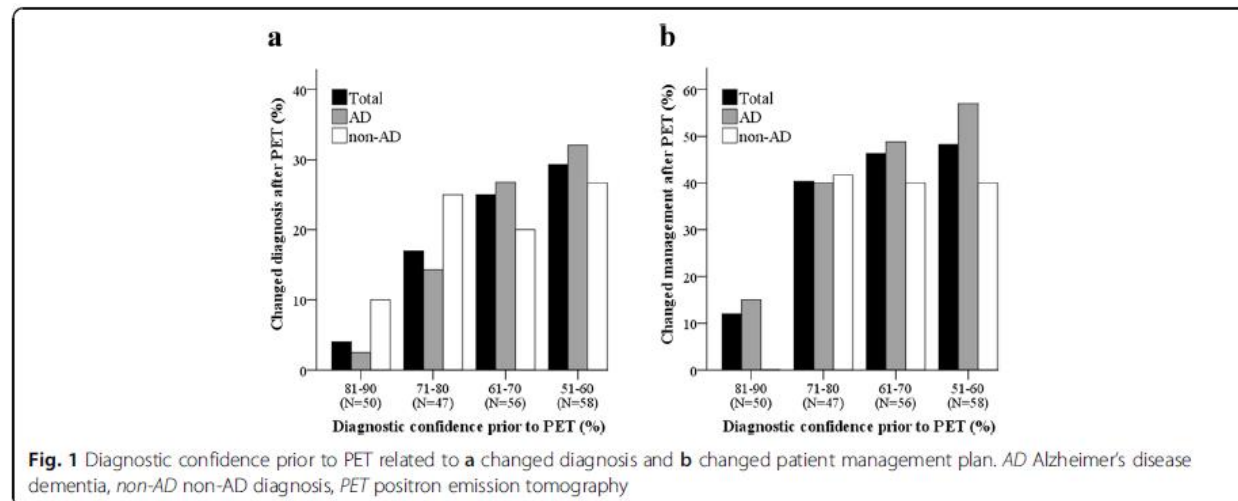
Diagnostic impact of [18F]flutemetamol PET in early-onset dementia

Marissa D. Zwan[1,2*], Femke H. Bouwman[1], Elles Konijnenberg[1], Wiesje M. van der Flier[1,3], Adriaan A. Lammertsma[2], Frans R. J. Verhey[4], Pauline Aalten[4], Bart N. M. van Berckel[2] and Philip Scheltens[1]

The present study included a consecutive series of patients visiting a Dutch tertiary memory clinic and suspected of mild dementia (defined as Mini Mental State Examination (MMSE) score ≥ 18) or early-onset dementia (defined by age at diagnosis ≤ 70 years), who had no firm diagnosis after the standardized dementia evaluation or persisting diagnostic uncertainty (defined as pre-PET diagnostic confidence < 90% as measured by a standardized study questionnaire). We excluded 17

Clinical diagnosis was established by consensus in a multidisciplinary meeting using established clinical criteria [13–17] without knowledge of PET or CSF results or APOE carrier status. Patients were divided

Fig. 1 Diagnostic confidence prior to PET related to **a** changed diagnosis and **b** changed patient management plan. *AD* Alzheimer's disease dementia, *non-AD* non-AD diagnosis, *PET* positron emission tomography

Conclusions

- This naturalistic study provides evidence that florbetaben PET has a significant diagnostic impact in patients eligible for CSF according to HAS and in whom uncertainty is particularly common (early-onset, atypical, mixed, rapidly progressing)

    - **Frequent diagnosis changes (67%)** reported, particularly for PET negative (84%)
    - **Diagnostic confidence increased for 81%** of patients, particularly for PET positive (88%)
    - **Management changes reported for 80%** of patients

- The results highlight the significant clinical utility of amyloid PET imaging for patients with complex dementia presentations in the context of the existing workup

Thanks to
the *NEUUS in AD* study group

- **Amiens** : Olivier Godefroy, Daniela Andriuta, Agnès Devendeville, Diane Dupuis, Ingrid Binot, Mélanie Barbay, Marc-Etienne Meyer, Véronique Moullard
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