中華民國核醫學學會
Society of Nuclear Medicine, Taiwan (R.O.C)

【Amyloid PET in Clinical Practice】

Amyloid PET 影像判讀及個案分享

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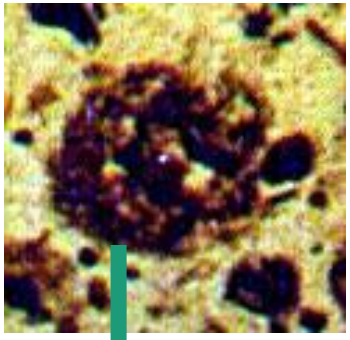
Outline

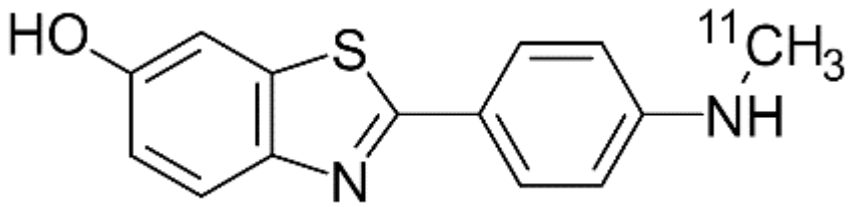
- 關於 類澱粉蛋白影像
- Clinical utility of amyloid PET
- Appropriate use criteria of amyloid PET imaging
- Take Home Message

β-amyloid and Alzheimer's disease

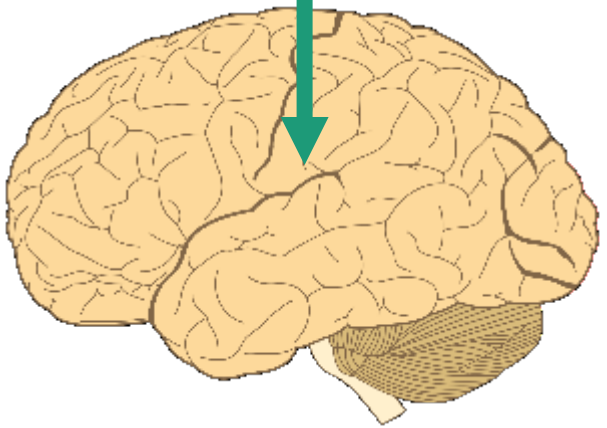
[^{11}C]Pittsburgh compound-B (PIB) PET



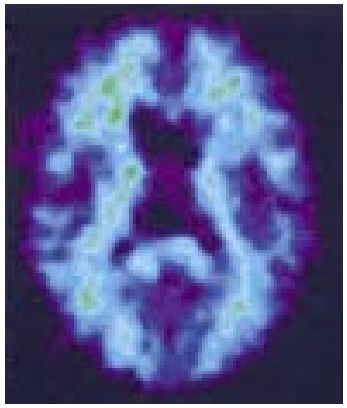
Pittsburgh Compound B (PIB), 半衰期 20 min



Amyloid PET技術發展，
使腦內類澱粉病理變化可在活體中觀察

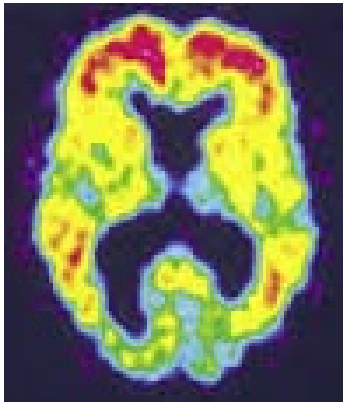


Negative



or

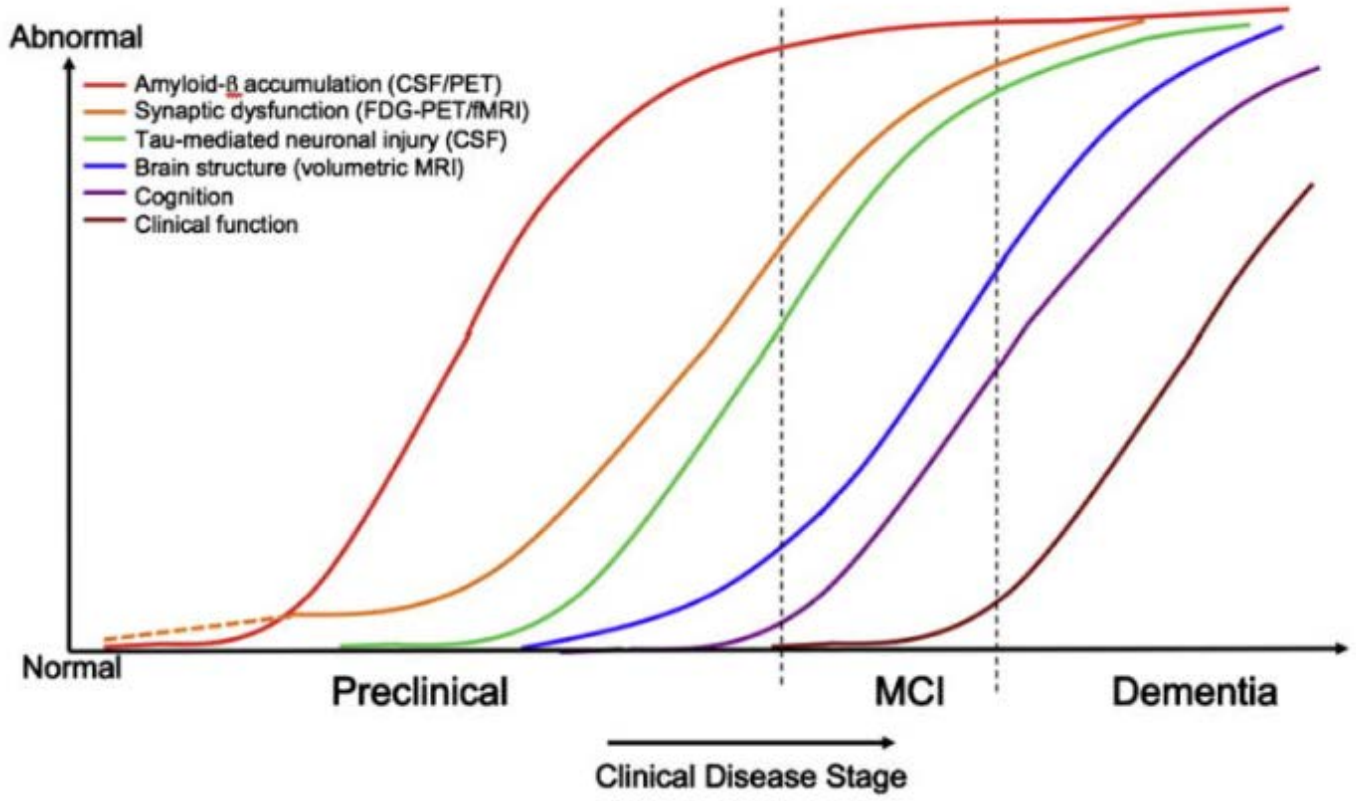
Positive



Klunk, William E., et al. "Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B." *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* 55.3 (2004): 306-319.

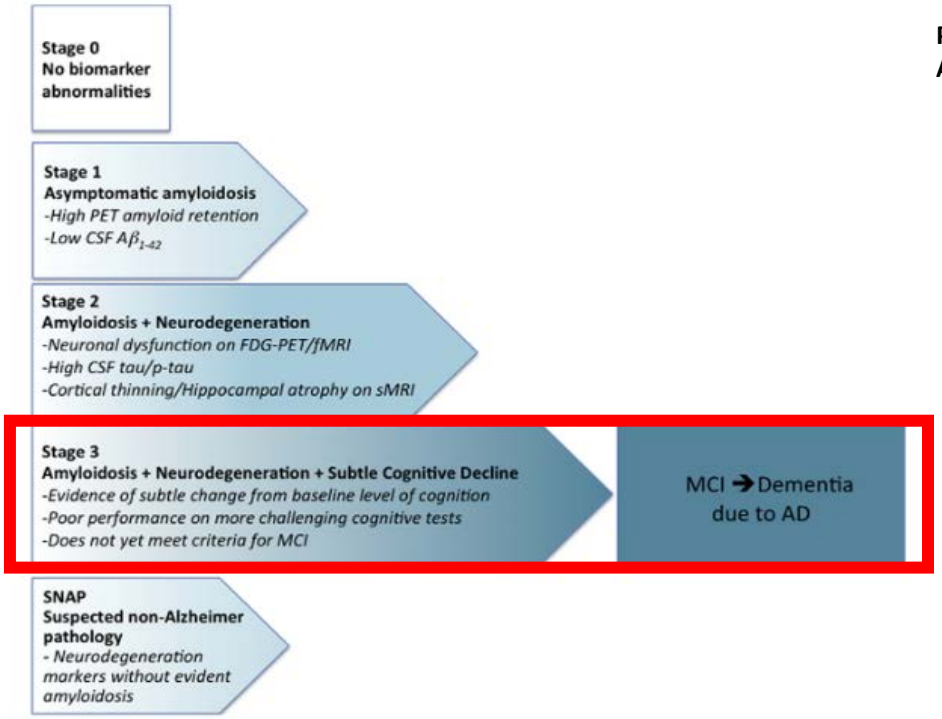
2011 NIA-AA Diagnostic Guidelines

定義臨床前階段與輕度認知障礙



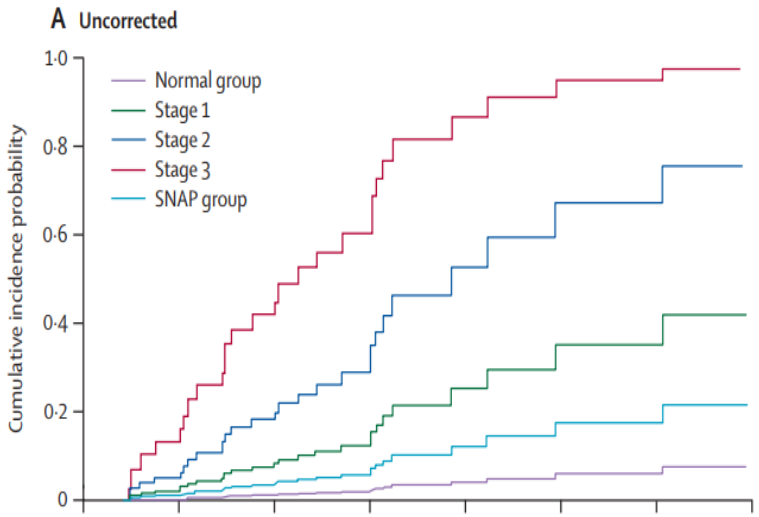
Sperling, Reisa A., et al. "Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." *Alzheimer's & dementia* 7.3 (2011): 280-292.

Preclinical Alzheimer's disease and it's outcome



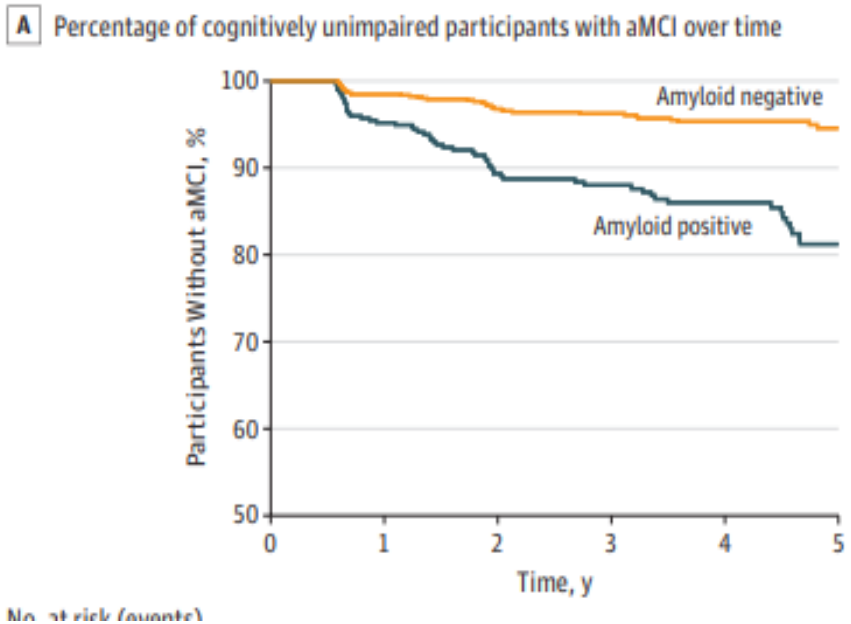
Sperling, Reisa, Elizabeth Mormino, and Keith Johnson. "The evolution of preclinical Alzheimer's disease: implications for prevention trials." *Neuron* 84.3 (2014): 608-622.

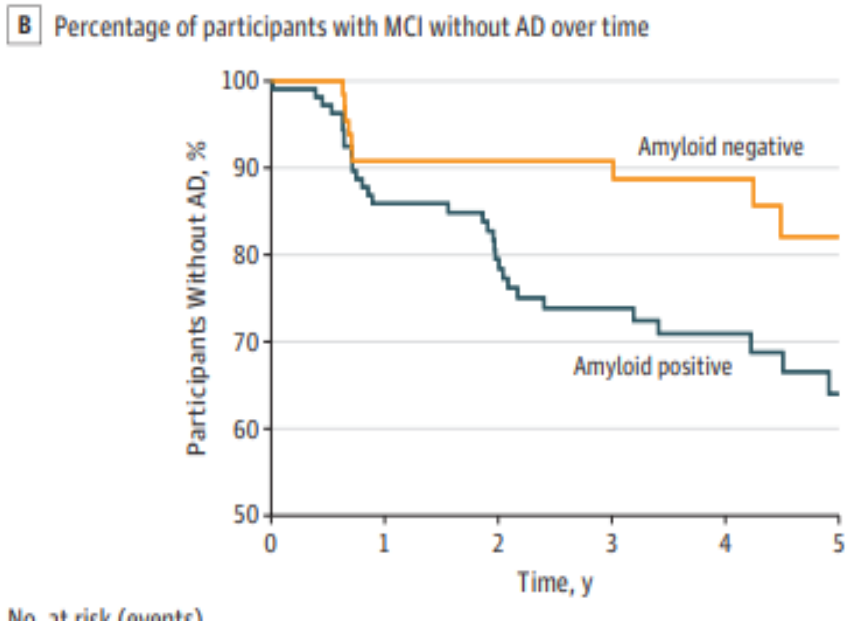
Progression to clinical dementia rating scale at least 0.5, symptomatic Alzheimer's disease by preclinical Alzheimer's disease stage



Vos, Stephanie JB, et al. "Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study." *The Lancet Neurology*12.10 (2013): 957-965.

Clinical outcomes of amyloid positivity in persons without dementia





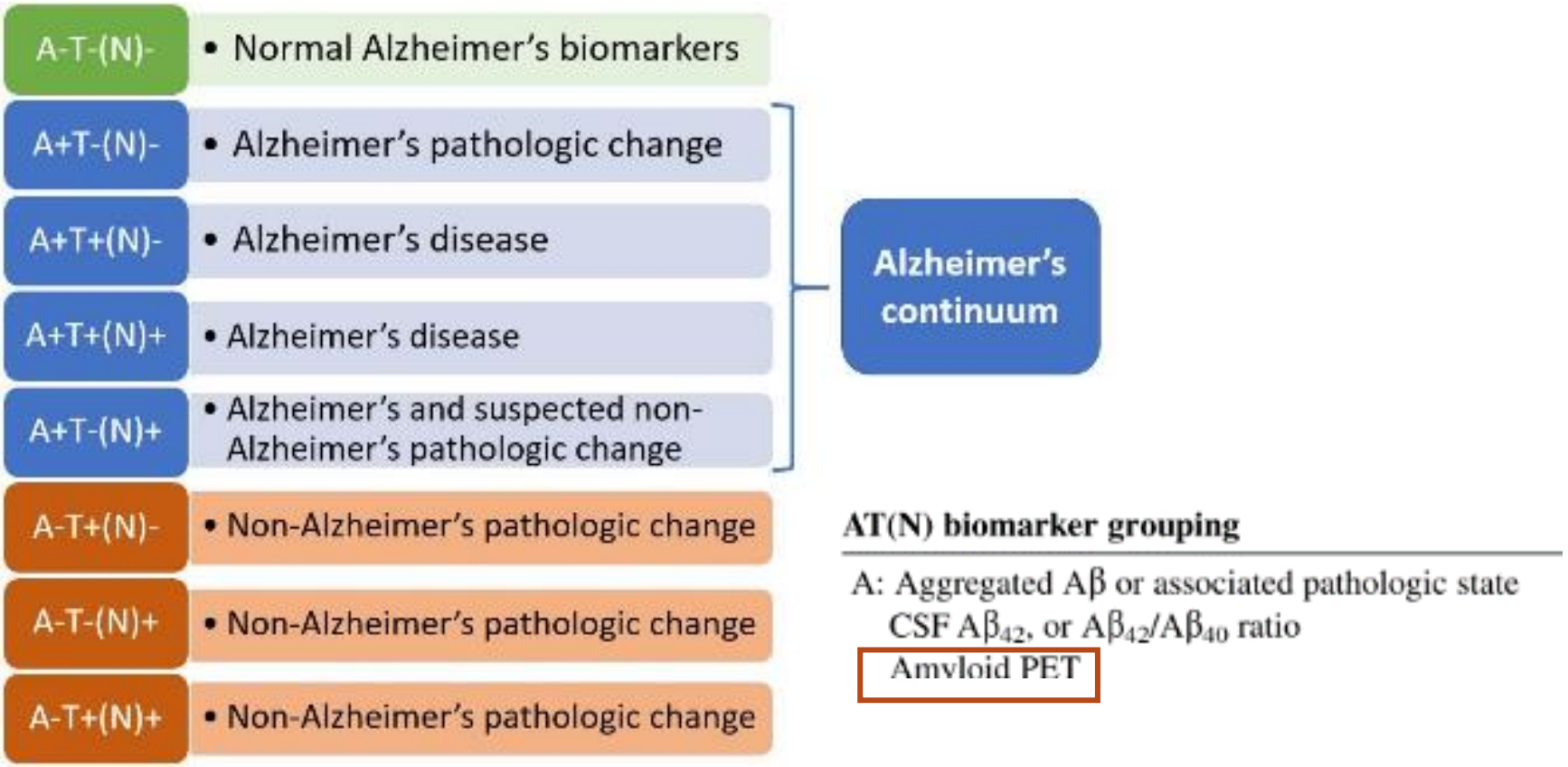
由正常至失憶型MCI風險提高2.3倍

由MCI至clinical AD風險提高1.9倍

Roberts, Rosebud O., et al. "Prevalence and outcomes of amyloid positivity among persons without dementia in a longitudinal, population-based setting." *JAMA neurology* 75.8 (2018): 970-979.

2018 NIA-AA Research Framework

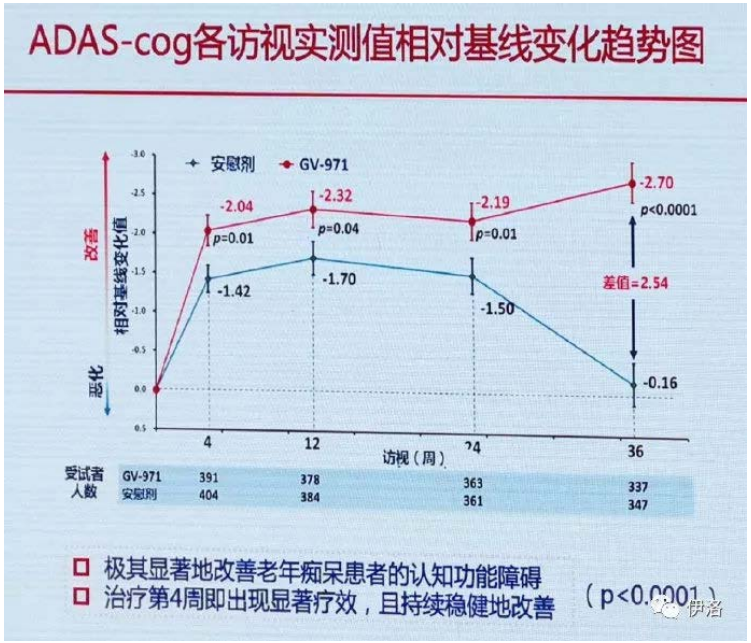
進展到阿茲海默病的生物定義

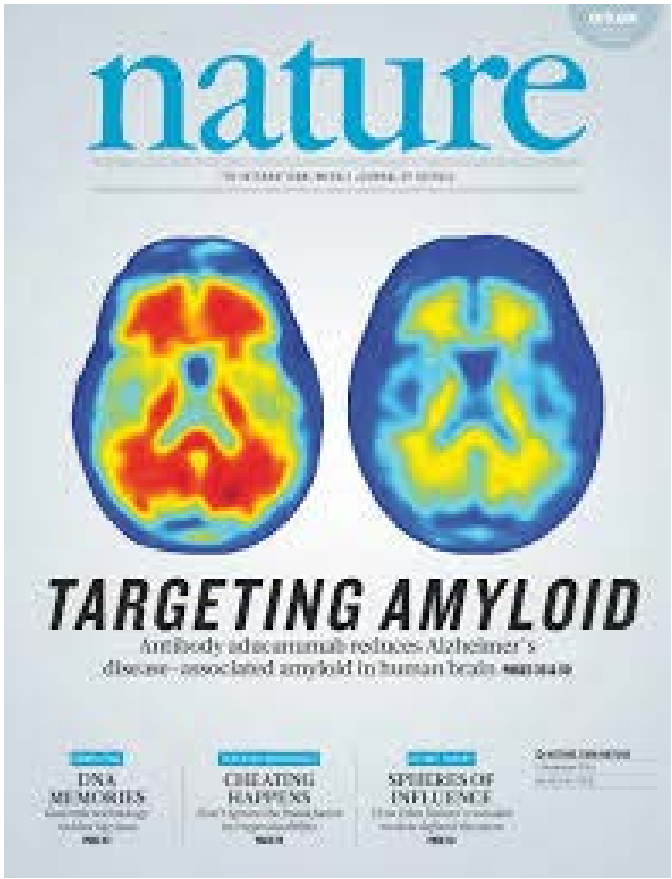


Jack, Clifford R., et al. "NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease." Alzheimer's & Dementia 14.4 (2018): 535-562

2020 Treatment breakthrough

阿兹海默病治療新里程

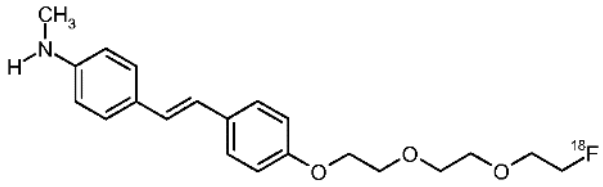




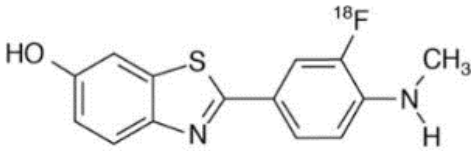
Appropriate use criteria of amyloid PET imaging

Commercial ^{18}F-Aβ PET tracer approved by FDA & EMA

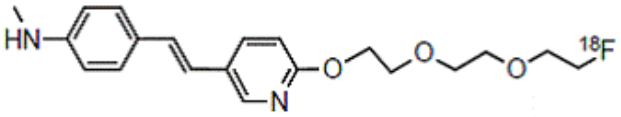
^{18}F-florbetaben (Neuraceq™)
U.S. FDA approved March 2014

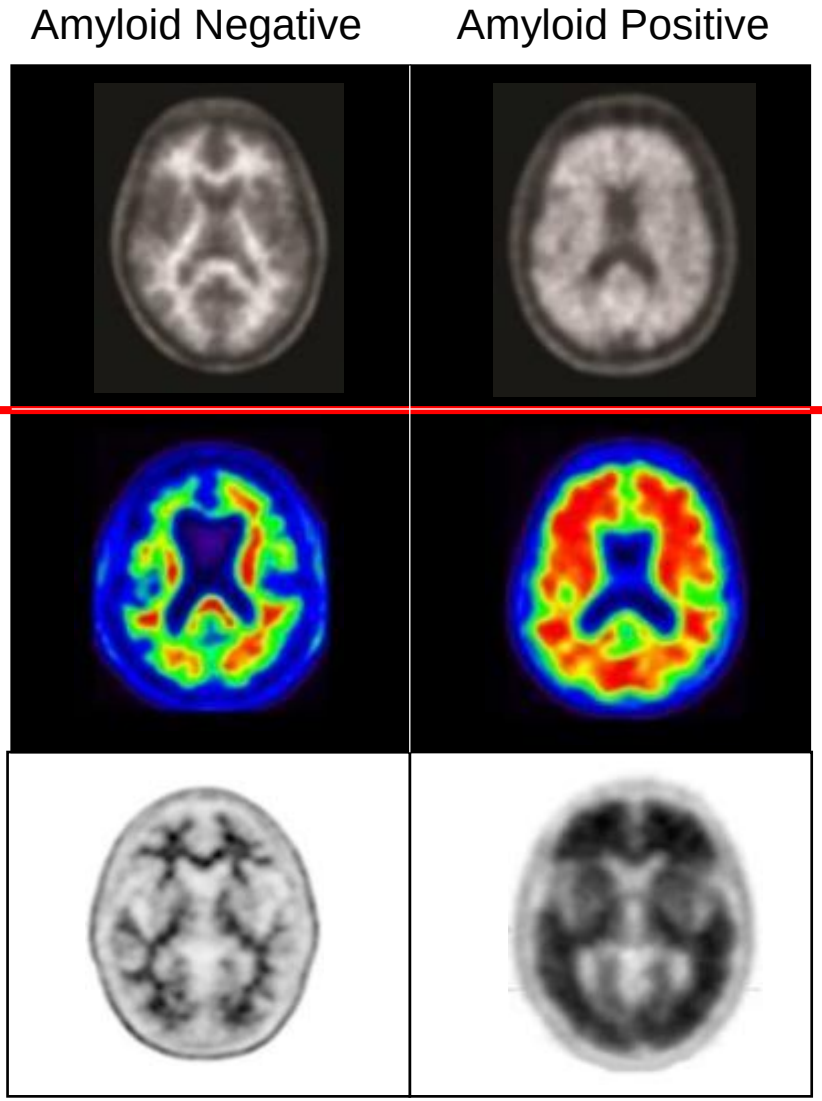


^{18}F-flutemetamol (Vizamyl™)
U.S. FDA approved October 2013

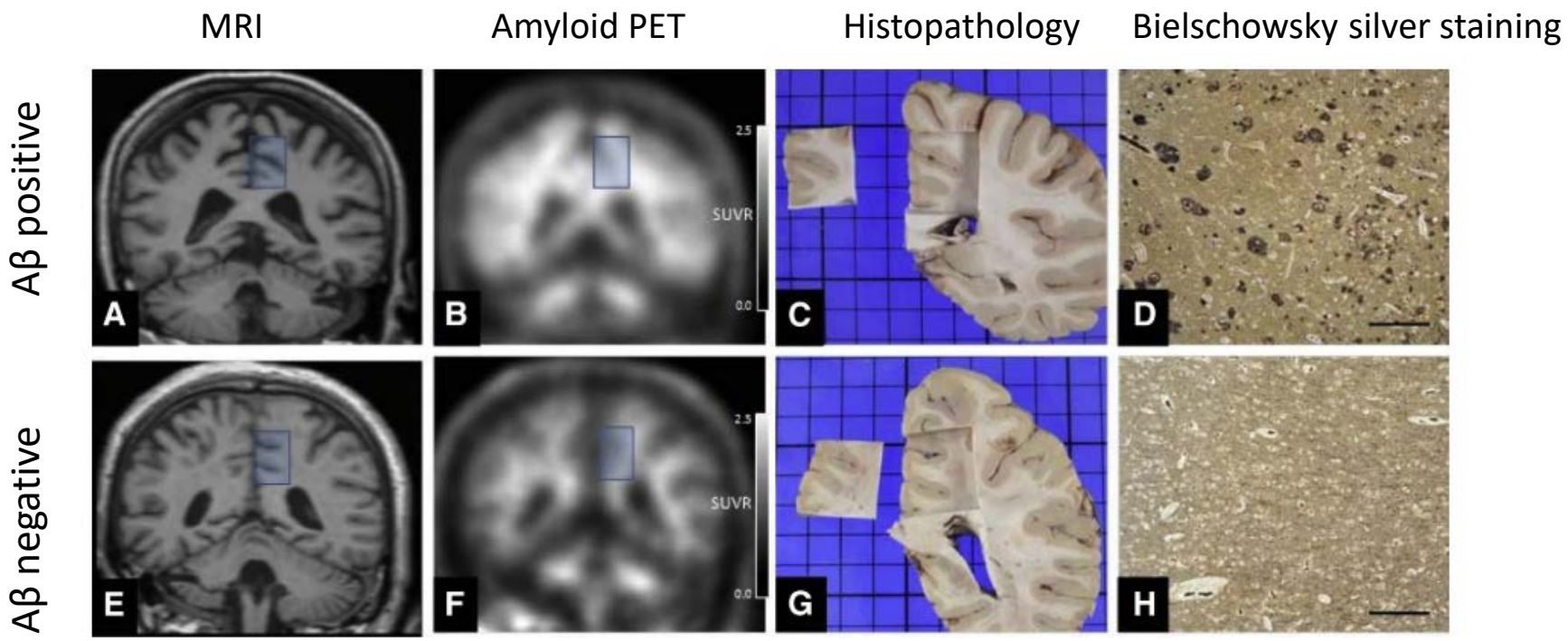


^{18}F-florbetapir (Amyvid™)
U.S. FDA approved April 2012





^{18}F-Florbetaben PET phase III clinical trial

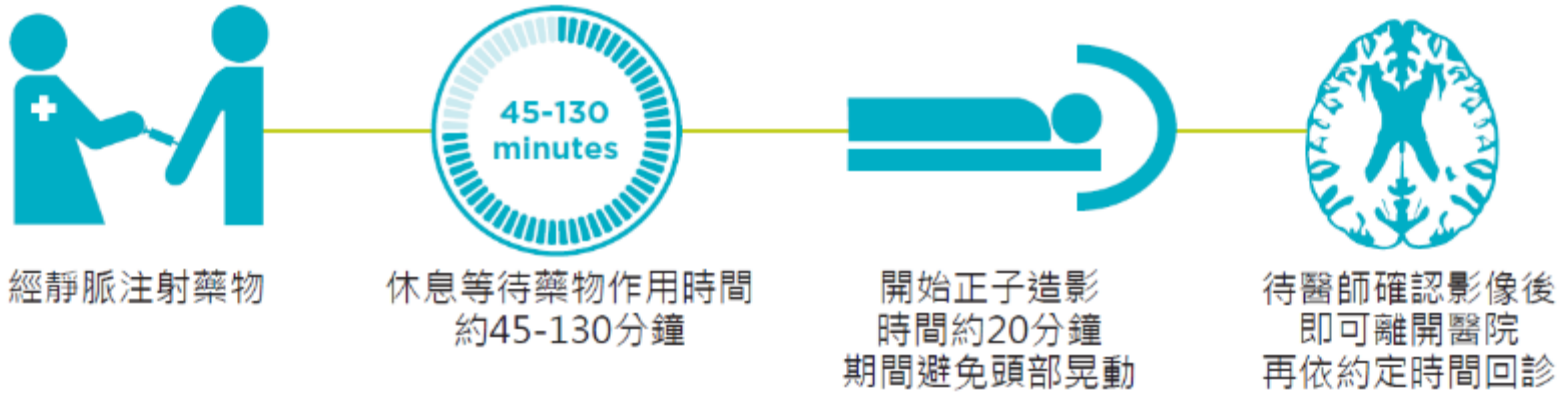


74位患者過世後捐出大腦，與生前^{18}F-Florbetaben PET 影像作比對病理切片結果有中度至高度神經炎斑塊 (CERAD)
敏感度: 97.9% 特異性: 88.9%

Alzheimer's & Dementia 11.8 (2015): 964-974.

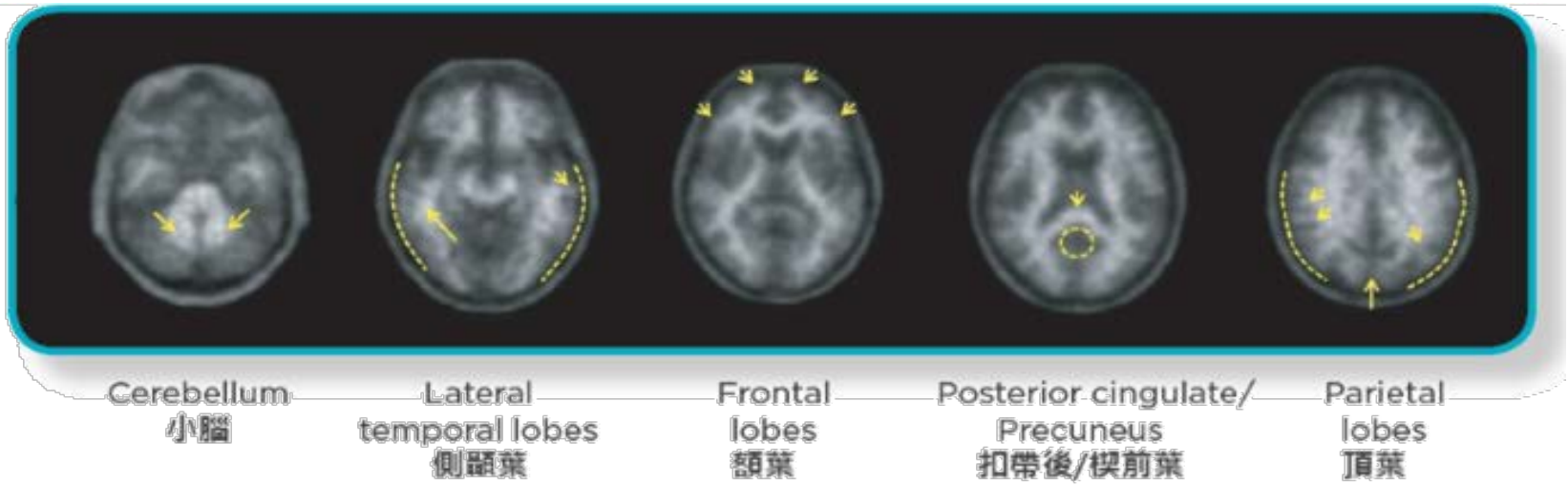
^{18}F-Florbetaben dosage and administration

- 300 MBq (8.1 mCi) as a slow single intravenous bolus (6 sec/mL) in a total volume of up to 10 mL。
- Obtain 15-20 minute PET images starting from 45 to 130 minutes after intravenous administration

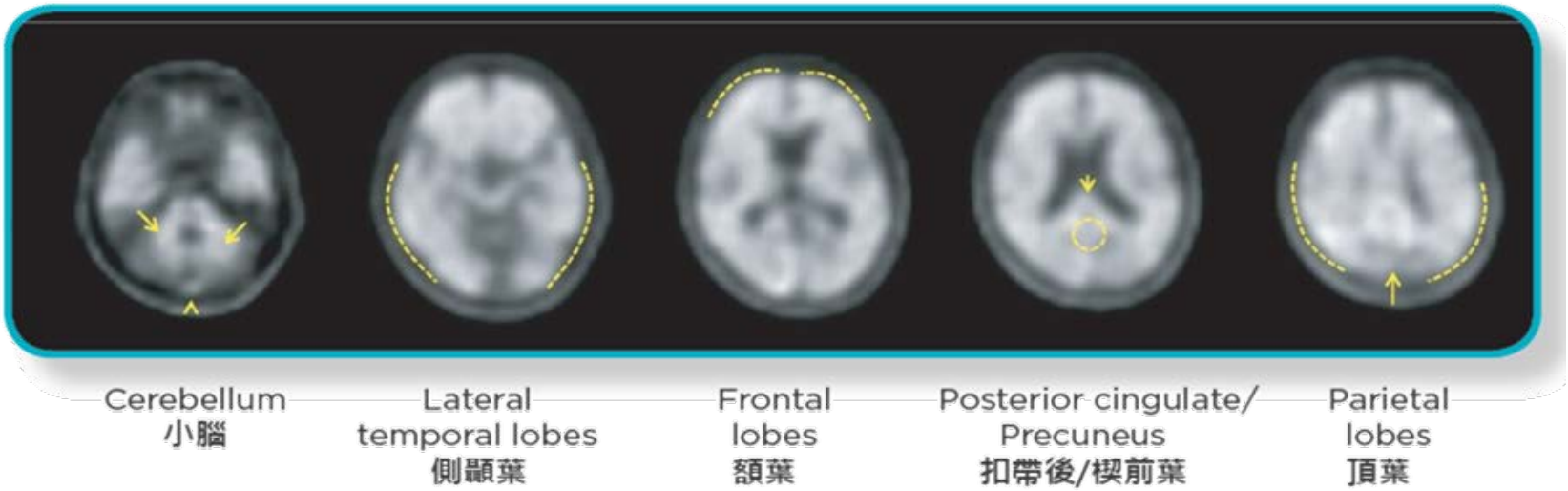


^{18}F-Florbetaben Image Interpretation

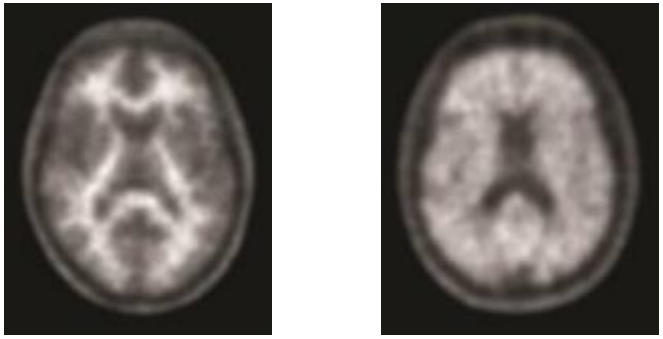
Negative



Positive



^{18}F-Florbetaben interpretation

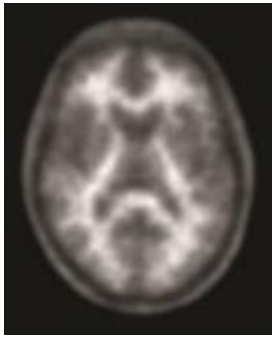


FBB Negative FBB Positive

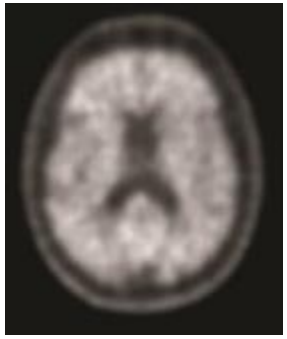
Negative FBB scan: sparse to no amyloid neuritic plaques and
Positive FBB scan: moderate to frequent amyloid neuritic plaques

For Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline.

^{18}F-Florbetaben interpretation

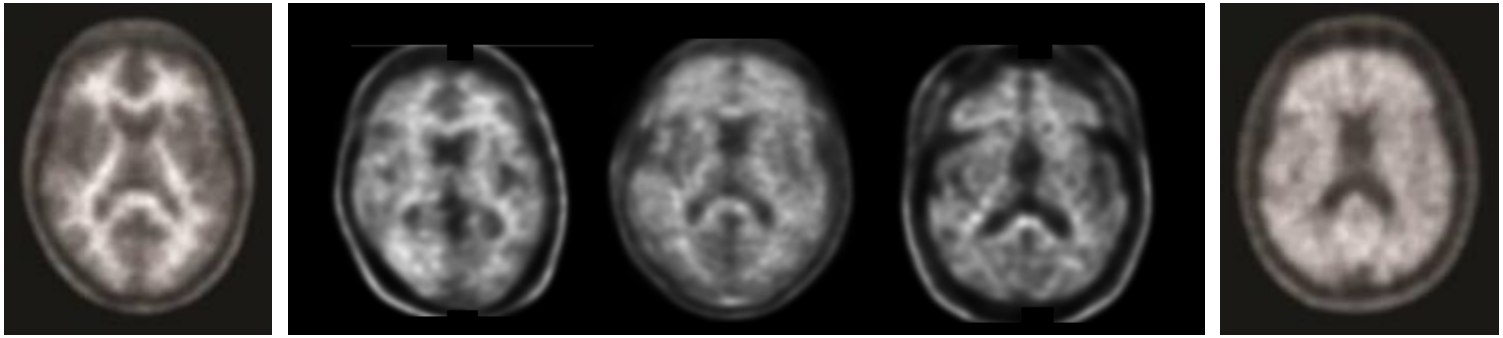


FBB Negative



FBB Positive

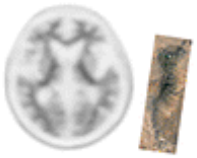
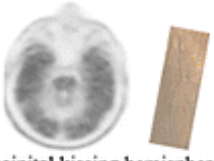
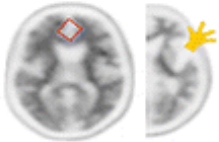
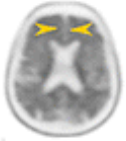
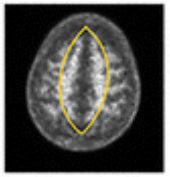
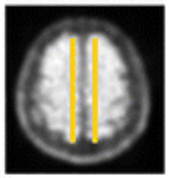
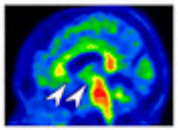
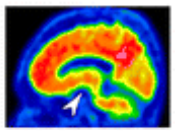
^{18}F-Florbetaben interpretation

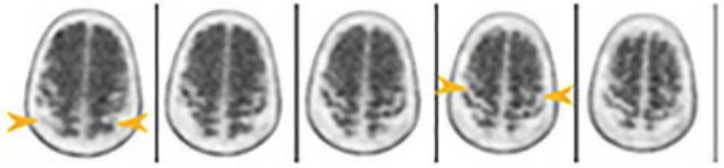


FBB Negative

FBB Positive

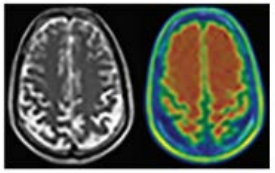
Signs and Artifacts in Amyloid PET

Cortical Region	Amyloid-negative	Amyloid-positive
Temporal/Occipital	 Temporal Ridge	 Occipital kissing hemispheres and temporal plain
Frontal	 Diamond clear space and cartoon hand	 Kissing hemispheres
	 Tree in winter	 Tree in summer
Parietal	 Double convex lens	 Kissing hemispheres
Striatum	 Striatal gap	 Striatal bridge

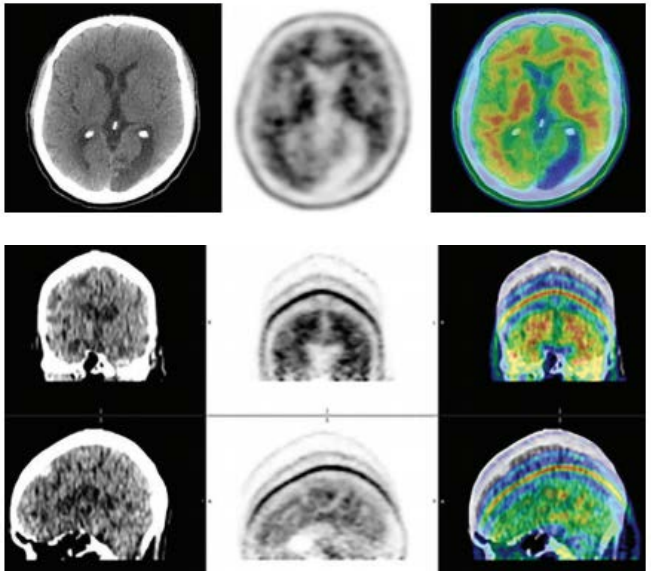


a.

Figure 13. Atrophy causing pseudo–white matter pattern in the parietal region of an amyloid-positive brain at ^{18}F-florbeta-pir PET. **(a)** On axial images of an amyloid-positive brain with significant atrophy, the widened sulci (arrowheads) can give the false impression of a white matter pattern owing to partial volume averaging of activity from thinner cortices and wider sulci. **(b)** Axial T2-weighted MR image (left) and fused PET/MR image (right) of the high parietal region for correlation of white matter anatomy.



b.



RadioGraphics 2018; 38:2123–2133

Regional read amyloid patterns with a positive scan End-of-life population

Combinations of regions positive (red) for [^{18}F]flutemetamol: autopsy study (71 + ve cases)

Frontal	Temporal	Temporo/parietal insula	Posterior Cingulate & Precuneus	Striatum	N	%
					54/71	76%
					6/71	8.5%
					4/71	5.6%
					3/71	4.6%
					1/71	1.4%
					1/71	1.4%
					1/71	1.4%
					1/71	1.4%
93%	87%	96%	100%	92%		

- 96% of the EoL patients showed positivity in four or all five regions. Only three patients showed positivity in three or fewer regions, and all these patients were older than the mean age of 81 years
- The posterior cingulate was positive in 100% of the EoL patients

European Journal of Nuclear Medicine and Molecular Imaging **volume 46**, pages1299–1308(2019)

Regional read amyloid patterns with a positive scan amnestic MCI population

Frontal	Temporal	Temporo/parietal insula	Posterior Cingulate & Precuneus	Striatum	N	%
					84/97	87%
					3/97	3%
					1/97	1%
					1/97	1%
					2/97	2%
					1/97	1%
					2/97	2%
					1/97	1%
					2/97	2%
93%	93%	91%	97%	98%		

- 87% of the patients showing positivity in all five regions and a further 5% showing positivity in four regions.
- 97–98% showed positivity in both the posterior cingulate and the striatum.

European Journal of Nuclear Medicine and Molecular Imaging **volume 46**, pages1299–1308(2019)

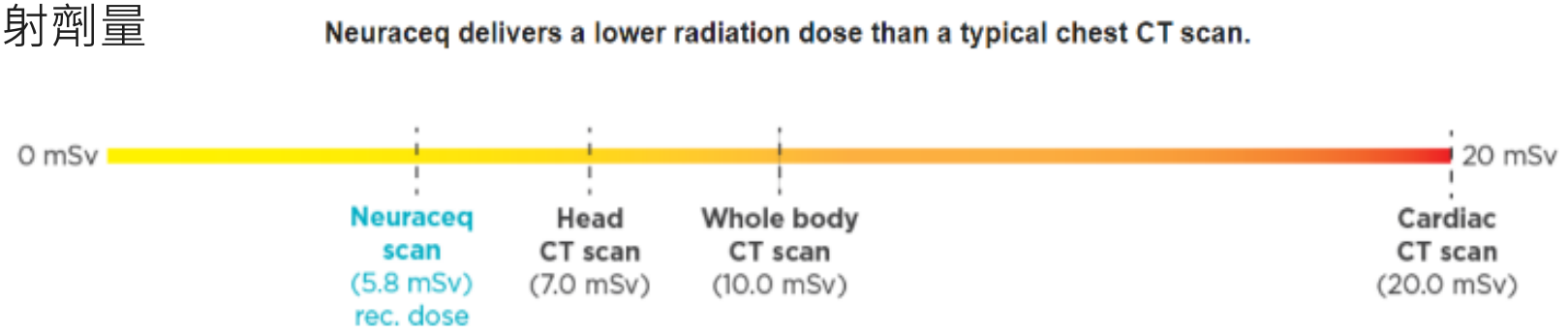
^{18}F-Florbetaben safety profile and dosimetry

安全性

- 總體安全性檔案基於1090次給藥的數據，其中包含872名受試者。
- 無發生與本藥相關的嚴重不良反應報告。
- 受試者中觀察到最常見的藥物不良反應為注射部位紅疹、刺激、疼痛，所有不良反應為輕至中度，且持續時間短。

藥物不良反應	不良反應次數 (百分比比例)
注射部位紅疹	18 (1.7%)
注射部位刺激	12 (1.1%)
注射部位疼痛	37 (3.4%)

輻射劑量



NEURACEQ [US package insert]. Matran, Switzerland: Piramal Imaging, S.A.; April 2014.

2013 Appropriate use criteria for amyloid PET

When should brain amyloid imaging be considered?

For patients with all of the following core elements:

1. A cognitive complaint with objectively confirmed impairment.
2. Alzheimer's disease is a possible diagnosis, but upon comprehensive evaluation by a dementia expert, the diagnosis remains uncertain.
3. The presence or absence of amyloid would increase certainty in the diagnosis and alter the treatment plan.

alzheimer's association

SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

由阿茲海默氏症協會與核醫與分子影像學會組織工作小組共同發表在*Journal of Nuclear Medicine*

Johnson, Keith A., et al. "Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association." *Journal of Nuclear Medicine,* (2013)

2013 Appropriate use criteria for amyloid PET

Amyloid imaging appropriate	Amyloid imaging inappropriate
1. Persistent or progressive unexplained MCI 2. core clinical criteria for possible AD because of unclear clinical presentation (either an atypical clinical course or an etiologically mixed presentation) 3. Patients with progressive dementia and atypically early age of onset (<65 yrs)	4. core clinical criteria for probable AD with typical age of onset 5. To determine dementia severity 6. Based solely on a positive family history of dementia or presence of APOE4 7. Solely subjective cognitive complaint that is unconfirmed on clinical examination 8. In lieu of genotyping for suspected autosomal mutation carriers 9. In asymptomatic individuals 10. Nonmedical use (e.g., legal, insurance coverage, or employment screening)

Johnson, Keith A., et al. "Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association." *Journal of Nuclear Medicine,* (2013)

2013 Appropriate use criteria for amyloid PET

1. 持續或漸進之不明原因輕度認知障礙(MCI)患者。

   Persistent or progressive unexplained MCI

2. 臨床表徵不明確(非典型或混和型)，符合“Possible AD” 臨床標準患者

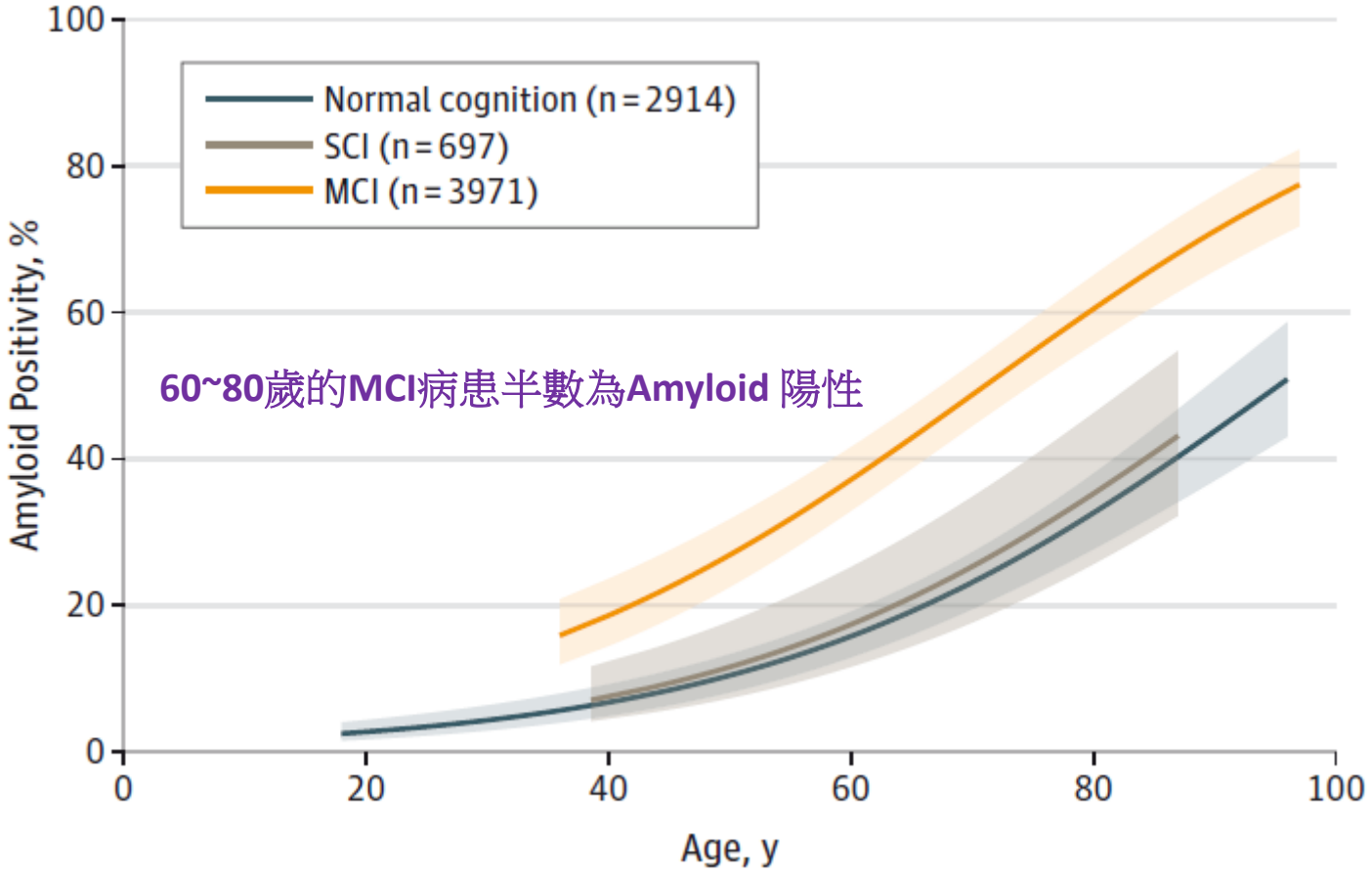
3. 早發型失智症患者(65歲前發病)

alzheimer's association®

SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

Johnson, Keith A., et al. "Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association." *Journal of Nuclear Medicine,* (2013)

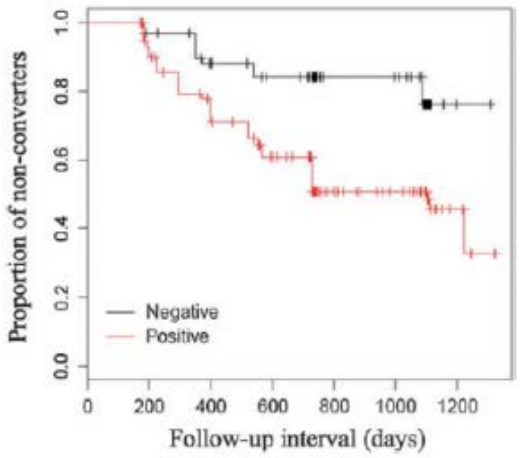
MCI患者類澱粉斑塊堆積發生率是認知正常者的兩倍



Jansen, Willemijn J., et al. "Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis." *Jama*313.19 (2015): 1924-1938.

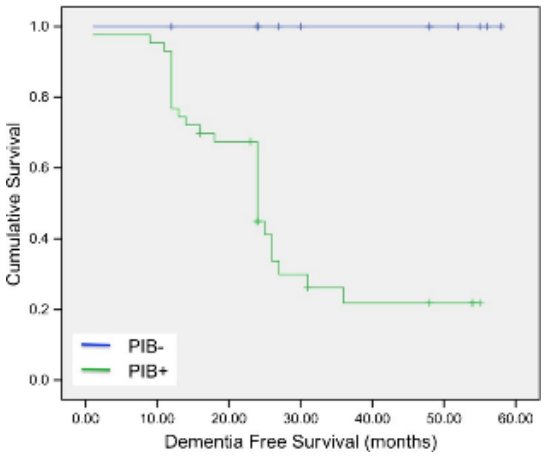
Amyloid positive versus negative in Mild Cognitive Impairments (MCI) patient

Survival plot for conversion from MCI to AD



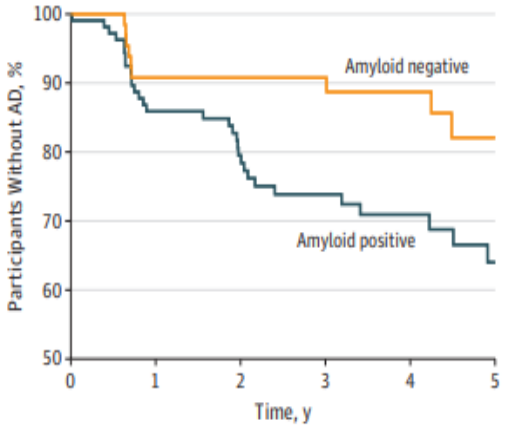
Ewers, Michael, et al., 2011

Dementia Free Survival in MCI



Nordberg, Agneta, et al., 2013

Percentage of participants with MCI without AD over time



Roberts, Rosebud O., et al., 2018

Amyloid PET 可釐清輕度認知障礙患者是否有AD病理變化，
評估疾病進展為AD的可能性

1. Ewers, Michael, et al. "CSF biomarker and PIB-PET–derived beta-amyloid signature predicts metabolic, gray matter, and cognitive changes in nondemented subjects." Cerebral cortex, (2011)
2. Nordberg, Agneta, et al. "A European multicentre PET study of fibrillar amyloid in Alzheimer's disease." European journal of nuclear medicine and molecular imaging, (2013)
3. Roberts, Rosebud O., et al. "Prevalence and outcomes of amyloid positivity among persons without dementia in a longitudinal, population-based setting." JAMA neurology 75.8 (2018): 970-979.

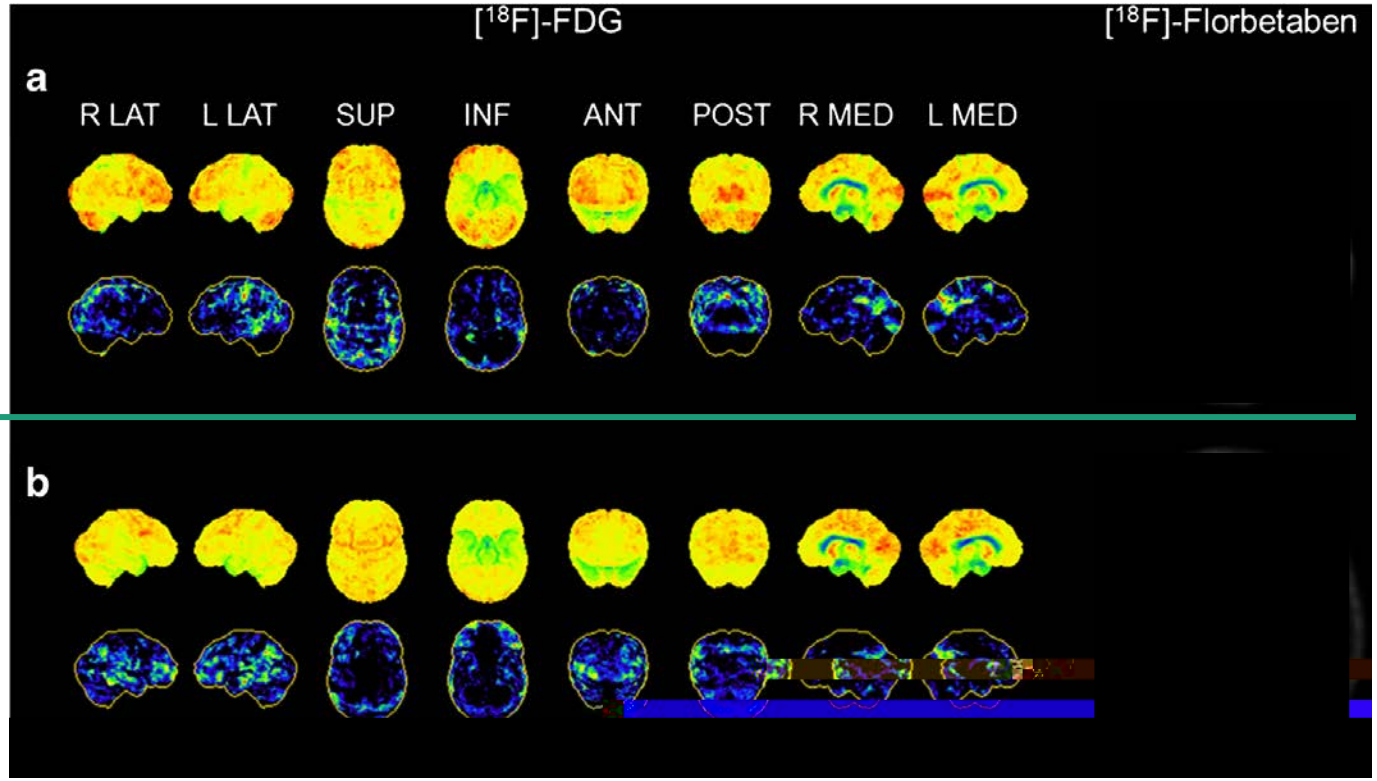
CASE 1

73歲女性

- FDG-PET顯示後扣帶皮層代謝下降，中度相似AD。

77歲女性

- FDG-PET顯示後扣帶皮層代謝下降，中度相似AD。



鑒清輕度認知障礙病患之初期突觸失能

Brendel, Matthias, et al. "Additive value of amyloid-PET in routine cases of clinical dementia work-up after FDG-PET." European journal of nuclear medicine and molecular imaging, (2017)

2013 Appropriate use criteria for amyloid PET

1. 持續或漸進之不明原因輕度認知障礙(MCI)患者。
   Persistent or progressive unexplained MCI
2. **臨床表徵不明確(非典型或混和型)，符合“Possible AD” 臨床標準患者**
3. 早發型失智症患者(65歲前發病)

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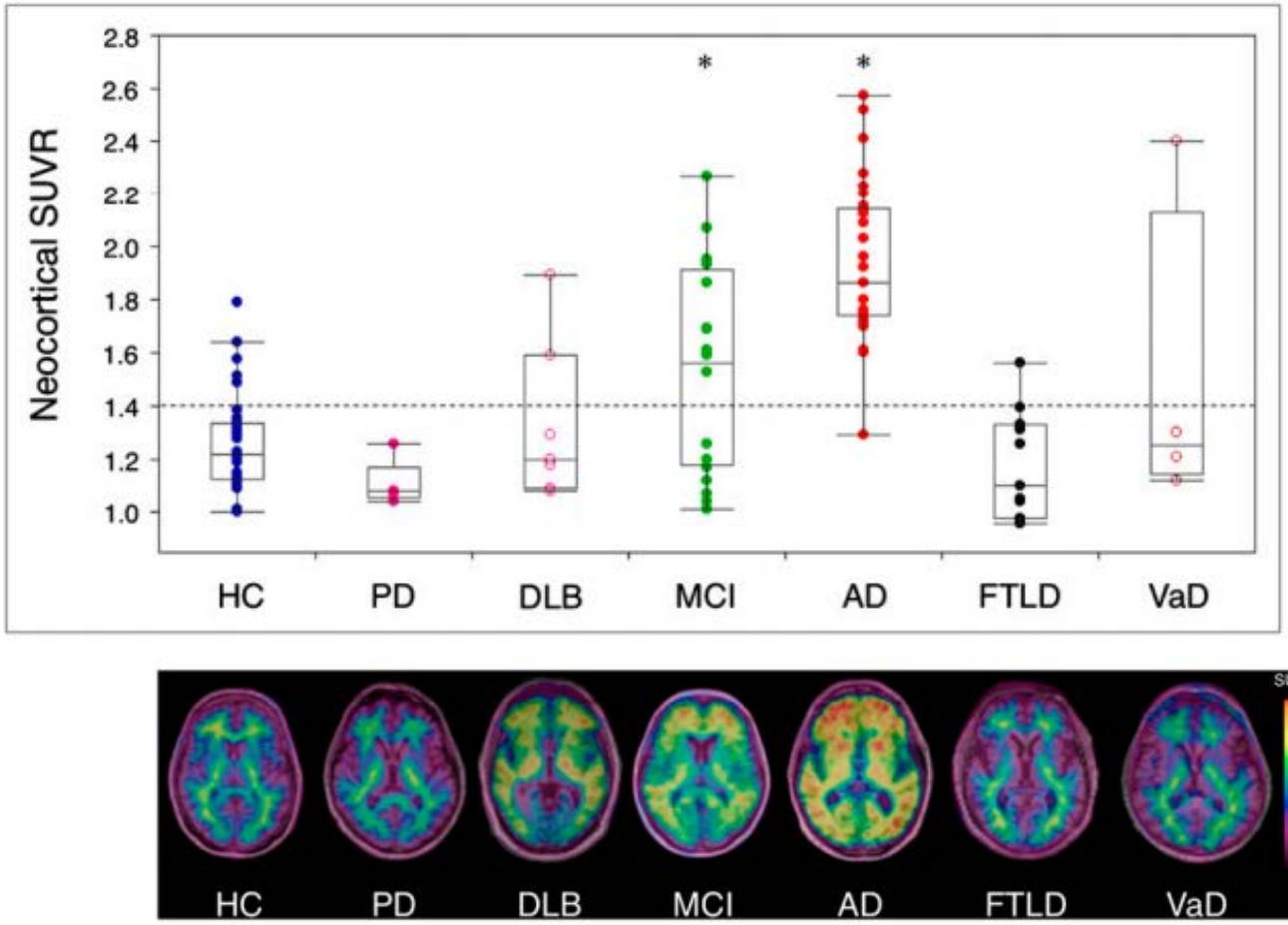
SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

Johnson, Keith A., et al. "Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association." *Journal of Nuclear Medicine,* (2013)

^{18}F-Florbetaben 用於AD與non-AD失智症



Villemagne, Victor L., et al. "Amyloid imaging with 18F-florbetaben in Alzheimer disease and other dementias." Journal of Nuclear Medicine, (2011).

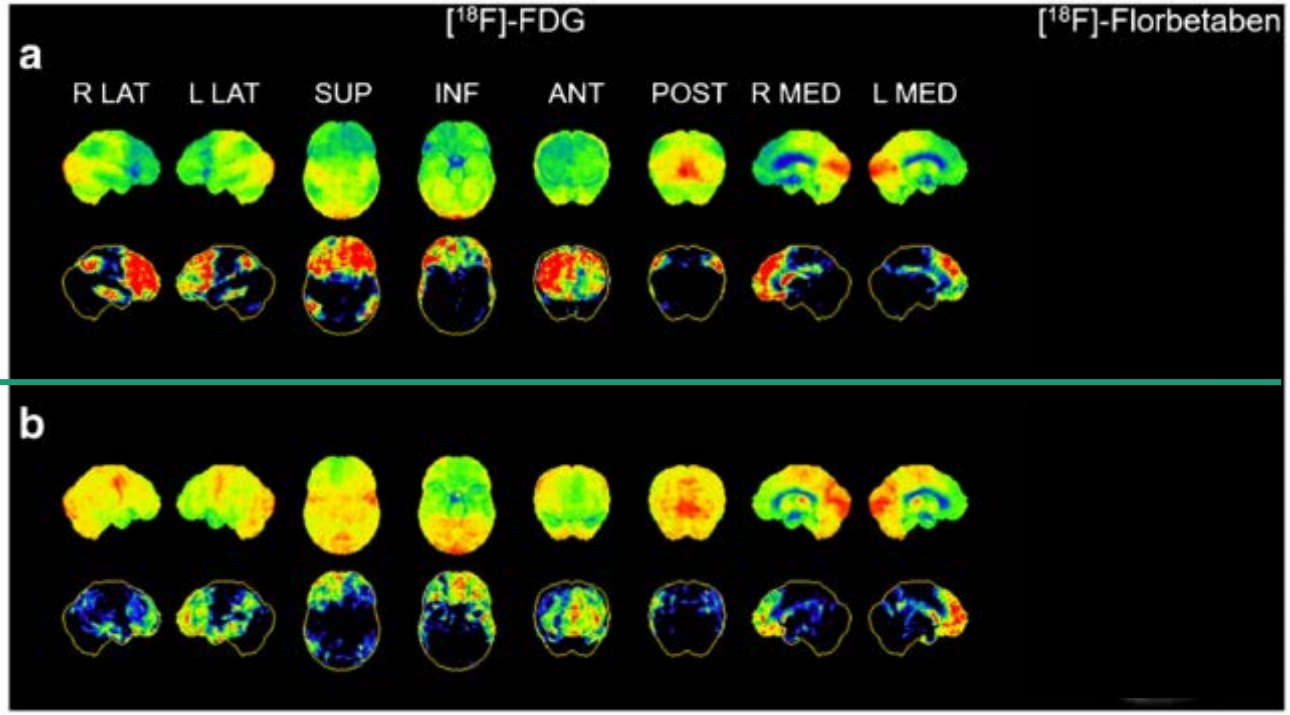
CASE 2

63歲女性

- FDG-PET 似額顳葉失智症的代謝下降特徵。

66歲男性

- FDG-PET 似額顳葉失智症的代謝下降特徵。



鑑別診斷:額顳葉型失智症 vs. 阿茲海默症額葉亞型

Brendel, Matthias, et al. "Additive value of amyloid-PET in routine cases of clinical dementia work-up after FDG-PET." European journal of nuclear medicine and molecular imaging, (2017)

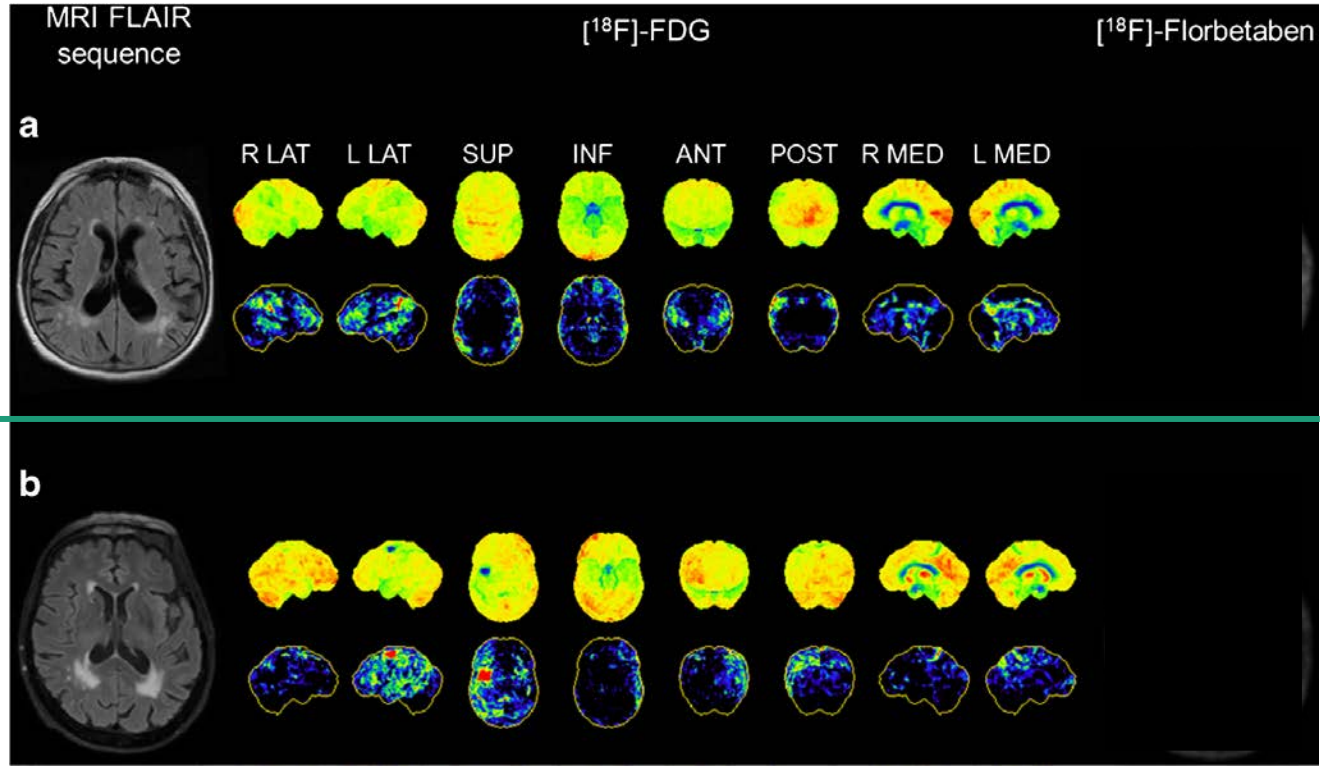
CASE 3

78歲女性

- 輕度認知障礙
- 腦白質病變 (MRI)
- FDG-PET 似血管型失智症的散佈代謝下降特徵

77歲女性

- 輕度認知障礙
- 腦白質病變 (MRI)
- FDG-PET 似血管型失智症



鑑別診斷: 血管型失智症 vs. 混和型失智症

Brendel, Matthias, et al. "Additive value of amyloid-PET in routine cases of clinical dementia work-up after FDG-PET." European journal of nuclear medicine and molecular imaging, (2017)

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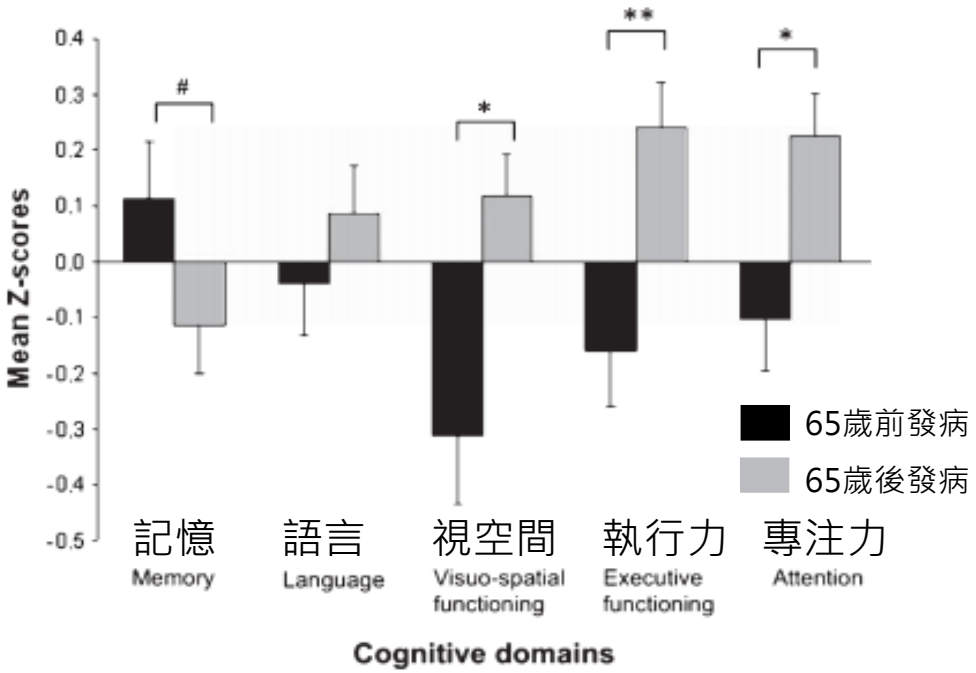
早發型阿茲海默氏症的診斷挑戰

- 相較晚發型AD多以記憶力下降為特徵，早發型的症狀常發生在其他認知領域



Smits, Lieke L., et al. "Early onset Alzheimer's disease is associated with a distinct neuropsychological profile." *Journal of Alzheimer's Disease* 30.1 (2012): 101-108.

阿茲海默氏症的非典型亞型: PCA, lvPPA, fvAD
在年輕發病的族群中常被誤診

Liana G. Apostolova, lecture in Dementia Care Expo 2018, Tainan

早發性失智症的延遲確診

失智症自症狀出現至確診的時間(年)				
診斷種類	早發型失智症(65歲前)		晚發型失智症(65歲後)	
	Mean (S.D.)	n	Mean (S.D.)	n
All	4.4 (3.1)	235	2.8 (2.1)	167
AD	4.2 (3.0)	139	3.0 (2.2)	122
FTD	6.4 (3.6)	29	3.3 (2.1)	3
VaD	3.9 (2.7)	35	2.2 (1.8)	33
Other	4.1 (3.3)	32	3.4 (1.3)	9

自發病到確診的平均時間，比65歲以上發病者多1.6年

1. Van Vliet, D., et al. "Time to diagnosis in young-onset dementia as compared with late-onset dementia." Psychological medicine 43.2 (2013): 423-432.

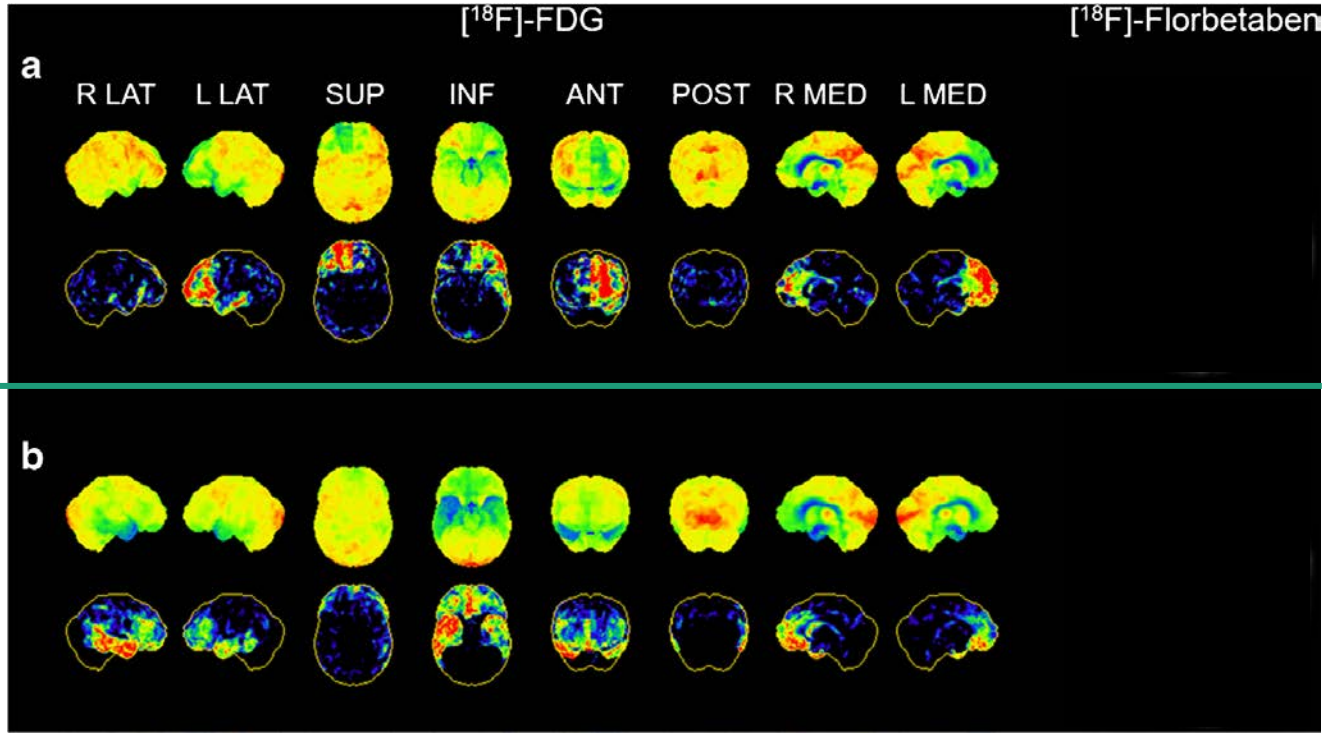
CASE 4

59歲女性

- 臨床表現原發漸進性失語症(分類未確定)
- FDG-PET 似額顳葉失智症的代謝下降特徵。

59歲男性

- 臨床表現原發漸進性失語症(分類未確定)
- FDG-PET 似額顳葉失智症的代謝下降特徵。



鑑別診斷: 原發性進行性失語症

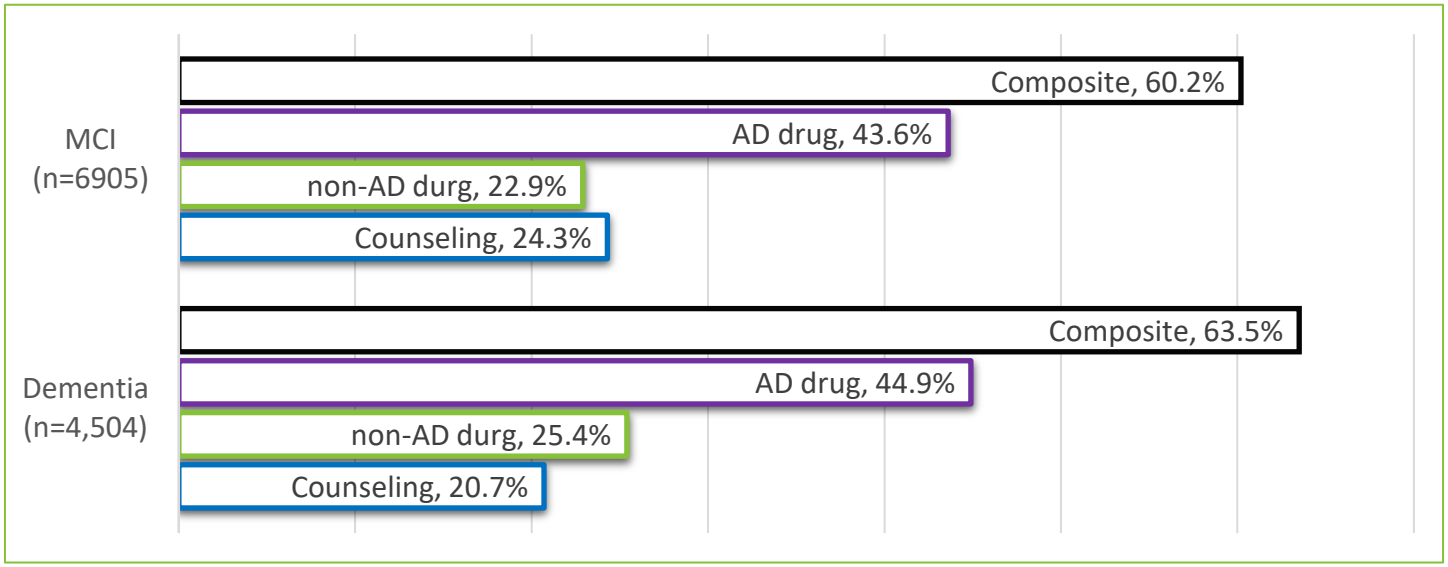
Brendel, Matthias, et al. "Additive value of amyloid-PET in routine cases of clinical dementia work-up after FDG-PET." European journal of nuclear medicine and molecular imaging, (2017)

Clinical utility of amyloid PET

(IDEAS) Study: the impact of amyloid PET on the management of patients

JAMA | Original Investigation

Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia

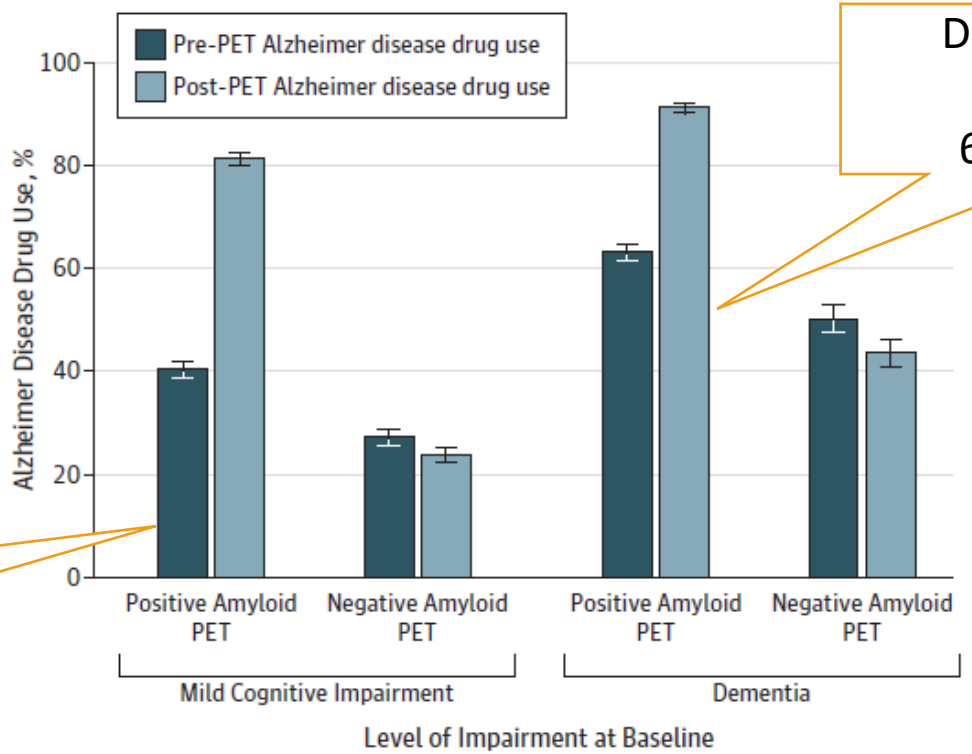


Amyloid PET改變了60%以上案例的病患處置計畫

Rabinovici, Gil D., et al. "Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia." JAMA 321.13 (2019): 1286-1294.

(IDEAS) Study: the impact of amyloid PET on hospital admissions

Figure 2. Changes in Overall Use of Alzheimer Disease Medications



All contrasts between pre–positron emission tomography (PET) and post-PET use were significant ($P < .001$). Error bars indicate 95% CIs.

Dementia, Aβ(+)
AD用藥比例
63.2%→91.2%

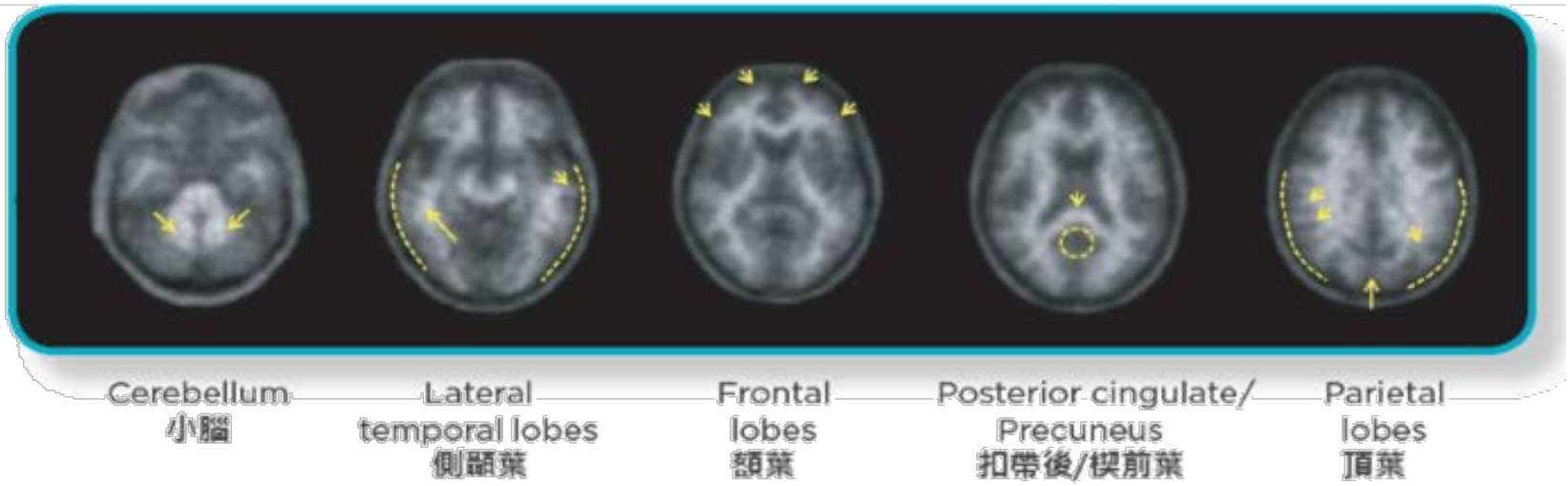
MCI, Aβ(+)
AD用藥比例
40.4%→81.5%

Rabinovici, Gil D., et al. "Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia." JAMA 321.13 (2019): 1286-1294.

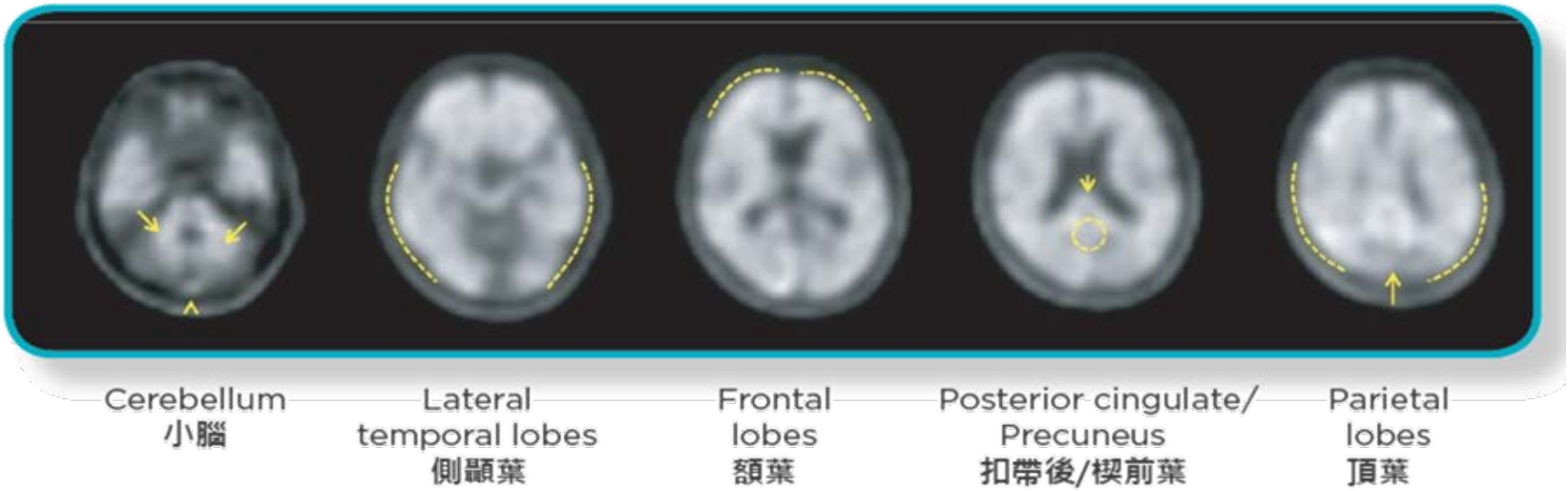
Take home message

^{18}F-Florbetaben Image Interpretation

Negative



Positive



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類澱粉蛋白之腦部造影

何時應使用類澱粉蛋白正子造影來幫助阿滋海默症之診斷？

失智症專家執行診斷需求之評估

- ☑ 是否符合已客觀確認有認知功能損傷？
- ☑ 是否經其他臨床診斷仍具不確定性？
- ☑ 是否可藉此增加確診性及改善治療計畫？

不適合檢測

- o 65歲以上且符合典型定義之阿滋海默症狀患者
- o 認知損傷未經臨床診斷
- o 用於鑑別失智症嚴重程度
- o 僅依家族病史而要求檢測
- o 做基因分序之替代方法
- o 用於非醫療原因

適合檢測

- o 常規醫學測試之臨床表現具有無法解釋之反覆性及持續性的記憶障礙及損傷
- o 非經常性之臨床表現
- o 非典型之早期發病

病患醫護影響

- ☑ 改變醫藥之管理
- ☑ 改變診斷之醫序
- ☑ 改變醫療之認知價值

提醒

- ☑ 類澱粉蛋白正子造影僅是診斷方法之一
- ☑ 健保尚未給付，檢查費用需數萬元

Learn more: www.snmmi.org/amyloidauc

Source

Appropriate use criteria for amyloid PET: A report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *J Nucl Med* 2013 jnumed.113.120618.

SNMMI Value Initiative
SOCIETY OF NUCLEAR MEDICINE & MOLECULAR IMAGING

Acknowledgement:
Team members of Department of Nuclear Medicine and Department of Neurology at Chang Gang Memorial Hospital.

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Chang Gung Memorial Hospital

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Society of Nuclear Medicine, Taiwan (R.O.C)

台灣臨床失智症學會
TDS
SINCE 2006
Taiwan Dementia Society