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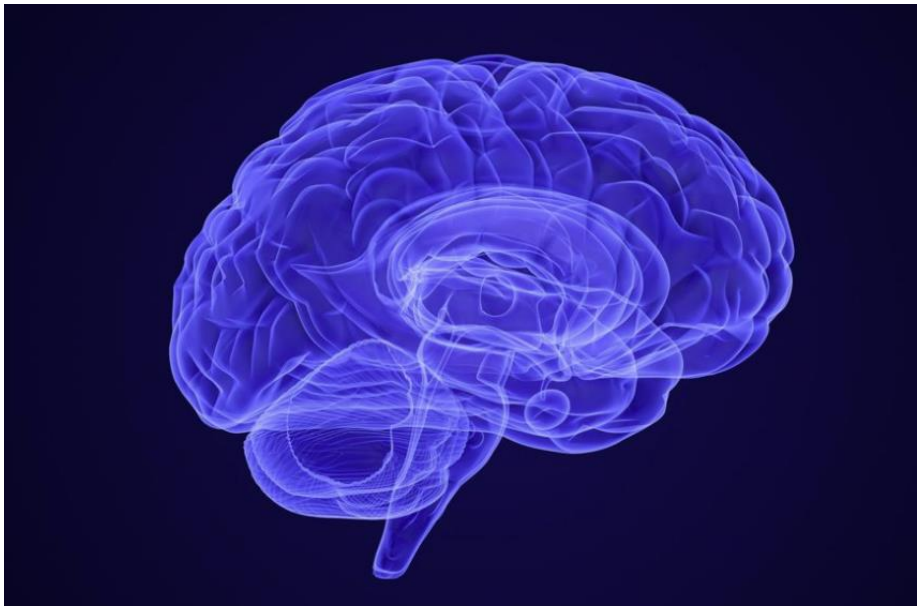

# Newer Approach to Alzheimer's Dementia Diagnosis and Management


Dr Mohan Bhat

Consultant Old Age Psychiatrist

Chair of Faculty of Old Age Psychiatry

Royal College of Psychiatrists. UK


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**Overview of Current understanding and management of Dementia**

**Overview of the developments in assessment and management and its drivers.**

**Implications**

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# Current assessment Clinical based

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**At the initial assessment Take a history**

(including cognitive, behavioural and psychological symptoms, and the impact symptoms have on their daily life):

**Dementia is suspected after initial assessment:**

**cognitive testing**

. a **physical examination and**

**blood and urine tests** to exclude reversible

Offer **structural imaging**

**Diagnose a dementia subtype**

**Only consider further tests if**

it would help to diagnose a dementia subtype **and**

knowing more about the dementia subtype would change management

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# Current management.

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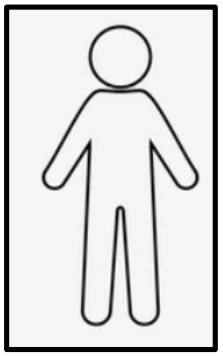

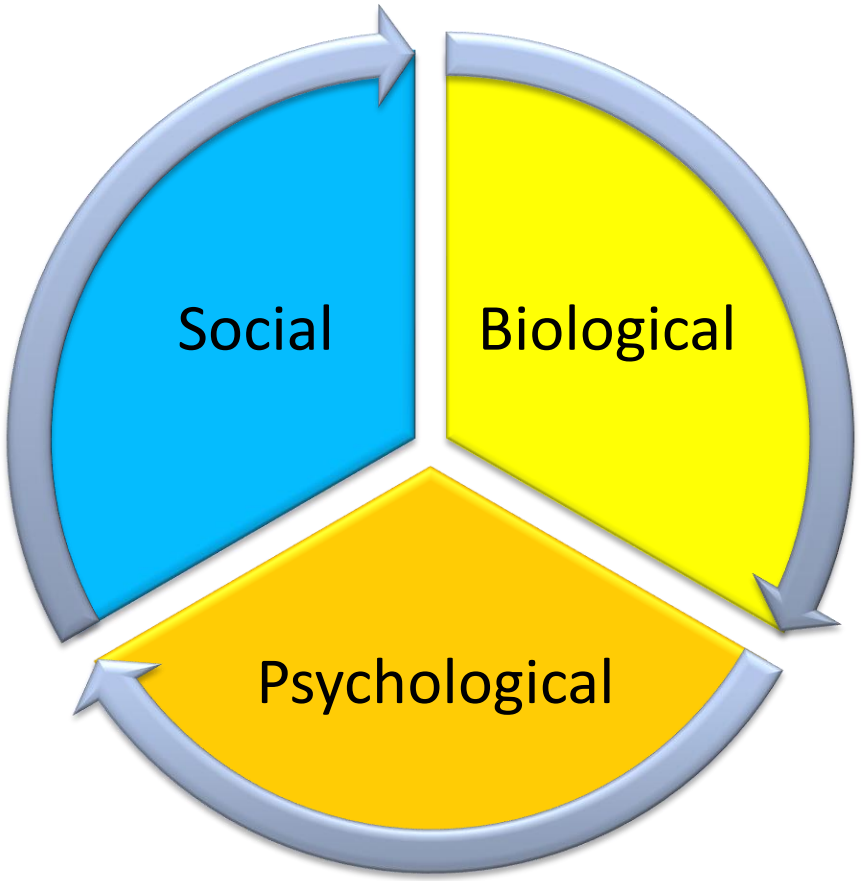


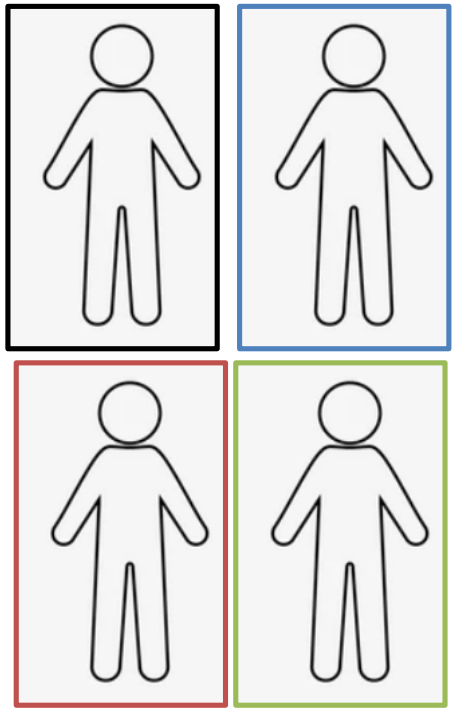

Person with Dementia

Carers and Family

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# Current management.

**Pharmacological management of Alzheimer's disease**

- Three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine as monotherapies
- Memantine monotherapy
- Consider Memantine in addition to an AChE inhibitor

**Interventions to promote cognition, independence and wellbeing**

Range of activities to promote wellbeing that are tailored to the person's preferences.

- Group cognitive stimulation therapy
- Group reminiscence therapy
- Cognitive rehabilitation or
- Occupational therapy

**Pharmacological management of non-Alzheimer's dementia**

**Lewy Body Dementia**
Offer Donepezil and Rivastigmine initially before considering Memantine

**Vascular Dementia**
Only consider AChE inhibitors or memantine if suspected comorbid Alzheimer's disease, Parkinson's disease dementia or dementia with Lewy bodies

Social Care packages
Residential needs
Carers support and education

# Management of BPSD

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**Explore possible reasons for patients' distress**

**Psychosocial and environmental interventions**

**ONLY offer anti-psychotics:**

***At risk of harming themselves or others**

***Experiencing agitation, hallucinations or delusions that are causing severe distress**

**Discuss benefits and harms with the person and their family or carers**

**When using anti-psychotics .**

**Only Haloperidol and Risperidone are licensed in the UK.**

**Lowest effective dose.**

**Reassess the person at least 6 weeks**


**Stop treatment**

**If no clear benefit**

**After discussion with the person and their family or carers**

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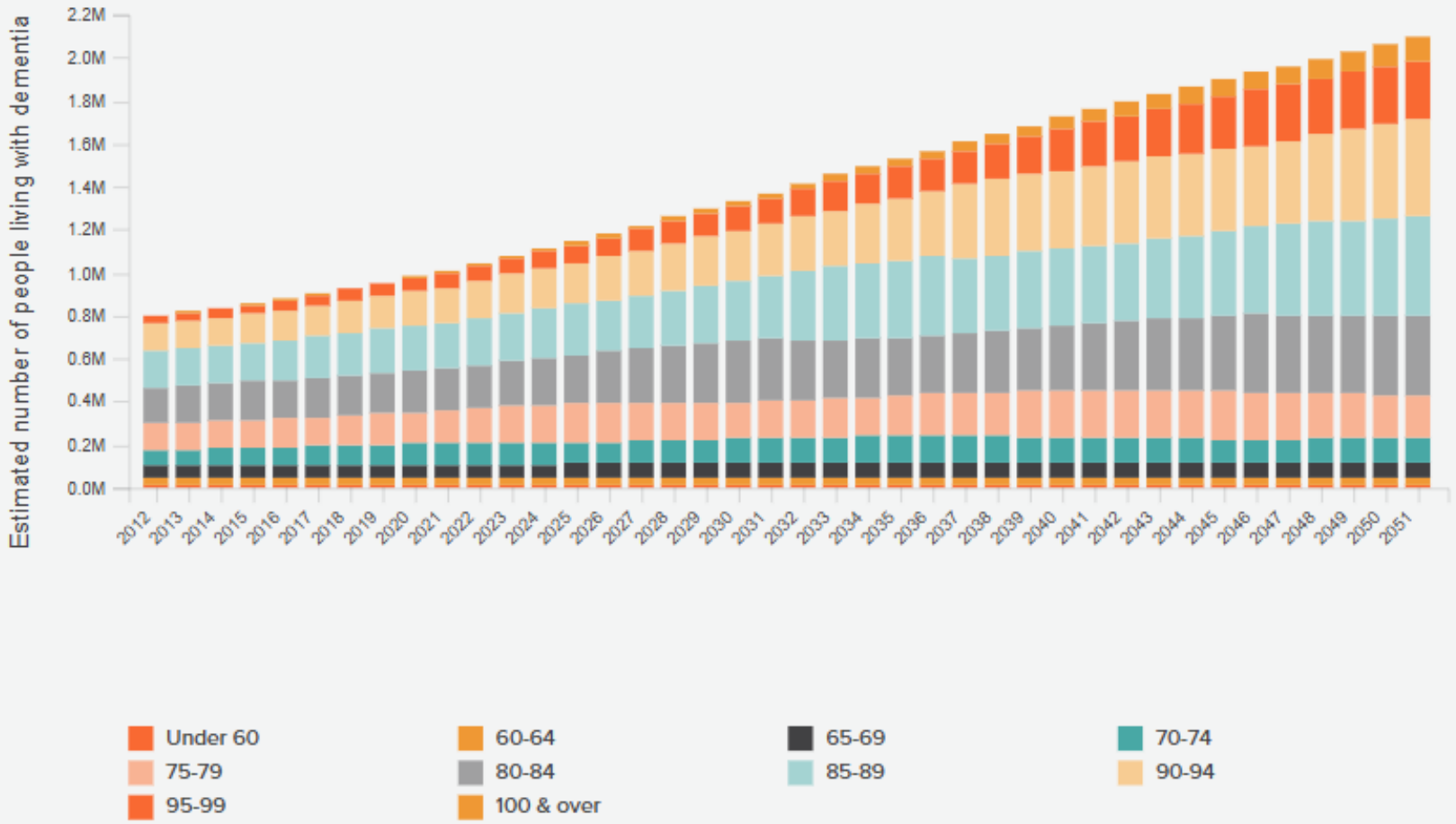
# UK PREVALENCE PROJECTION BY 5 YEAR AGE GROUP TO 2050



**One in two of us will be affected by dementia in our lifetime.**

Either by caring for someone with the condition, developing it ourselves, or both.

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**50% of people with Down's syndrome will develop dementia.**

By the age of 40, most people with Down's syndrome will have begun to develop signs of Alzheimer's disease in the brain.

ALZHEIMER'S RESEARCH UK FOR A CURE

Alzheimer's Disease in people with Down's syndrome.

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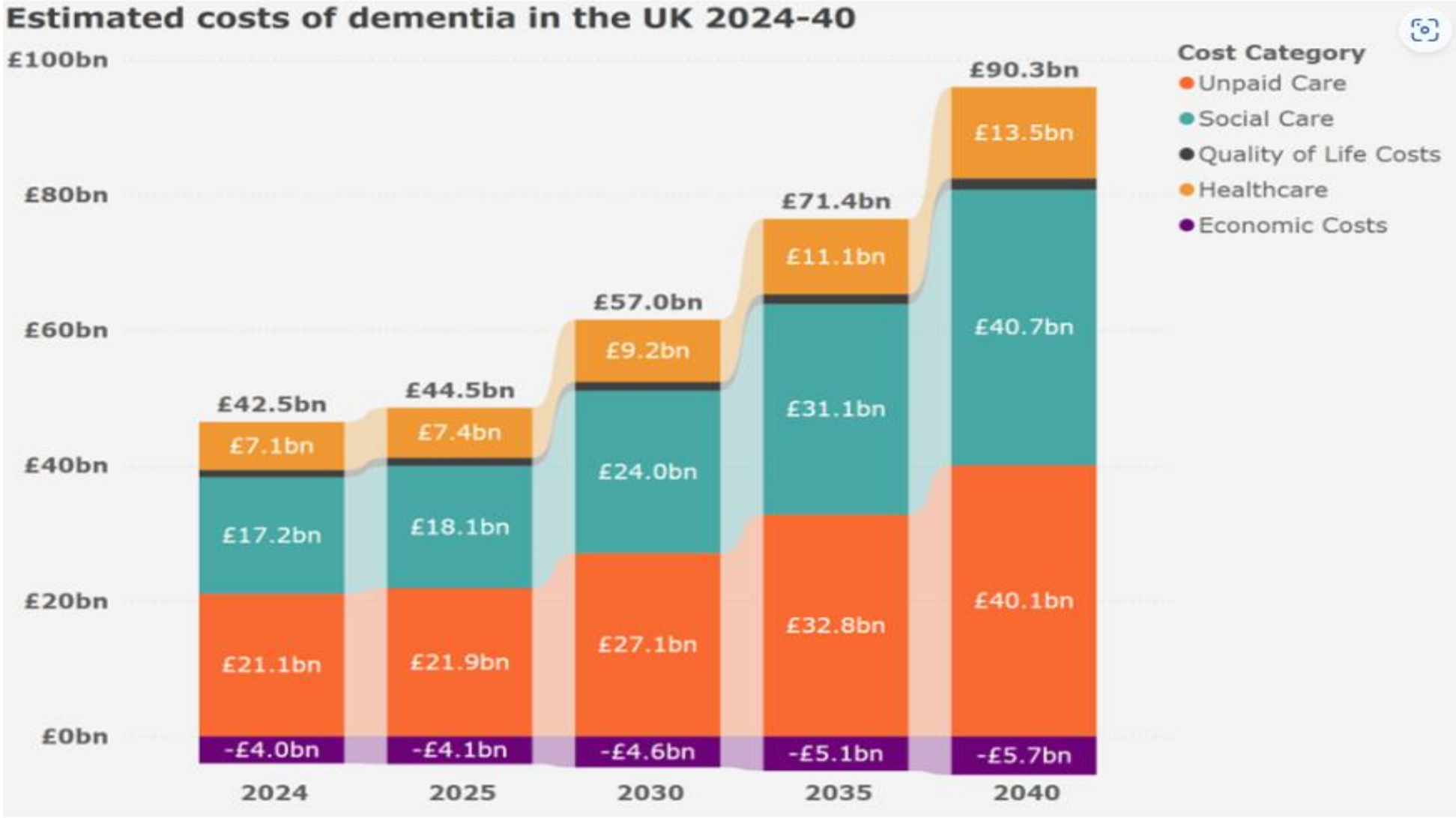


Source: Alzheimer's Society & Carnell Farrar (2024), The Economic Impact of Dementia – Module 1

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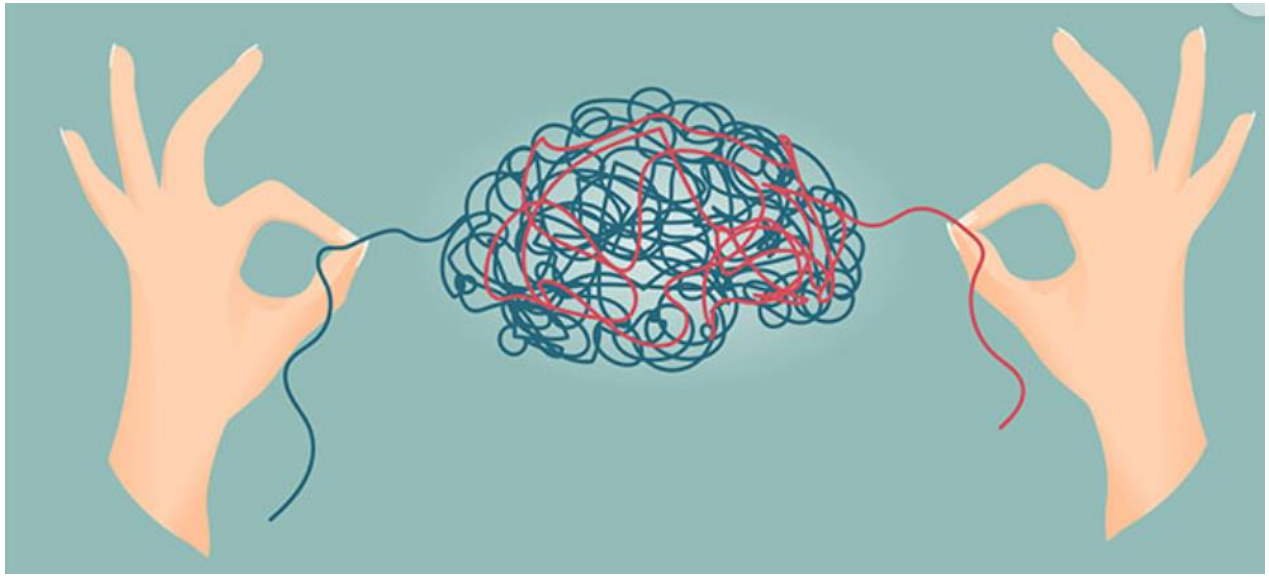
# A quick update on the progress



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# Drivers for the changes

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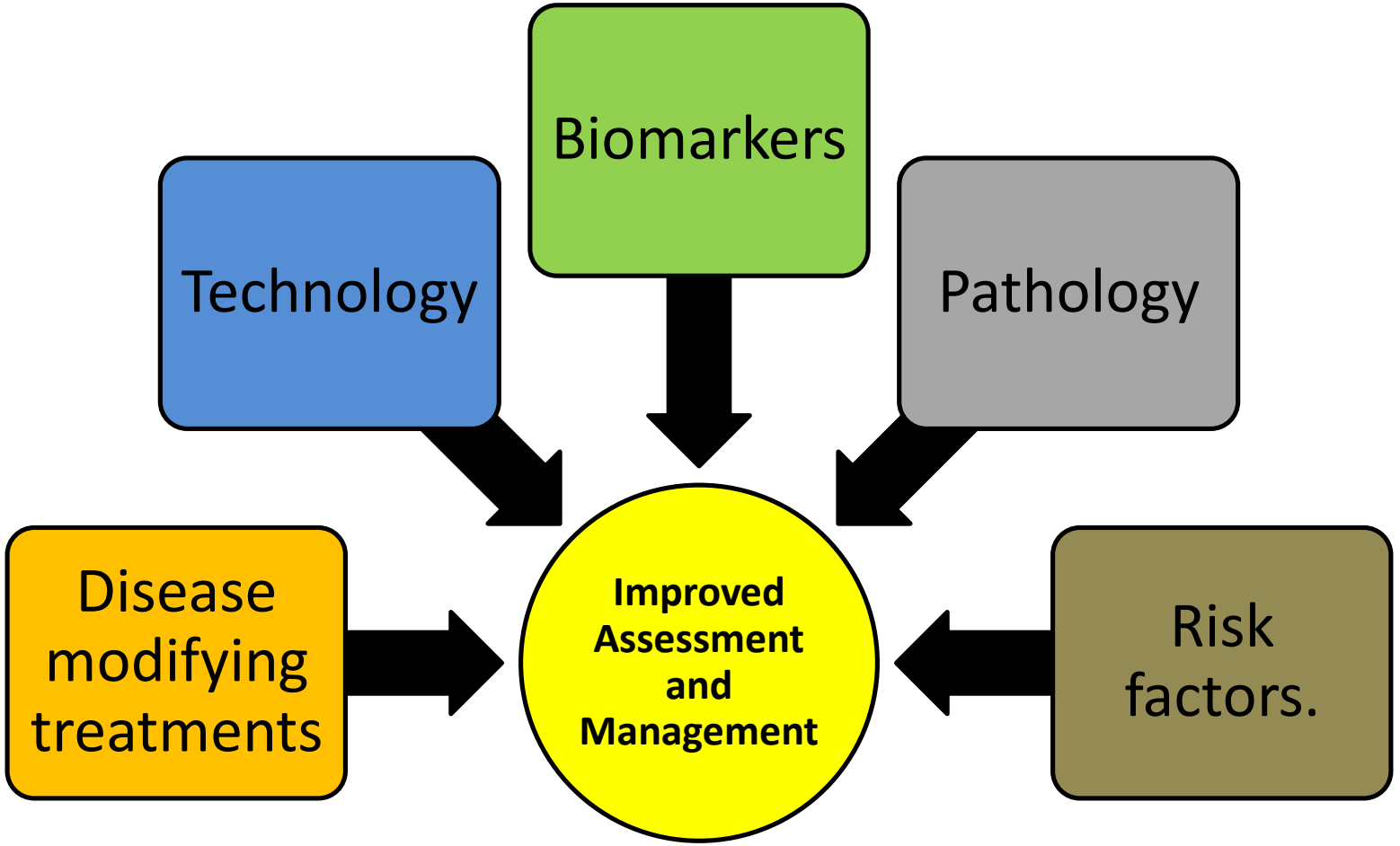

# Drivers for the changes

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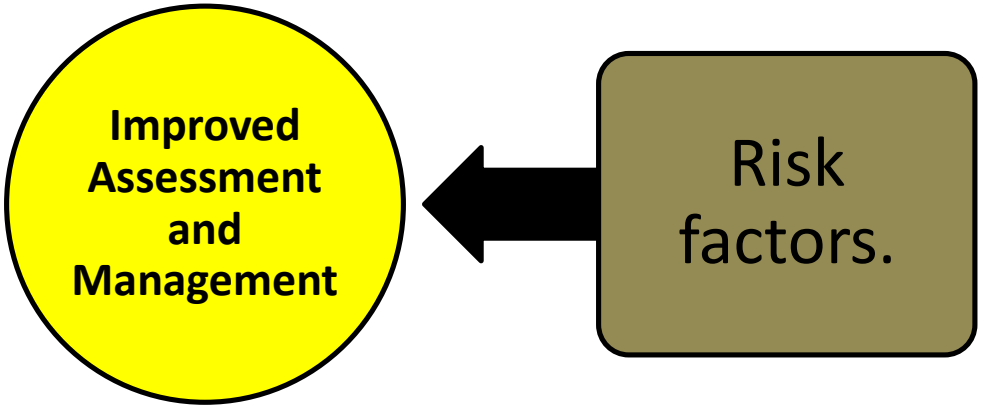
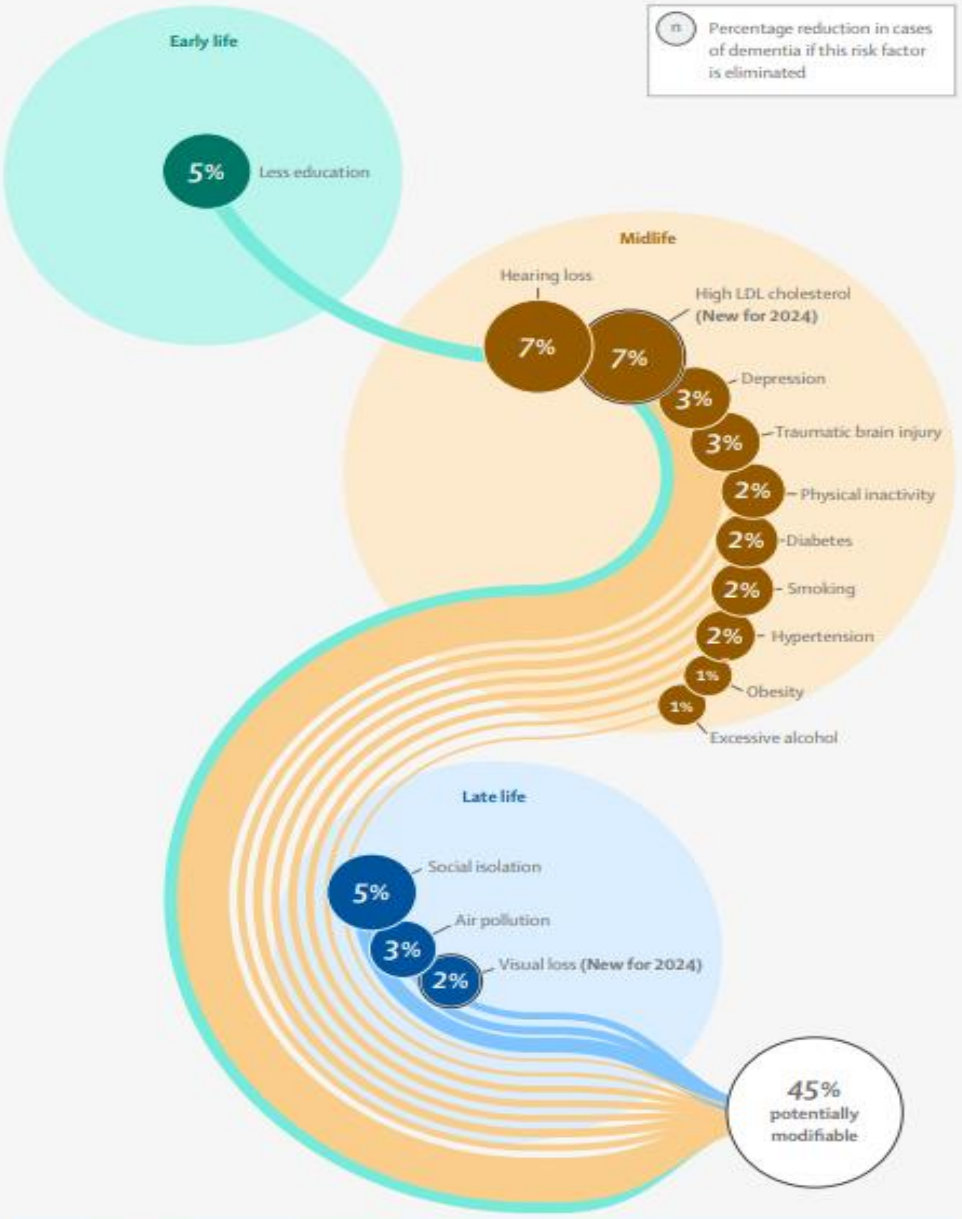


## Risk factors for dementia — 2024 update

The 2024 update to the standing Lancet Commission on dementia prevention, intervention, and care adds two new risk factors (high LDL cholesterol and vision loss) and indicates that nearly half of all dementia cases worldwide could be prevented or delayed by addressing 14 modifiable risk factors.




Read the full commission update at thelancet.com/commissions/dementia-prevention-intervention-care

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Up to 45% of dementia cases could be prevented or delayed by addressing 14 risk factors, including:

- High LDL Cholesterol
- Hearing loss
- High blood pressure
- Air pollution
- Smoking
- Social isolation

# Drivers for the changes

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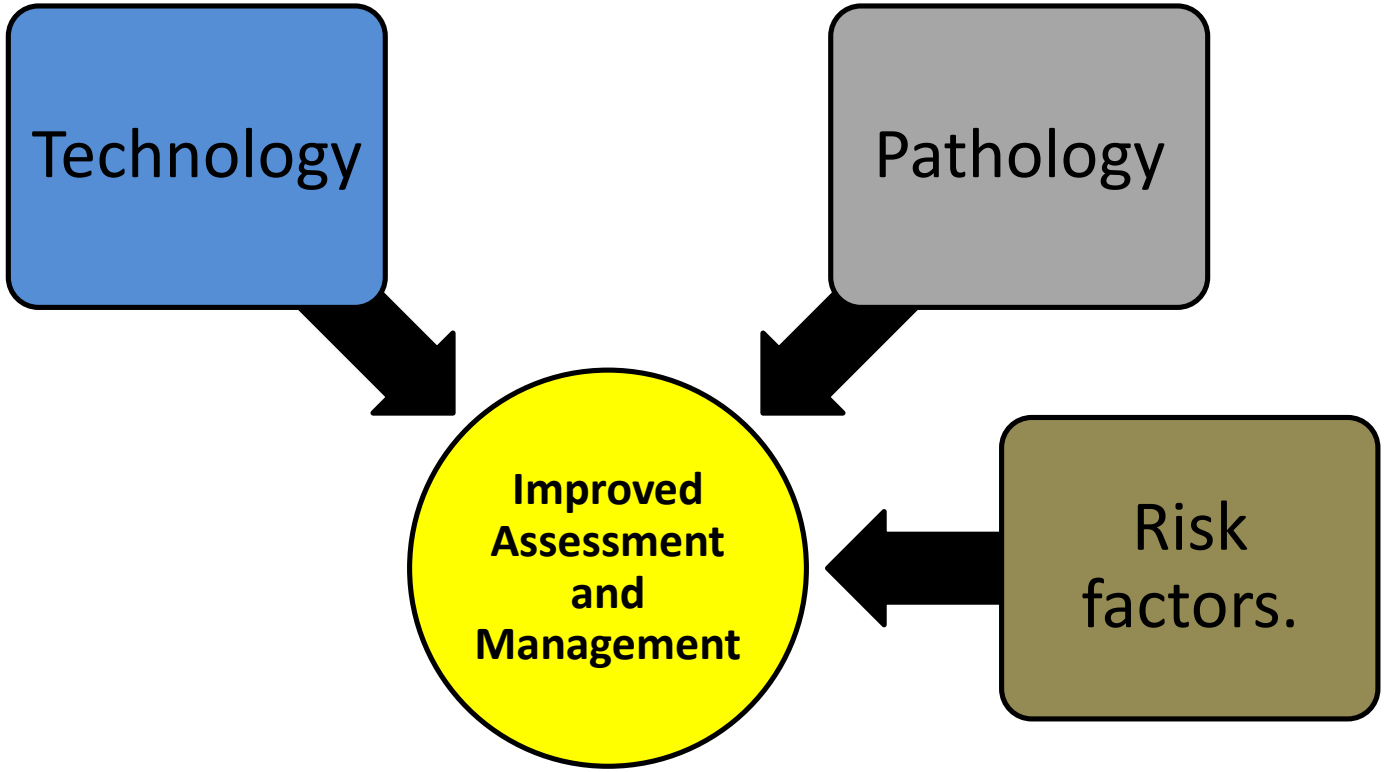


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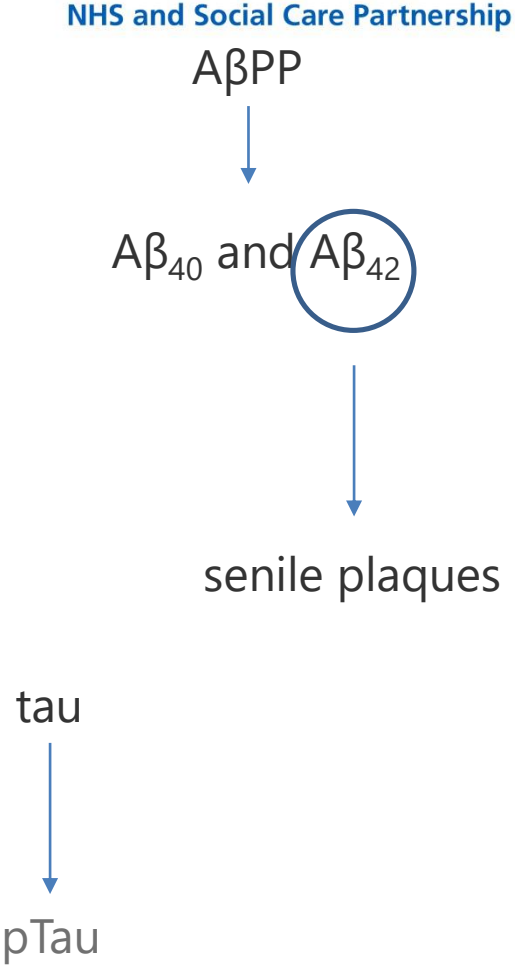
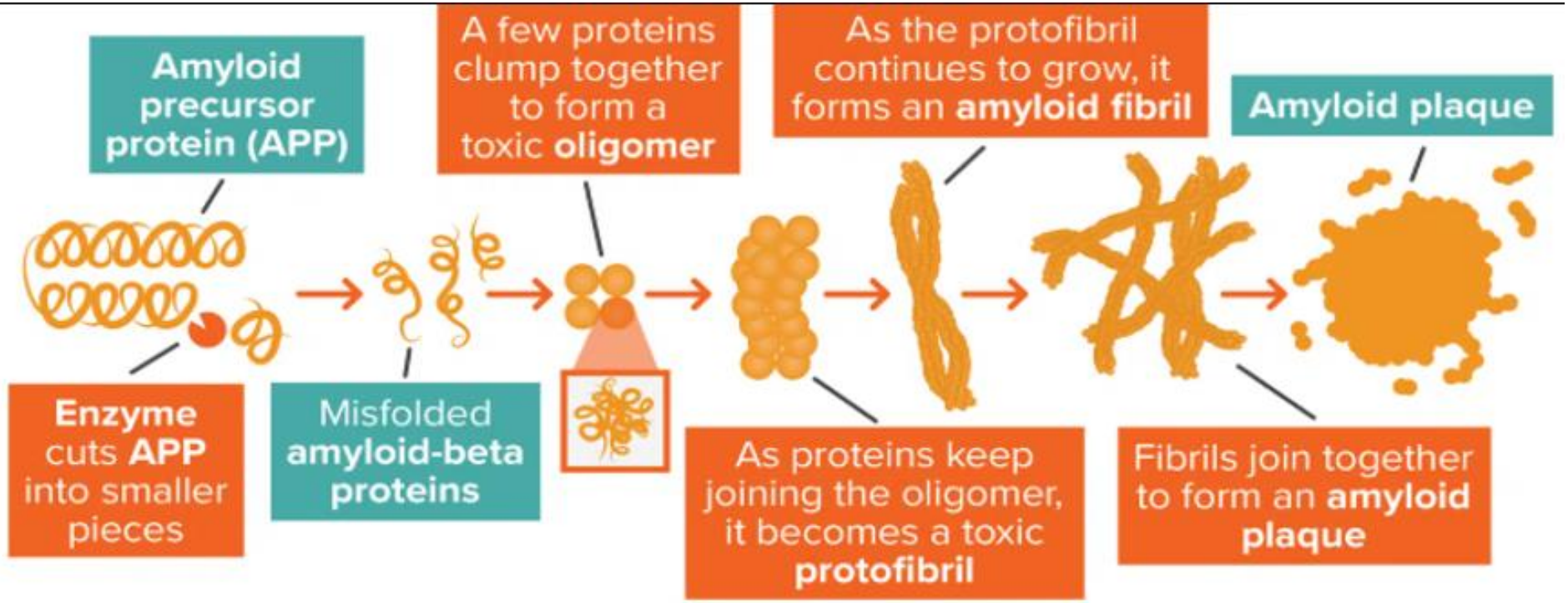
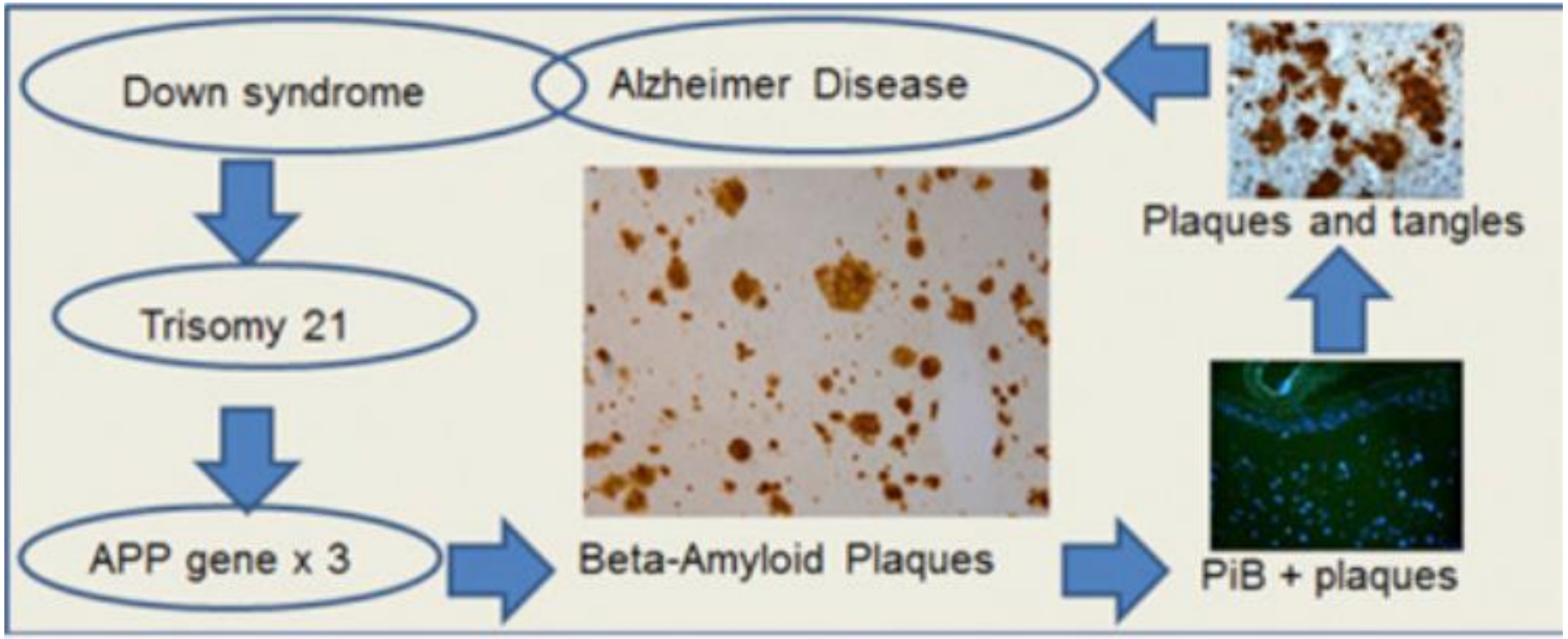
# The pathological features of AD

**The pathological features of AD are mainly characterized by the**

- *Deposition of a great deal of Aβ plaques (SP) in the cerebral cortex and hippocampus* **[A]**
- *P-tau induced Neurofibrillary tangles,* **[T]**
- *Neurodegeneration* **[N]**
- *Acetylcholine deficiency*




Amyloid precursor protein (APP)
Enzyme cuts APP into smaller pieces
Misfolded amyloid-beta proteins
A few proteins clump together to form a toxic oligomer
As proteins keep joining the oligomer, it becomes a toxic protofibril
As the protofibril continues to grow, it forms an amyloid fibril
Fibrils join together to form an amyloid plaque
Amyloid plaque


Down syndrome
Alzheimer Disease
Plaques and tangles
Trisomy 21
APP gene x 3
Beta-Amyloid Plaques
PiB + plaques

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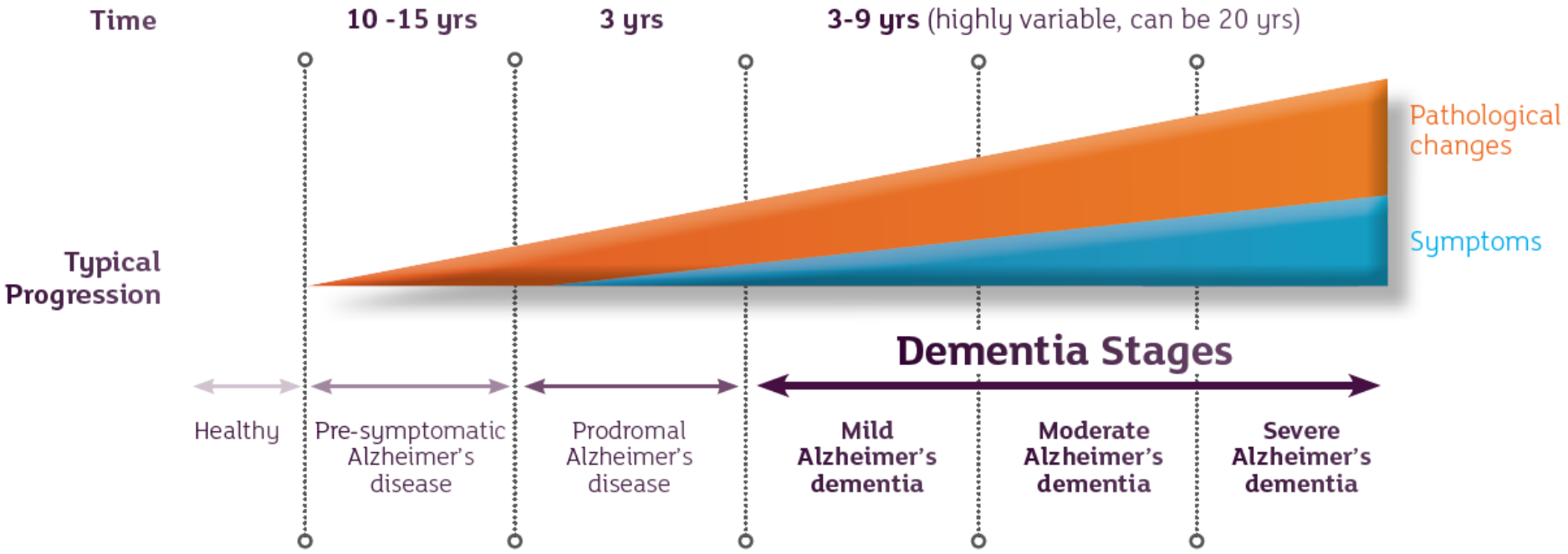
# The continuum model of Alzheimer's disease

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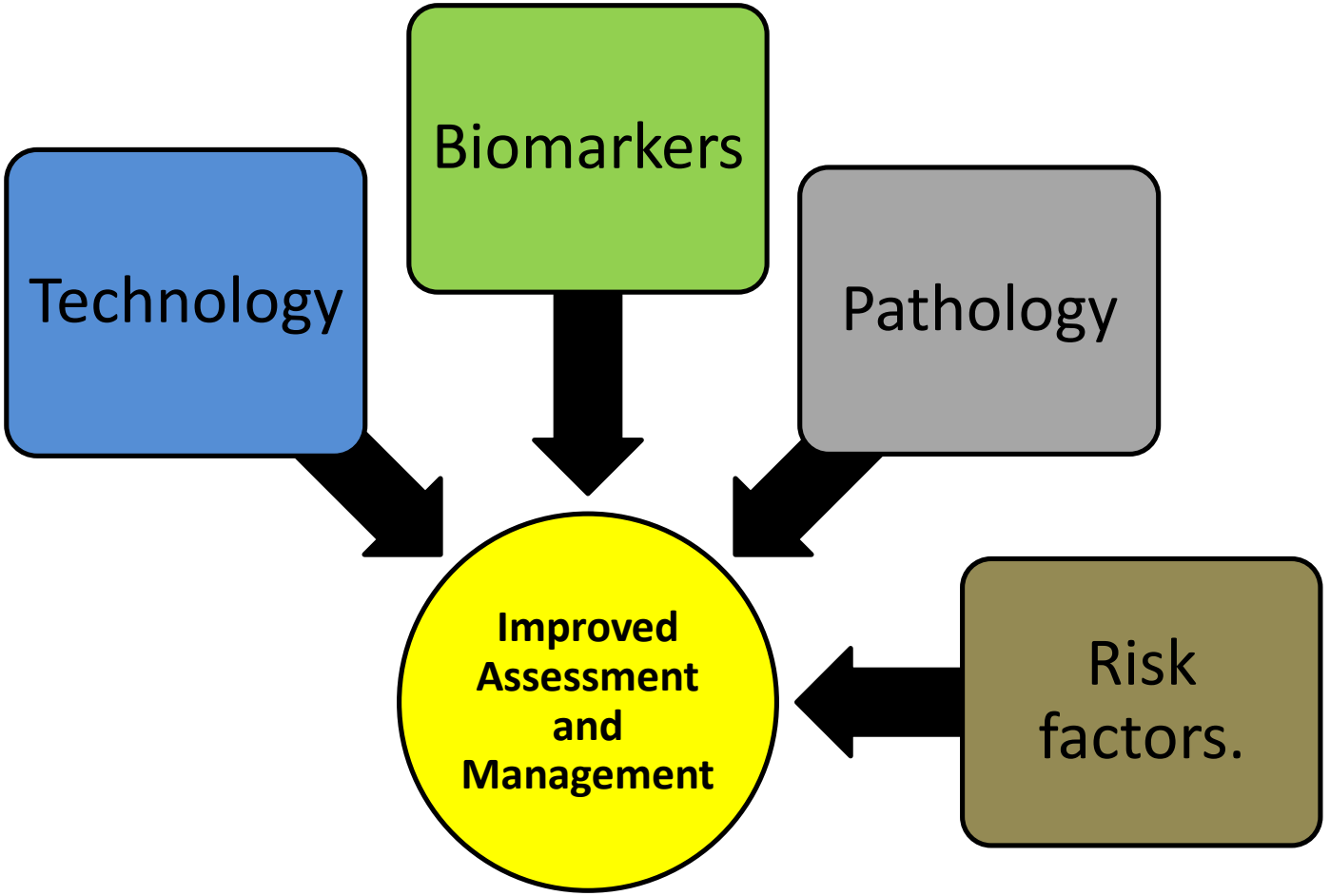

**TABLE 2. KNOWN PATHOLOGIC FACTORS IN ALZHEIMER'S DISEASE AND RELATED BIOMARKERS**

| Factor | Imaging | CSF | Blood |
|---|---|---|---|
| Amyloid-β load | [$^{11}$C]-PIB | Amyloid-β (1-42) | APP 699-711 |
| | [$^{18}$F]-NAV4694 | | Amyloid-β (1-42) |
| | [$^{18}$F]-florbetapir | | Amyloid-β (1-40) |
| | [$^{18}$F]-florbetaben | | |
| | [$^{18}$F]-flutemetamol | | |
| Neurofibrillary tangles | [$^{18}$F]-Ro948 | Phosphorylated tau | The association of serum phosphorylated tau with tangles is unclear |
| | [$^{18}$F]-AV1451 | | |
| | [$^{18}$F]-MK6240 | | |
| | [$^{18}$F]-PI2620 | | |
| | [$^{11}$C]-PBBB3 | | |
| Neurodegeneration | MRI | Total tau | Neurofilament light chain (NFL) |
| | [$^{18}$F]-FDG | Neurofilament light chain (NFL) | |
| | | Neurogranin (Ng) | |
| | | Synaptosomal-associated protein 25 (SNAP-25) | |
| | | Neuron-specific enolase (NSE); heart fatty acid binding protein (HFABP) | |
| Vascular load | MRI | CSF albumin:plasma albumin ratio | α-synuclein |
| Lewy body load | N/A | α-synuclein | N/A |
| Neuroinflammation | Microglial activation: | Microglial activation: | Microglial activation: |
| | [$^{11}$C]PK11195 | Chitinase-3-like protein 1 (YKL-40) | Chitinase-3-like protein 1 (YKL-40) |
| | [$^{11}$C]PBR28 | Soluble TREM2 (sTREM2) | Cytokines: |
| | [$^{11}$C]DAA1106 | Cytokines: TNF-α, IL-6, IL-1β | TNF-α, IL-1 β, |
| | [$^{18}$F]DPA714 | Chemokines: | Chemokines: |
| | [$^{11}$C]DPA713 | Monocyte chemotactic protein 1 [MCP-1] | Monocyte chemotactic protein 1 |
| | [$^{18}$F]ER176 | | |
| | [$^{18}$F]GE180 | | |
| | [$^{11}$C]L-des-deprenyl | | |

Serge Gauthier, Pedro Rosa-Neto, PRACTICAL NEUROLOGY JUNE 2019

# Bio markers

Kent and Medway NHS and Social Care Partnership Trust

## NICE recommended

- Structural imaging (CT/ MRI)
- Glucose (FDG) PET
- Perfusion (HMPAO) SPECT
- Dopamine (FP-CIT) SPECT or PET
- MIBG Cardiac imaging
- CSF (amyloid and tau)

## In Development

- **Amyloid PET –limited availability**
- **Tau PET –not clinically available in most countries**
- **Blood (amyloid, ptau, NFL, GFAP etc) –rapidly developing, approaching clinical use**

Blood biomarkers have the potential to be a cost-effective and noninvasive screening tool for dementia.

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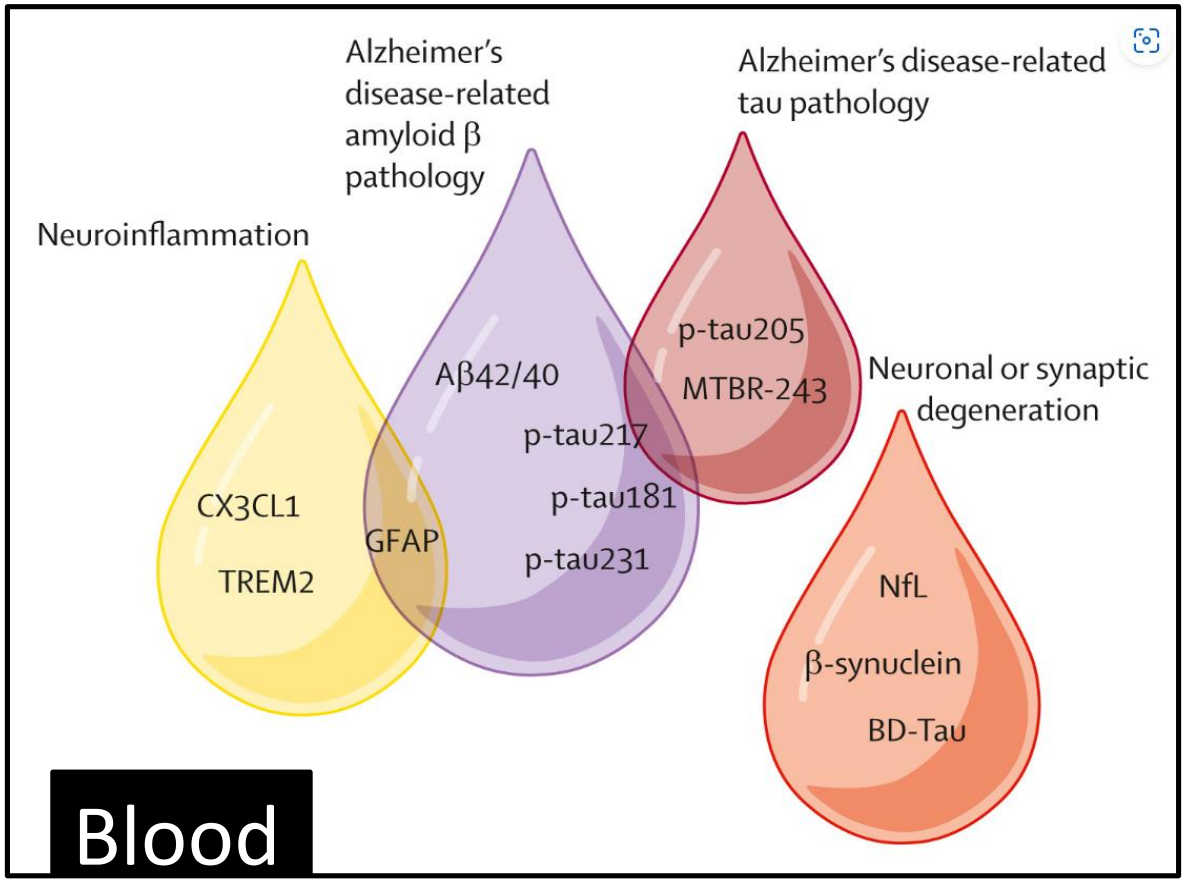


Blood biomarkers need to be standardized across different analytical platforms and patient populations.

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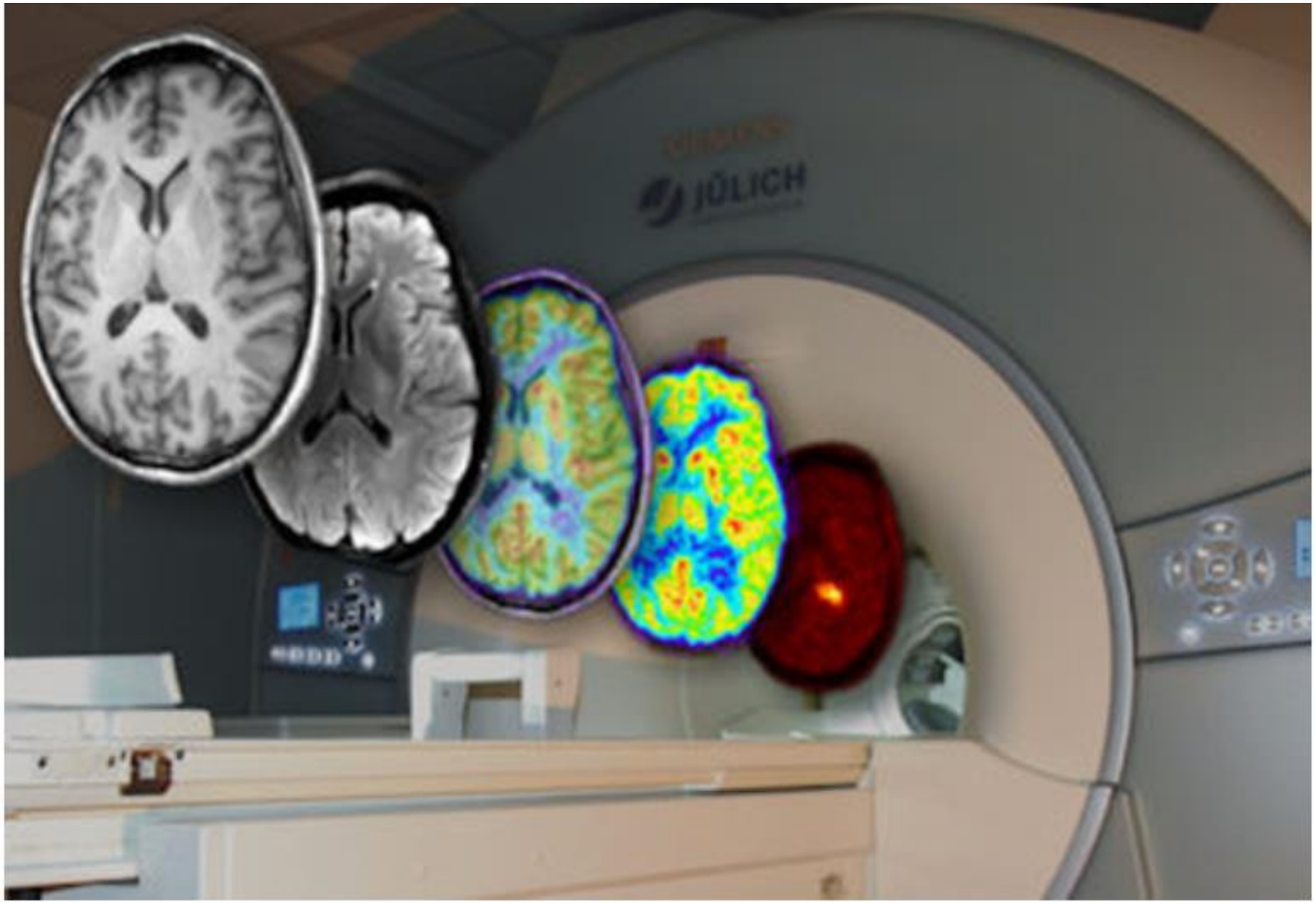


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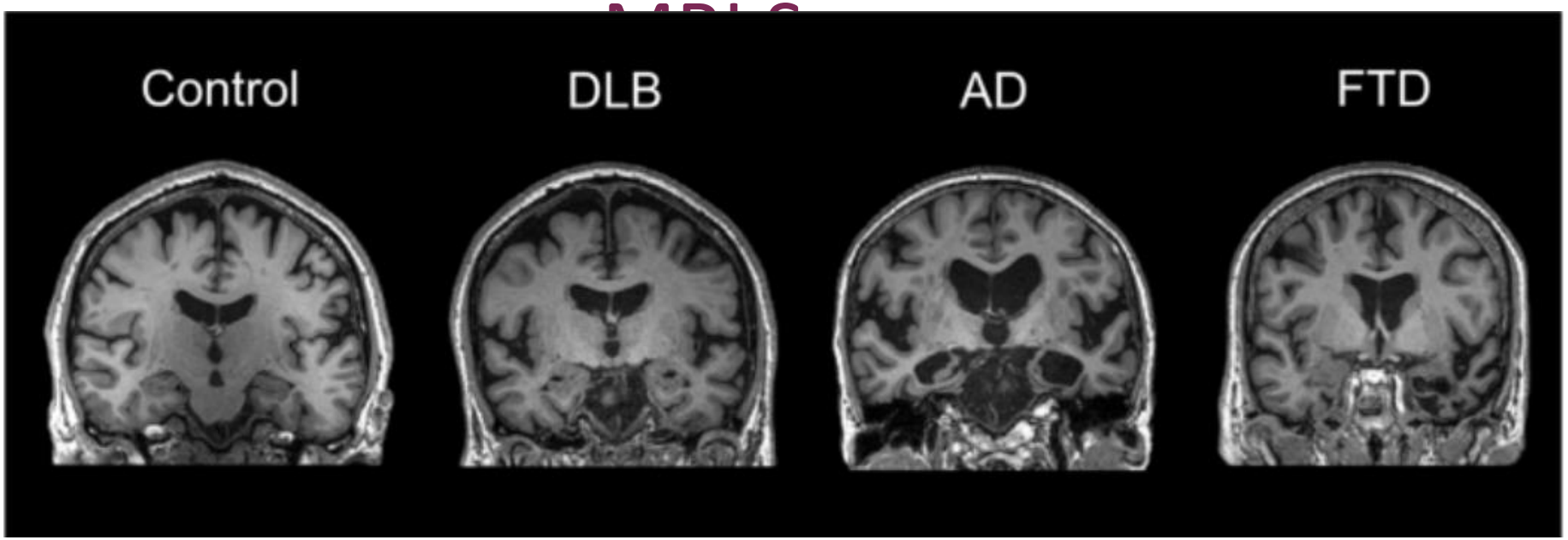
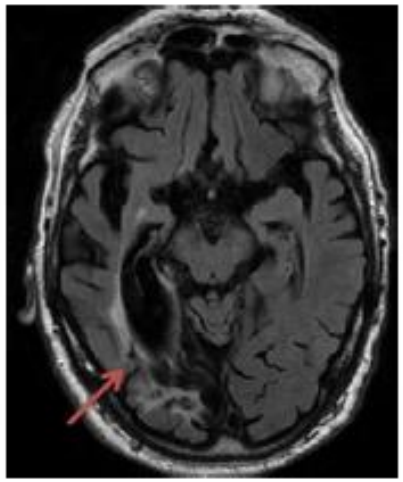
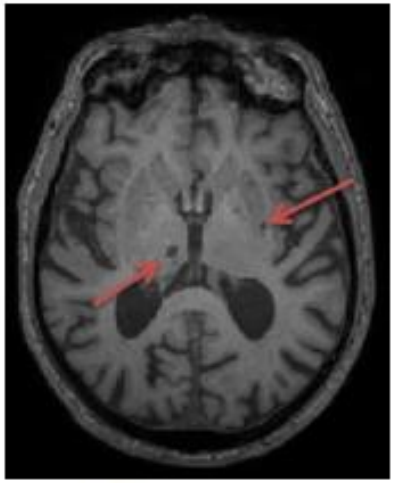
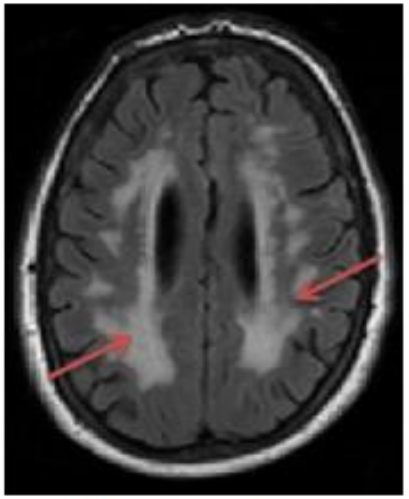

Control
DLB
AD
FTD



Cortical infarcts



Lacunar
Infarcts



Extensive
>25%) WML

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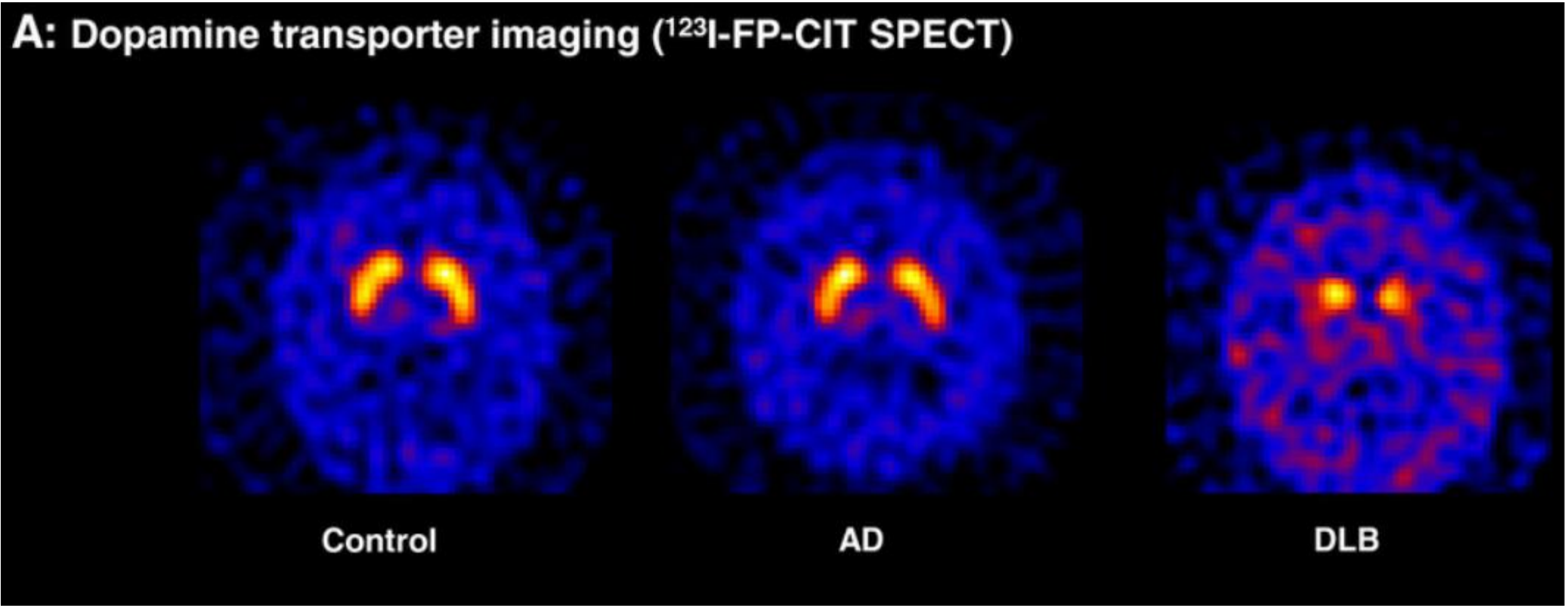
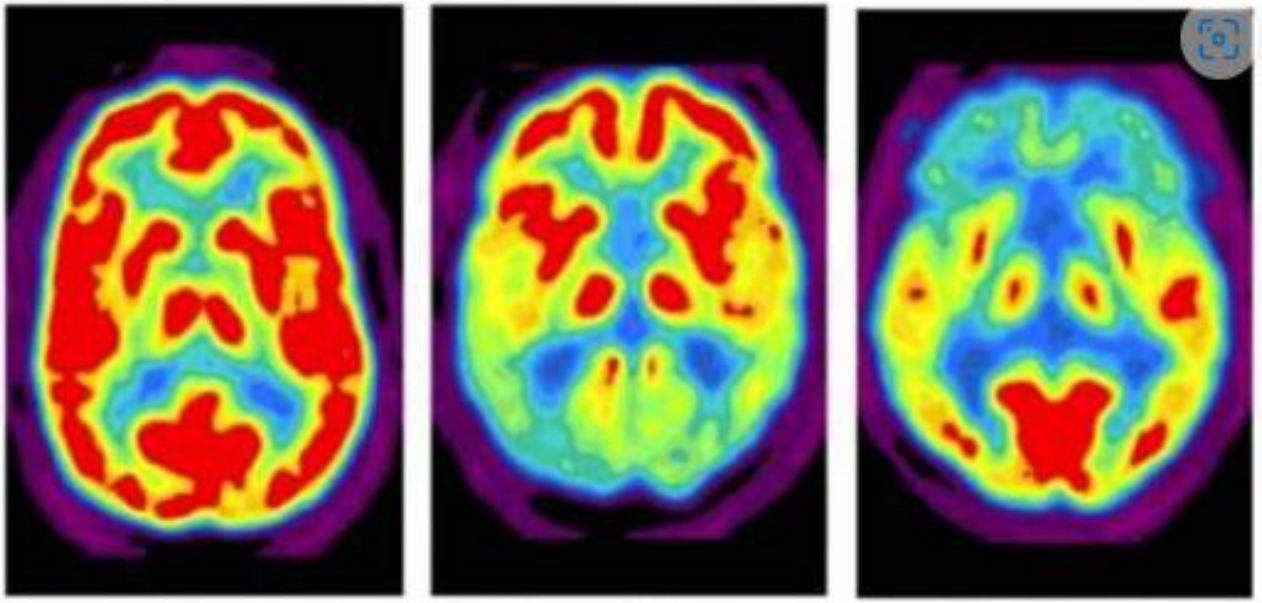
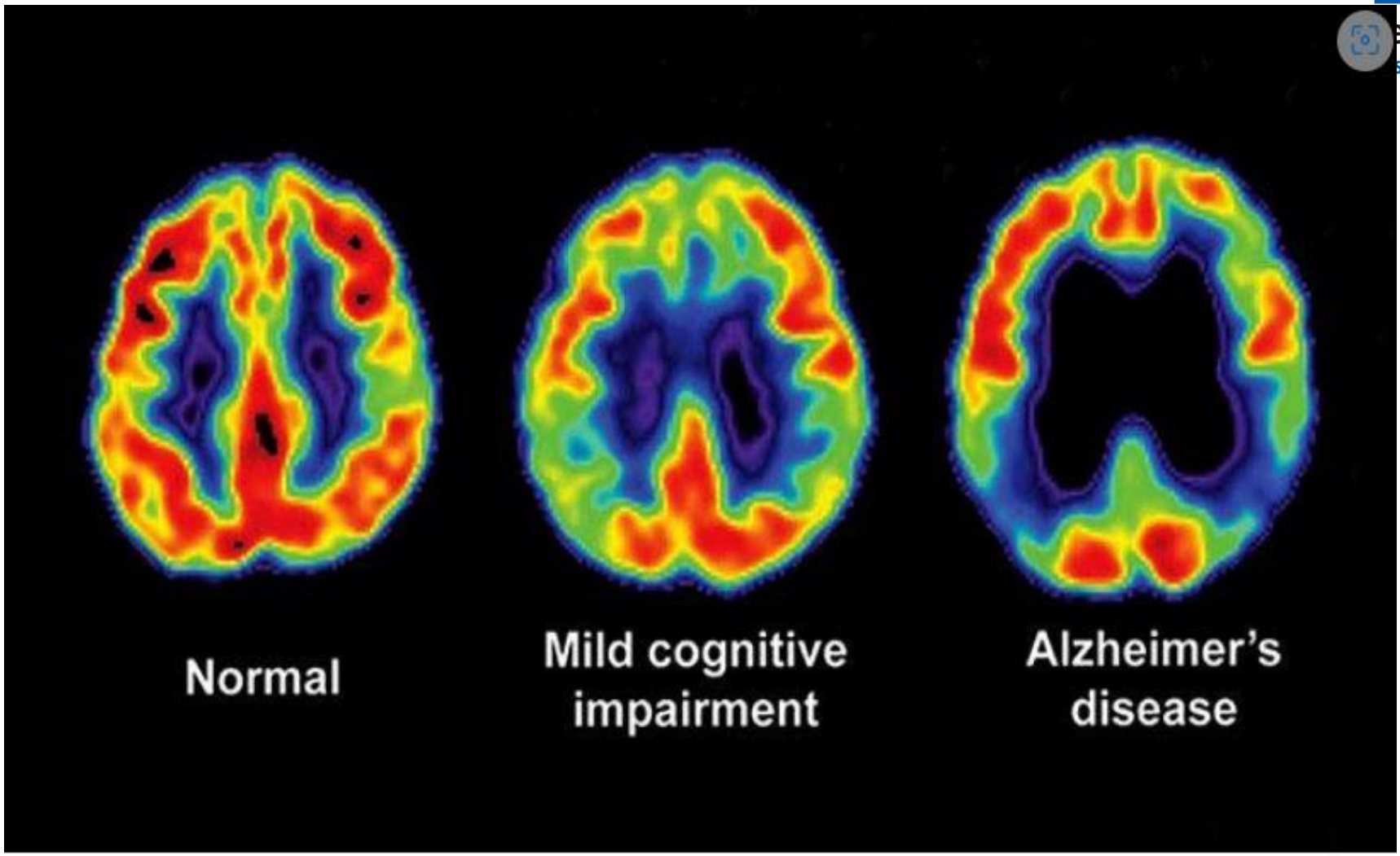
# SPECT scan (DAT Scan)

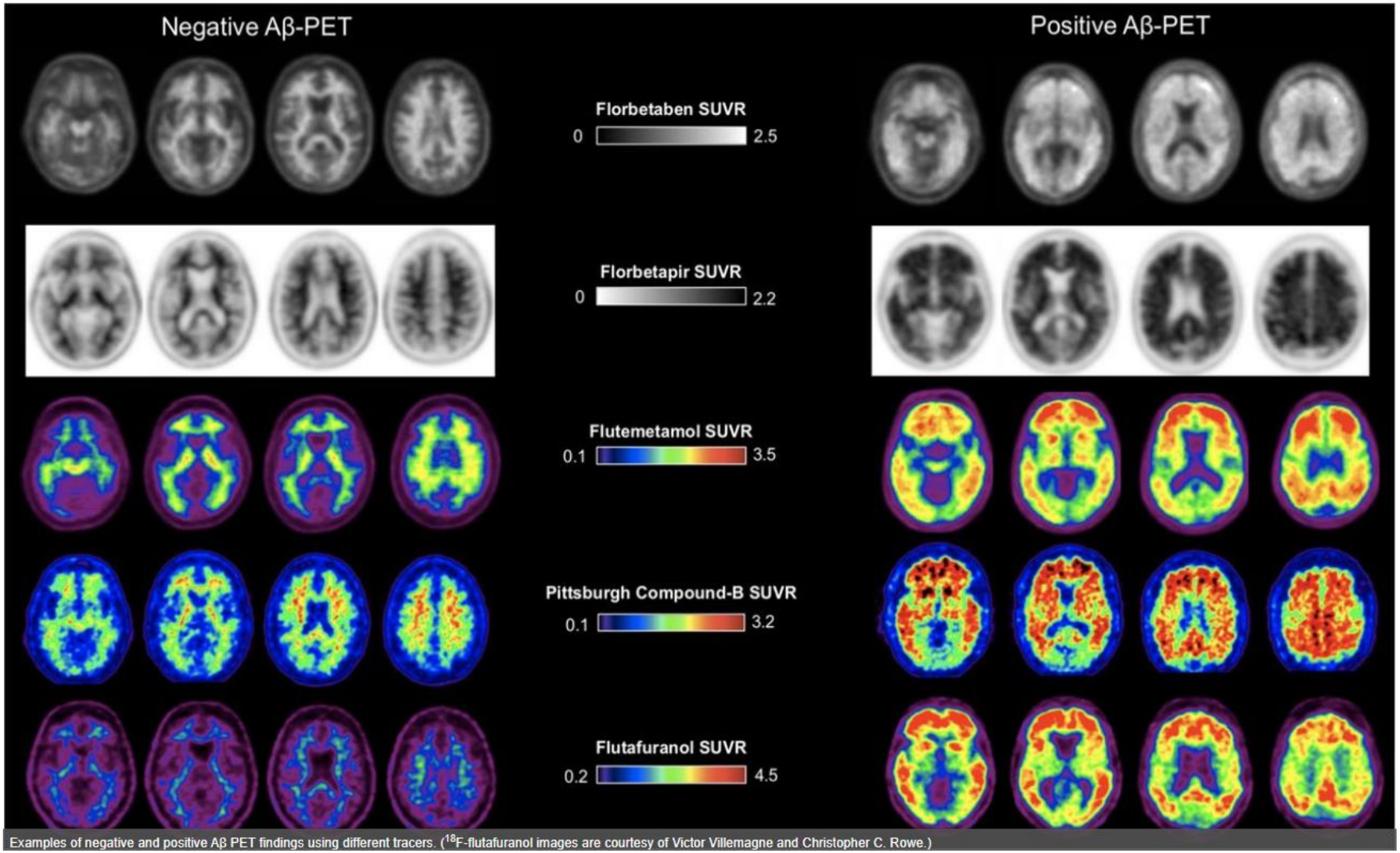


# FDG-PET (fluorodeoxyglucose-positron emission tomography-CT)

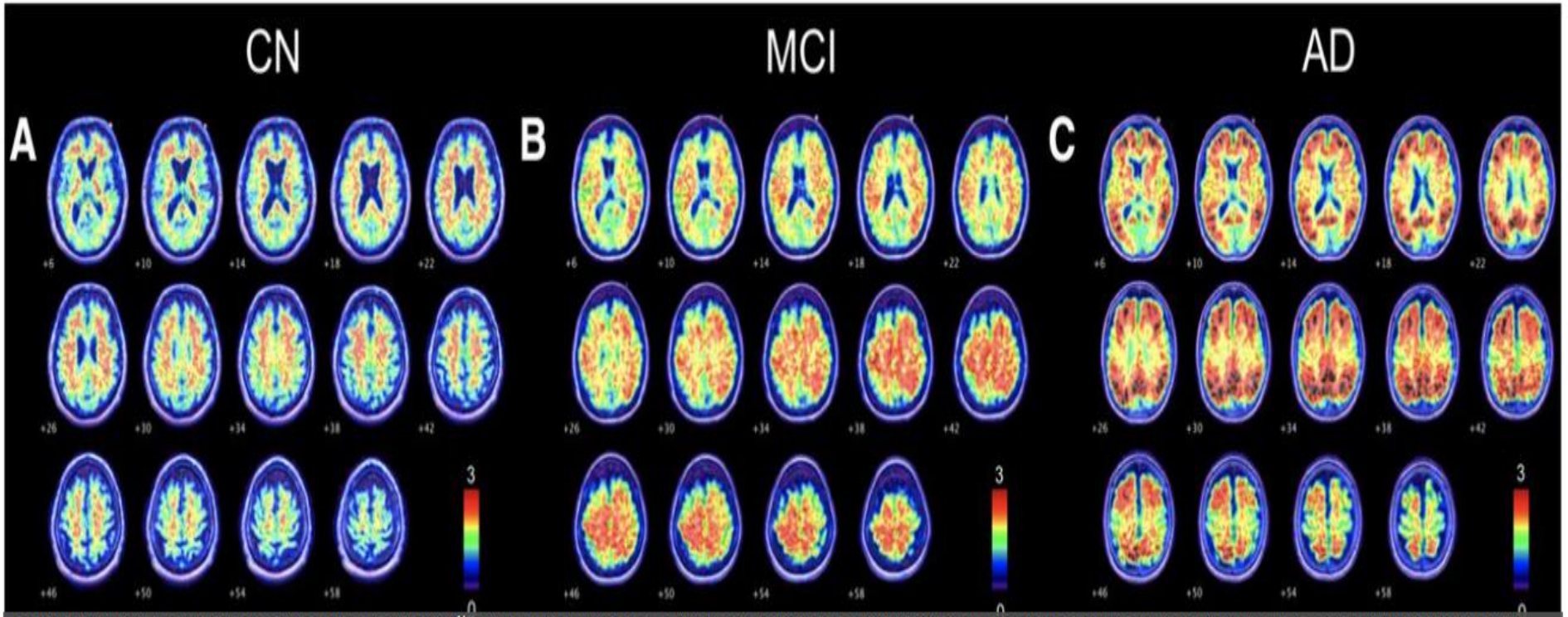


| Normal | Alzheimer's Dementia | Frontal Lobe Dementia (Pick's Disease) |
|---|---|---|
| Consistent metabolic activity throughout the cerebral cortex | Reduced metabolic activity in the temporal and parietal lobes | Reduced metabolic activity in the frontal lobe |


Normal
Mild cognitive impairment
Alzheimer's disease




Examples of negative and positive Aβ PET findings using different tracers. ($^{18}$F-flutafuranol images are courtesy of Victor Villemagne and Christopher C. Rowe.)




Evolution of amyloid PET positivity across AD spectrum. (A) Positive $^{11}$C-PiB scan of cognitively normal (CN) participant, in which significant binding is observed in precuneus, posterior cingulate cortex, and medial prefrontal areas. (B)

# Proposed AD criteria are becoming more biological

| | Preclinical AD | | MCI due to AD | AD Dementia | | |
|---|---|---|---|---|---|---|
| | **Stage 1** | **Stage 2** | **Stage 3**** | **Stage 4** | **Stage 5** | **Stage 6** |
| **Pathophysiological changes – biomarkers** | + | ++ | +++ | ++++ | +++++ | +++++ |
| **Cognition** | Nil | Subtle abnormalities on sensitive measures | More apparent detectable abnormalities on sensitive measures | Mild Dementia | Moderate Dementia | Severe Dementia |
| **Function** | Nil | Nil | Mild but detectable functional impairment | Yes + | Yes ++ | Yes +++ |

**FDA: "This stage roughly corresponds to "mild cognitive impairment" and may also encompass patients in late Stage 2 or early Stage 4".

Jack et al, 2024; FDA Guidelines March 2024

# Drivers for the changes

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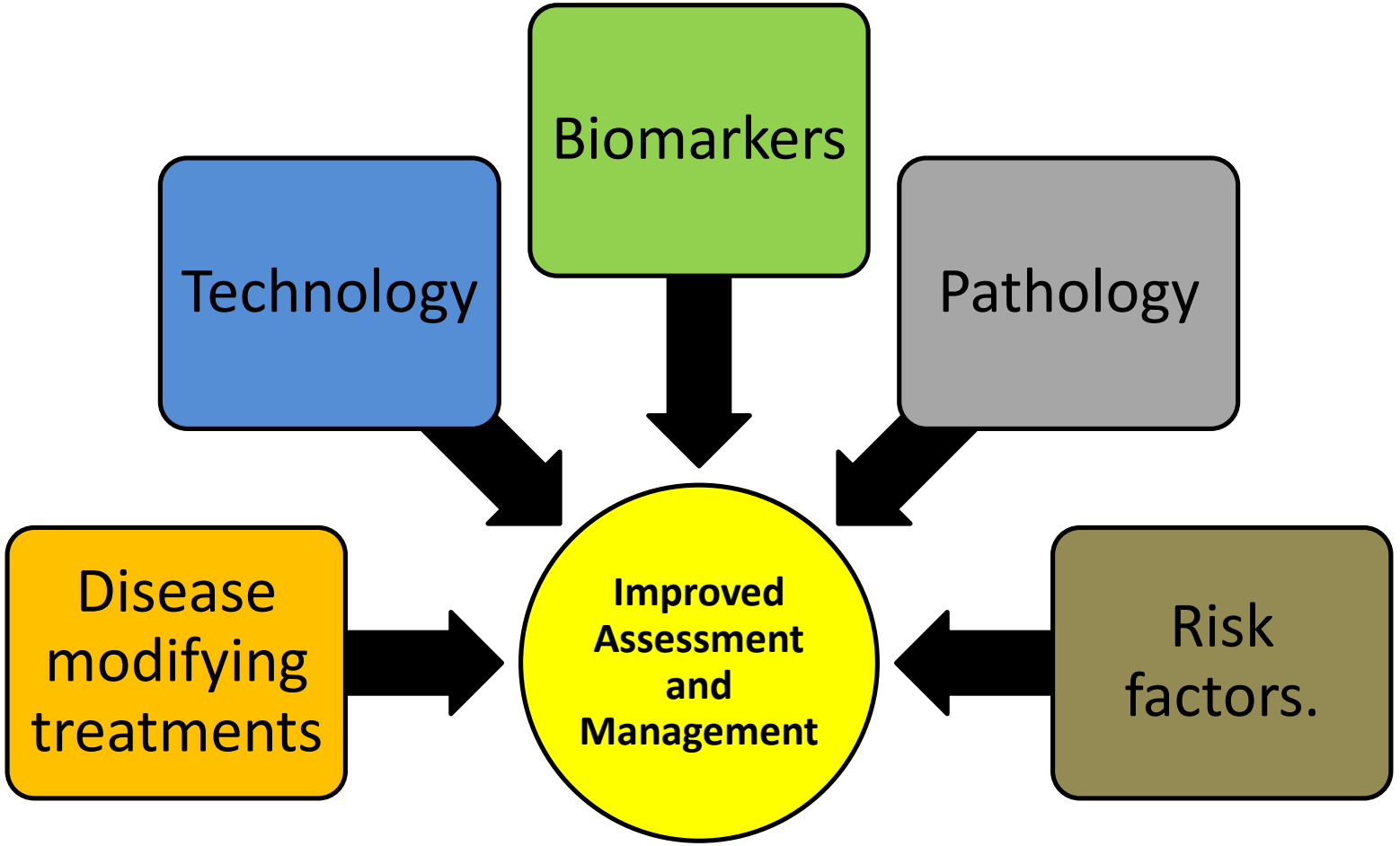
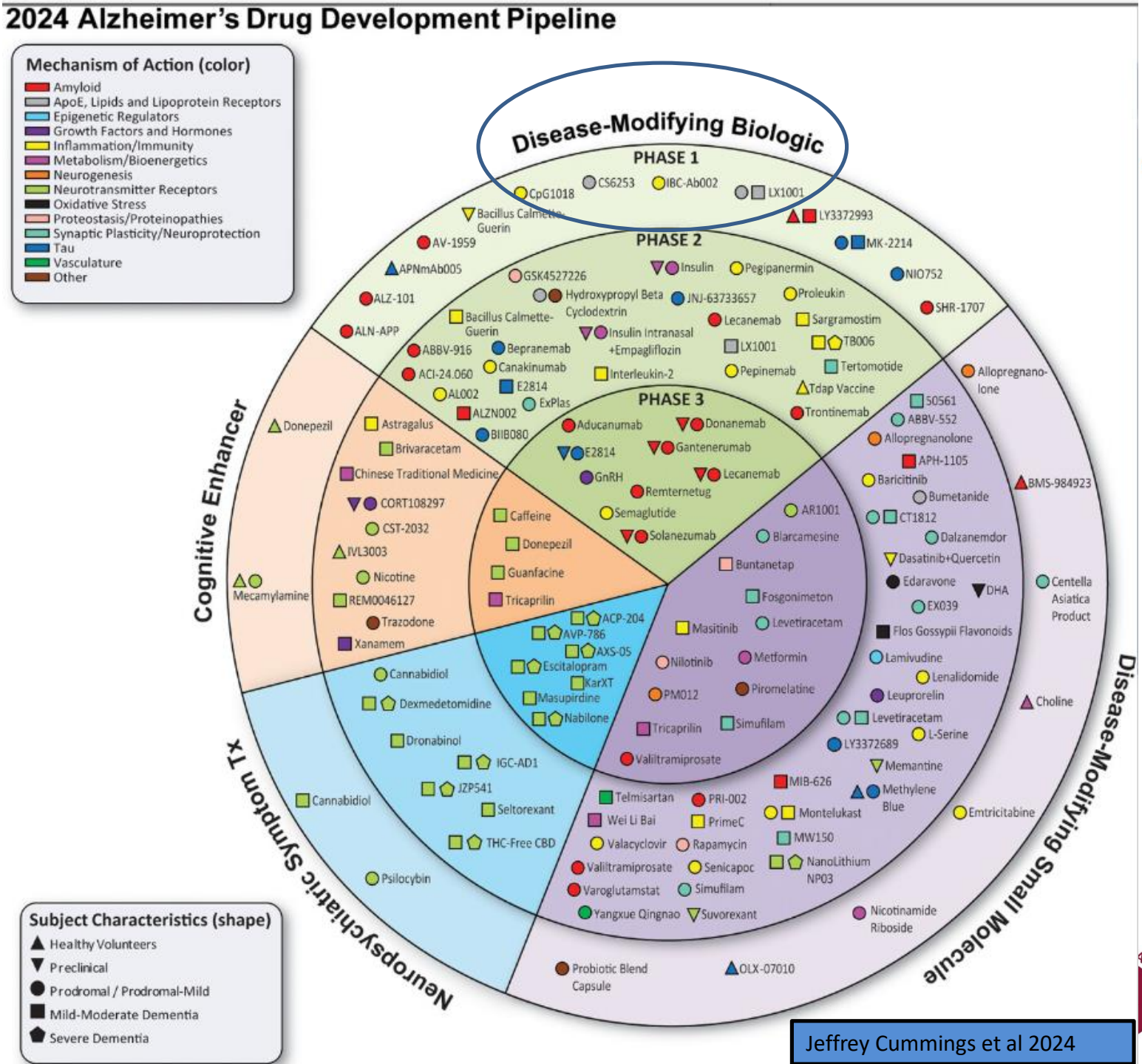


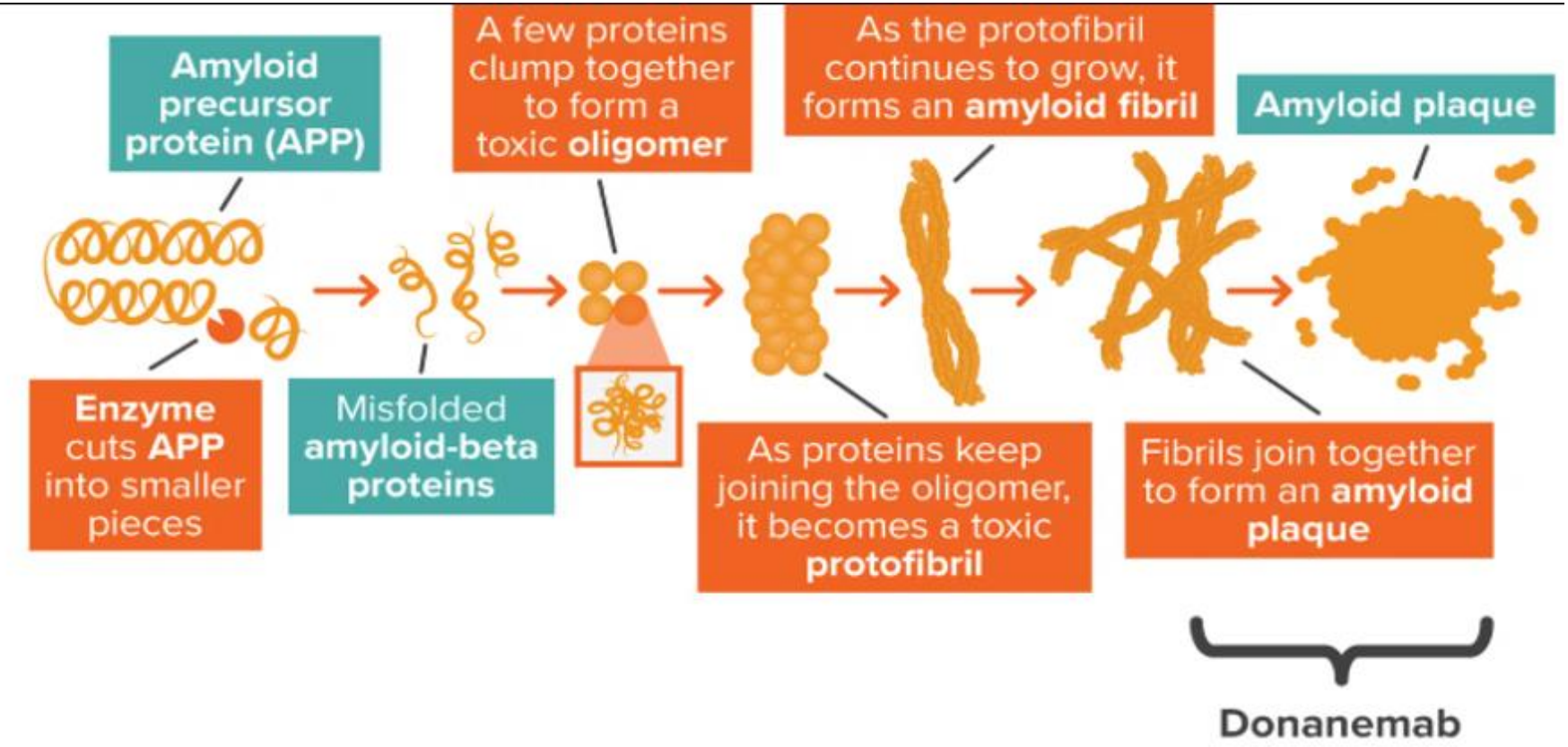
# 2024 Alzheimer's Drug Development Pipeline

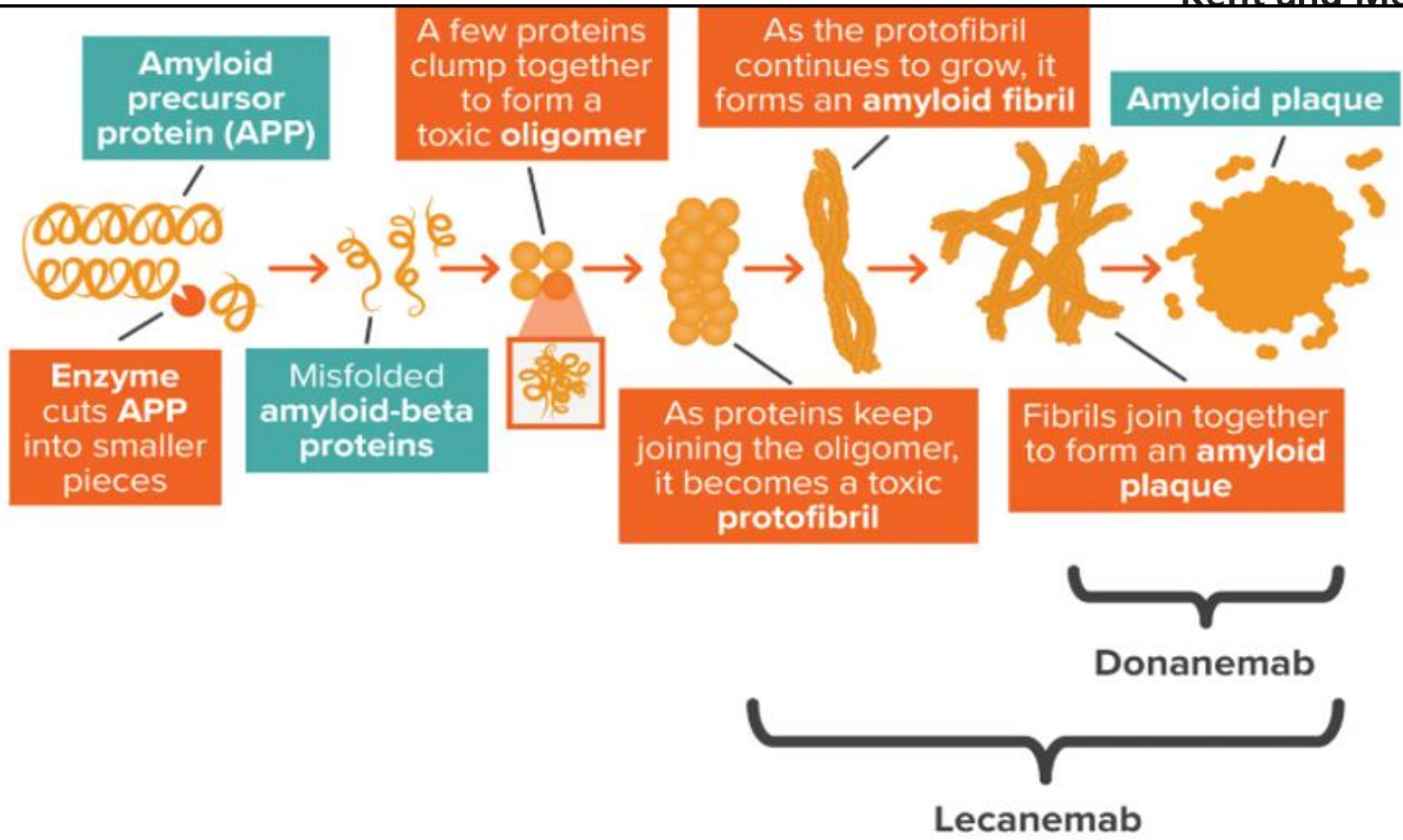



In the 2024 Alzheimer's disease drug development pipeline, there are 164 clinical trials assessing 127 drugs.

Common processes targeted include **Neurotransmitter receptors Inflammation Amyloid and Synaptic plasticity**

Jeffrey Cummings et al 2024


Amyloid precursor protein (APP)
A few proteins clump together to form a toxic oligomer
As the protofibril continues to grow, it forms an amyloid fibril
Amyloid plaque
Enzyme cuts APP into smaller pieces
Misfolded amyloid-beta proteins
As proteins keep joining the oligomer, it becomes a toxic protofibril
Fibrils join together to form an amyloid plaque
Donanemab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Amyloid plaque
Donanemab
Lecanemab

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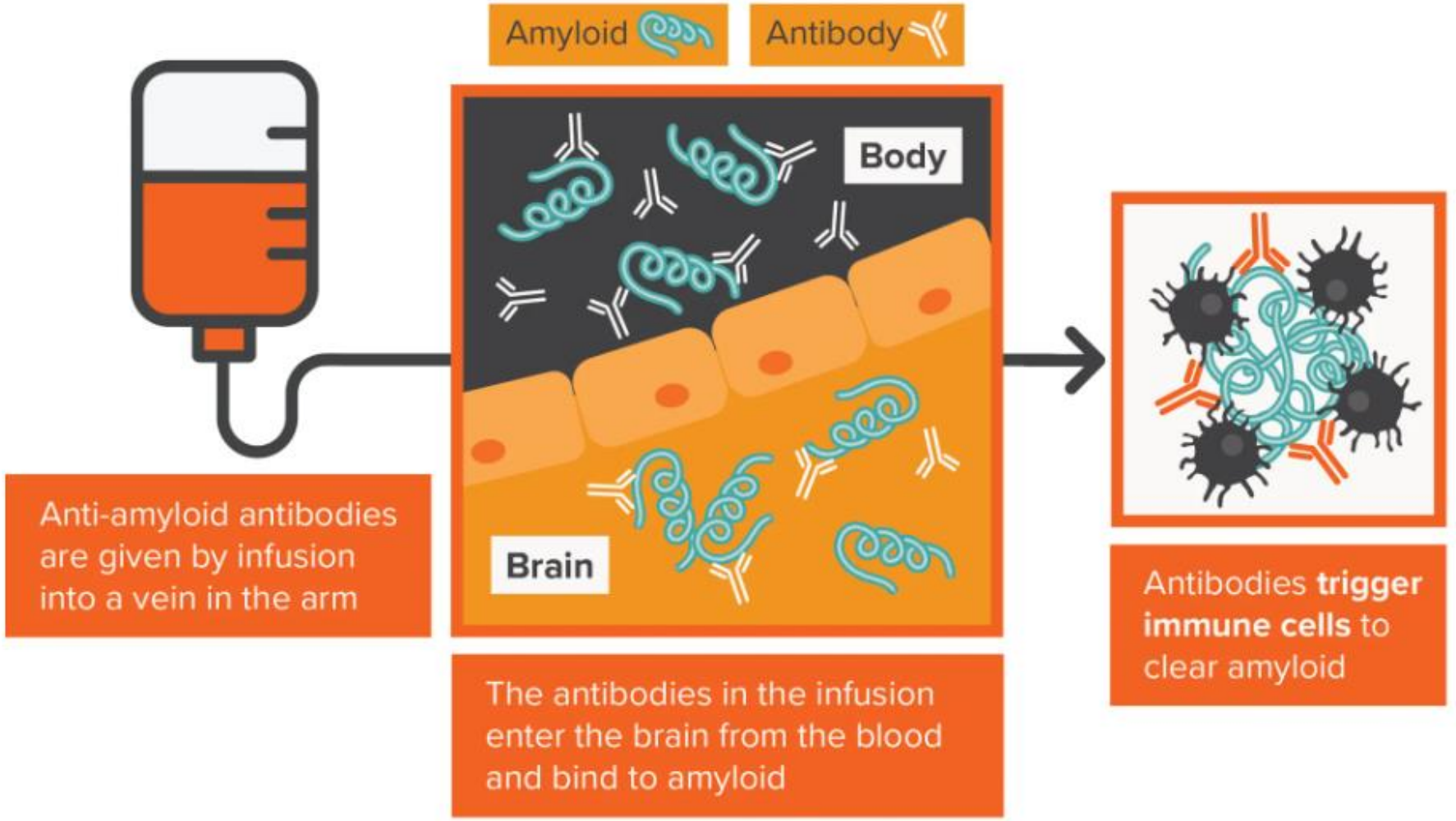


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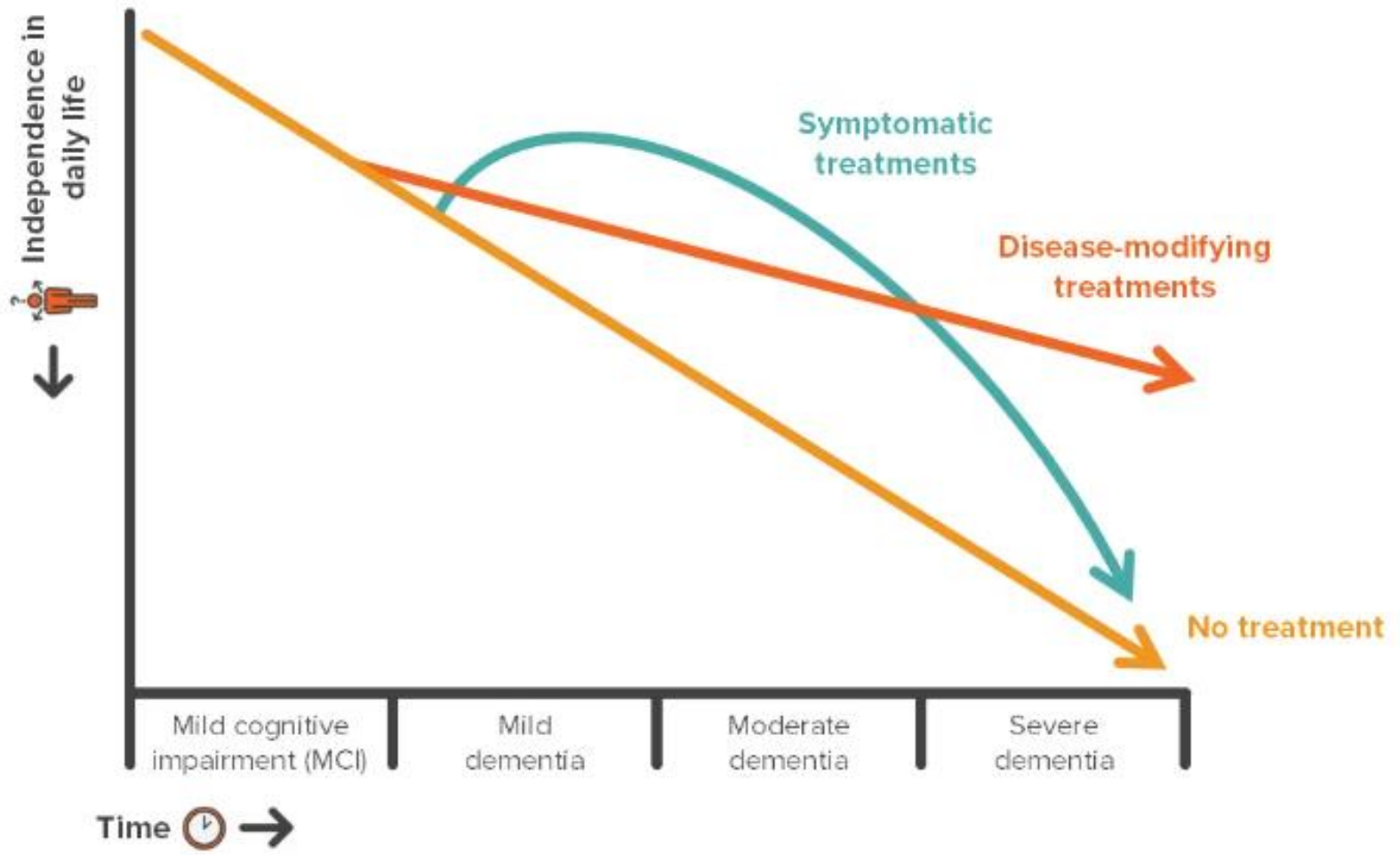
Independence in daily life
Symptomatic treatments
Disease-modifying treatments
No treatment
Mild cognitive impairment (MCI)
Mild dementia
Moderate dementia
Severe dementia
Time

# DISEASE-MODIFYING TREATMENTS FOR DEMENTIA

NHS
Kent and Medway

## Inclusion criteria

- Mild or early stage Alzheimer's disease.
- Mild cognitive impairment who have high levels of a Amyloid protein in their brain.

## Exclusion criteria

APOE 4 Homozyous

## Requirements

- Amyloid PET scan
- CSF analysis.

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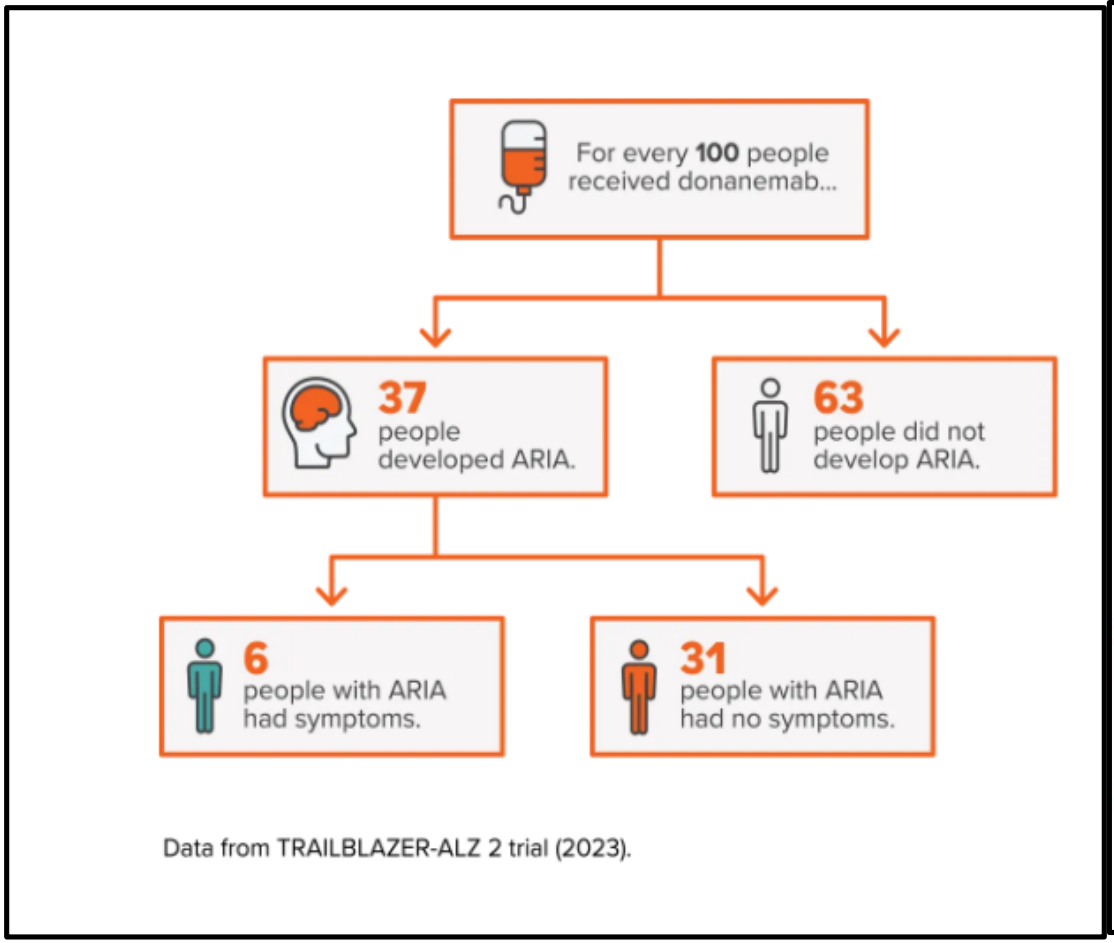


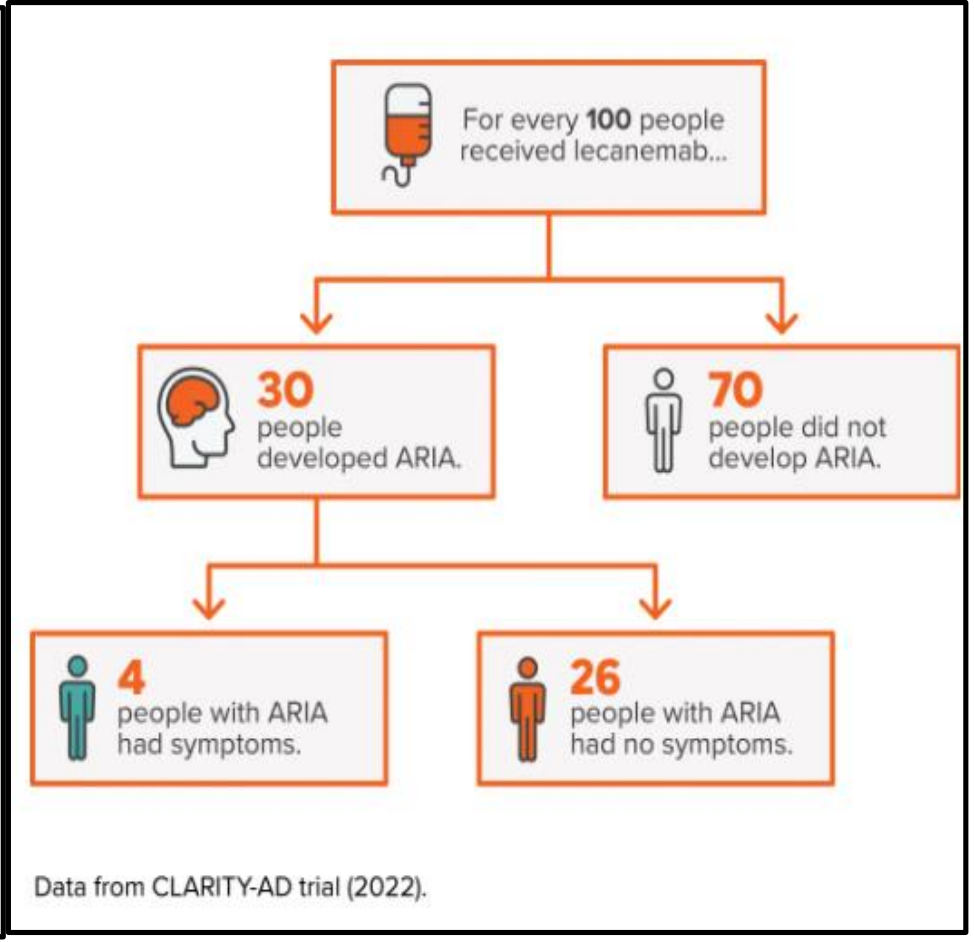


**Symptoms of ARIA may include**:

Headache
Dizziness
Nausea
Seizures.
Confusion
Vision changes
Difficulty walking

**Infusion related side effects:**

fever, redness and itchiness.

1in 4 for Lecanemab

1in 10 for Donanemab.

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| Aspect | Lecanemab | Donanemab |
|---|---|---|
| Binding to Amyloid Plaque | Attaches to amyloid in its early stage of fiber formation | Acts when fibers conglomerate to form more substantial plaques |
| Rate of Amyloid Plaque Removal | Potentially slower in plaque removal but diminishes oligomers, mitigating brain damage | Rapid plaque removal, showing a marked decline in amyloid presence as early as six months |
| Amyloid-related Imaging Abnormalities (ARIA) | ARIA manifestations tend to manifest over a more extended period | Associated with a higher occurrence rate of ARIA, predominantly in initial treatment phases |
| Treatment Regimen | Administered intravenously, requiring bi-weekly dosing | Administered intravenously, typically dispensed once a month |







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Medicines & Healthcare products Regulatory Agency


NH


GOV.UK

Home > Health and social care > Public health > Health conditions > Dementia

Press release

# Lecanemab licensed for adult patients in the early stages of Alzheimer's disease

NICE National Institute for Health and Care Excellence

## Benefits of new Alzheimer's treatment lecanemab are too small to justify the cost to the NHS

Our draft recommendation follows analysis of clinical trial evidence and reviewing the benefits of slowing disease progression, with the cost of treatment.

GOV.UK

Home > Health and social care > Medicines, medical devices

Press release

# Donanemab licensed for early stages of Alzheimer's disease in adult patients who have one or no copies of apolipoprotein E4 gene

## New Alzheimer's treatment donanemab does not currently demonstrate value for the NHS says NICE

More evidence is needed on the clinical and cost-effectiveness of donanemab, a new treatment for mild Alzheimer's disease.

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Original Investigation

August 19, 2024

# Lecanemab and Vascular-Amyloid Deposition in Brains of People With Down Syndrome

Lei Liu, MD, PhD[1]; Adriana Saba, MSc[1]; Jesse R. Pascual, BS[2]; et al

» Author Affiliations

*JAMA Neurol.* 2024;81(10):1066-1072. doi:10.1001/jamaneurol.2024.2579

**Findings** Lecanemab bound to amyloid plaques in all 15 Down syndrome cases studied in patients older than 43 years. Notably, lecanemab also extensively labeled cerebral amyloid angiopathy in Down syndrome.

**Conclusions and Relevance** These findings suggest significant binding of lecanemab to cerebral amyloid angiopathy in DS.
Lecanemab should be rigorously tested in clinical trials for AD in the DS population to determine its safety and efficacy, especially in those older than 43 years.

NHS Kent and Medway Social Care Partnership Trust

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**Semaglutide**

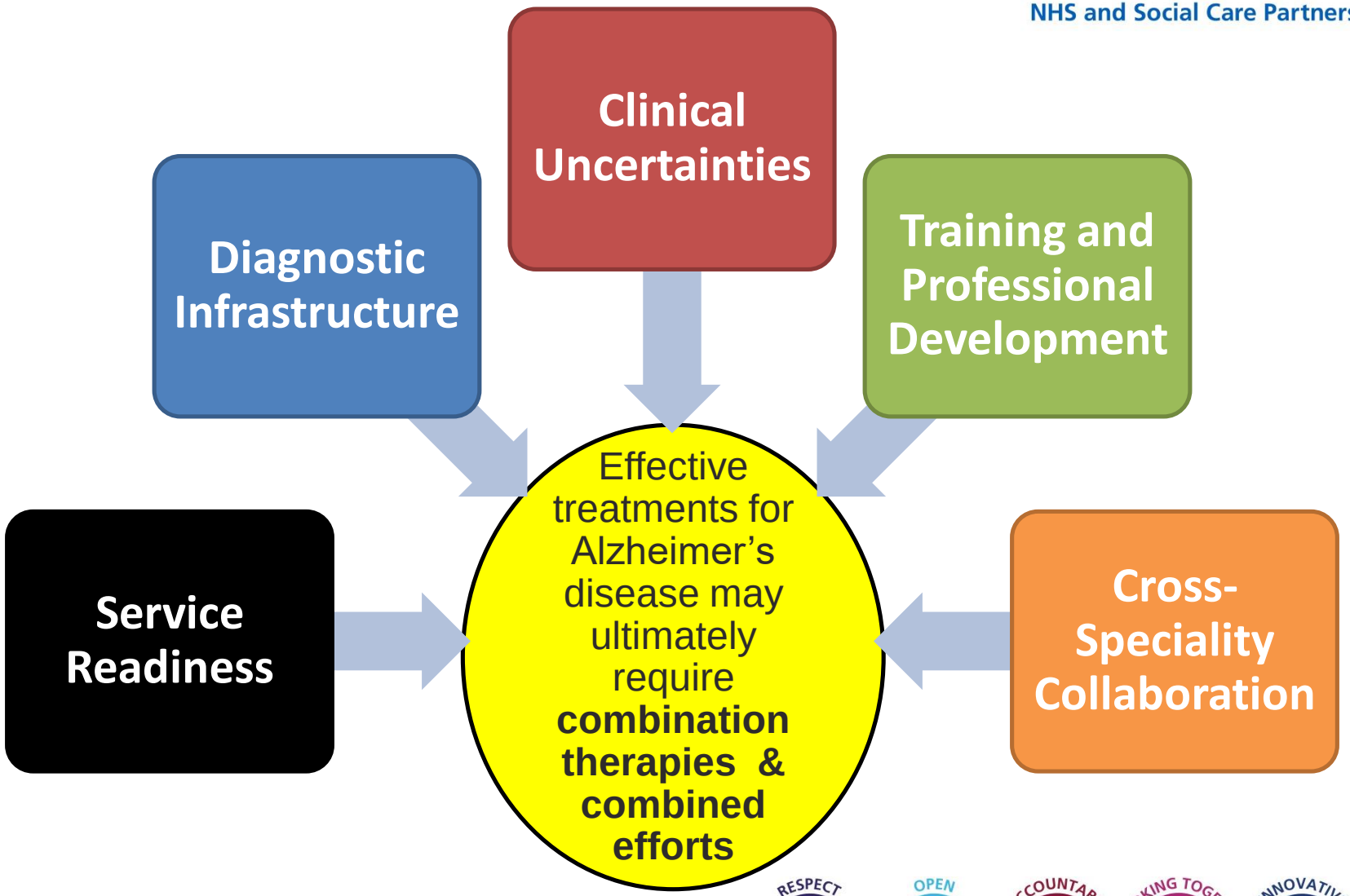
**Remternetug**

**Hydromethylthionine mesylate (HMTM)**

**Blarcamesine**

# Implications

Kent and Medway
NHS and Social Care Partnership Trust

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**Diagnosis : Clinical → Biological**

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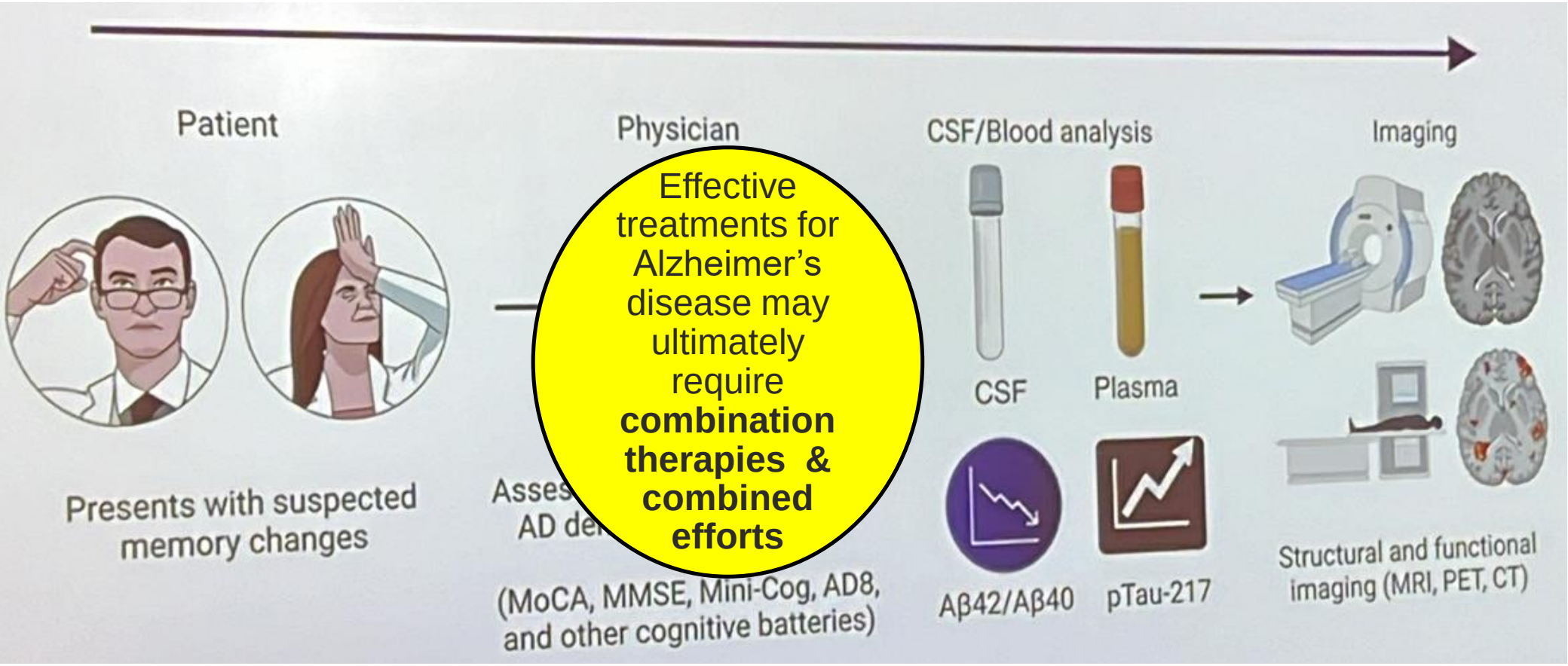


Effective treatments for Alzheimer's disease may ultimately require **combination therapies & combined efforts**

**Treatment : Symptoms → Disease modifying**

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Mohan.bhat1@nhs.net