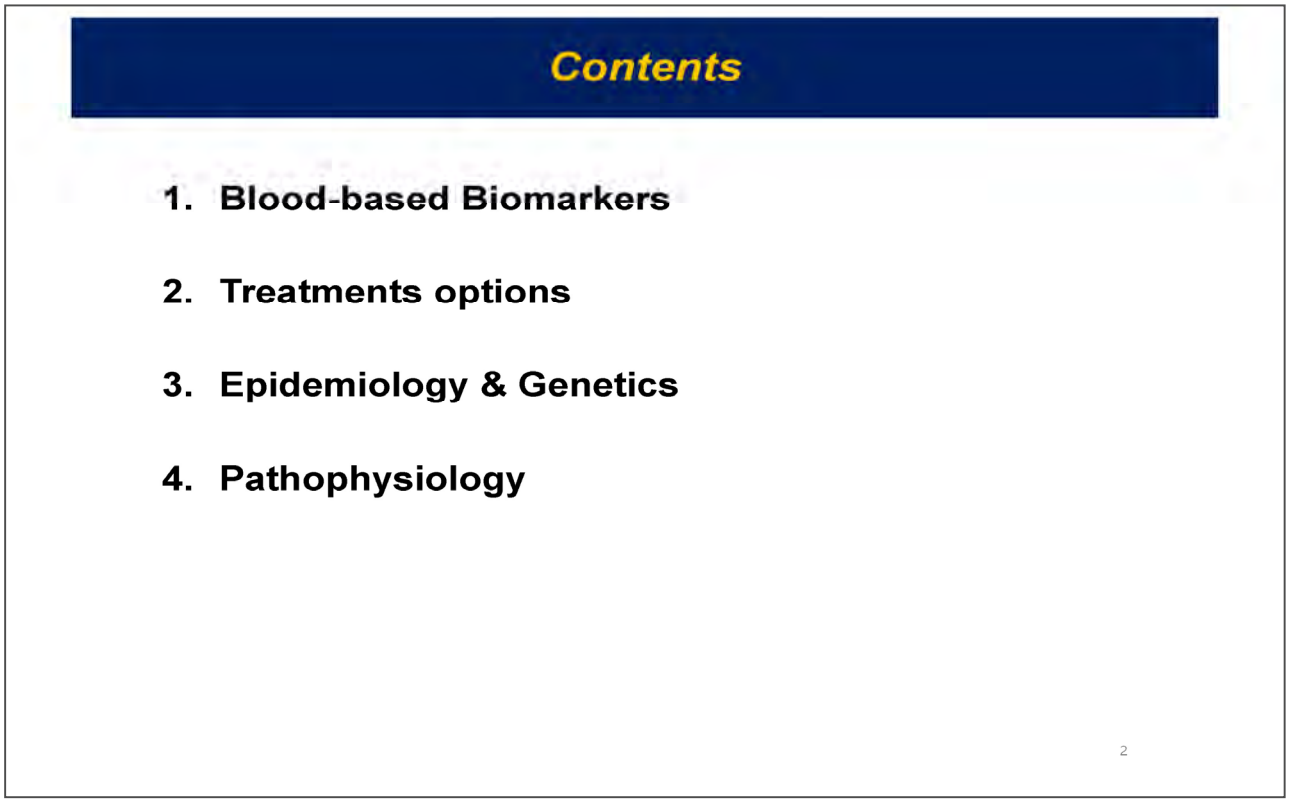
Dementia

김 고 운
전북의대 신경과



Blood-based Biomarkers

혈액검사로 치매를 진단할 수 있나요?

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Blood-based Biomarkers

- The key development has been the establishment of **plasma biomarkers** as reliable measures of Alzheimer's disease.
- Recent papers show strong evidence of **plasma p-tau 181 and 217** as diagnostic biomarkers for Alzheimer's disease versus other dementias, and for identification of both amyloid-β and p-tau pathology via PET.
- These findings make it increasingly likely that **a combination of plasma biomarkers**—p-tau, amyloid-β, neurofilament light chain and possibly others.

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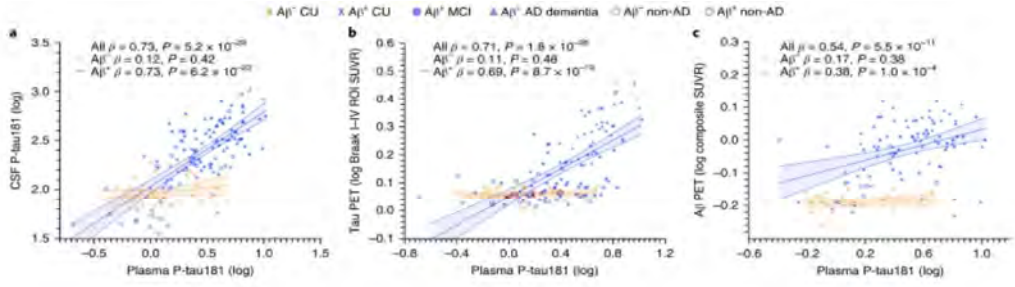
Blood-based Biomarkers

p-tau181 has been shown to be present in significantly higher levels in people who have preclinical Alzheimer's disease, defined as being cognitively unimpaired but amyloid positive.

Plasma p-tau181 correlates significantly with CSF p-tau181, tau and amyloid PET findings.



Janelidze et al. *Nat Med* 2020; **26:** 379–86.

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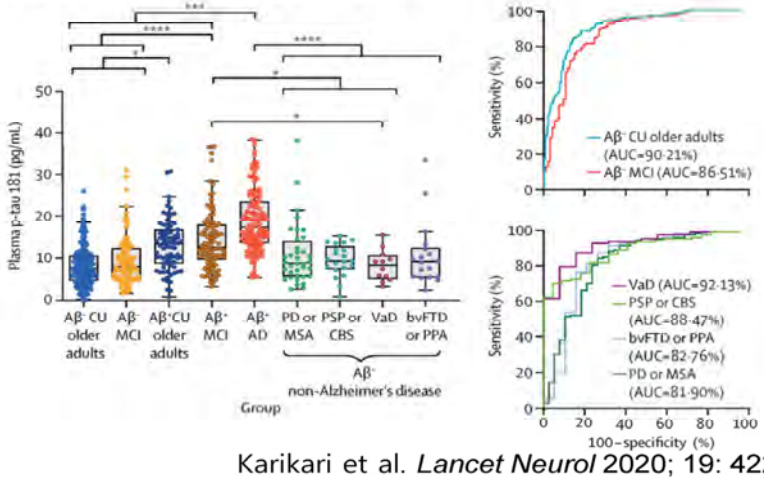
Blood-based Biomarkers

The study findings suggested that blood-based p-tau181 can predict tau and amyloid β neuropathology, differentiate Alzheimer's disease from other neurodegenerative disorders, and identify Alzheimer's disease across the clinical continuum



Karikari et al. *Lancet Neurol* 2020; 19: 422–33

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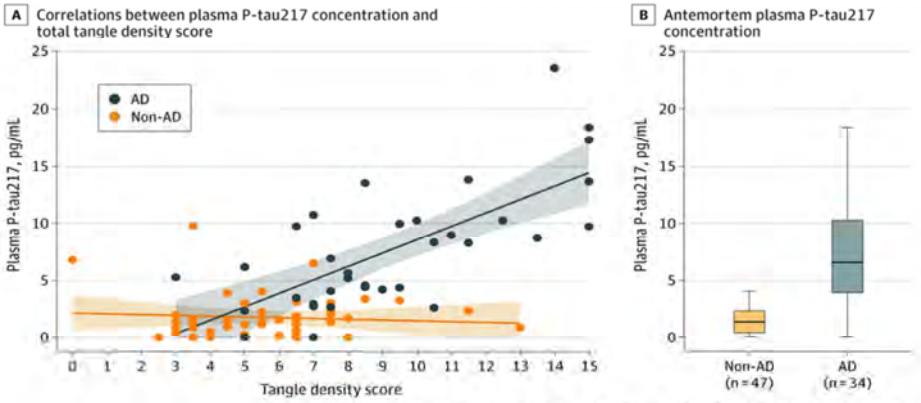
Blood-based Biomarkers

The diagnostic accuracy of **p-tau217** was superior to that of other Alzheimer's disease biomarkers, including plasma p-tau181, plasma neurofilament light chain, and structural neuroimaging (MRI).



Palmqvist S et al. *JAMA* 2020; **324:** 772–81

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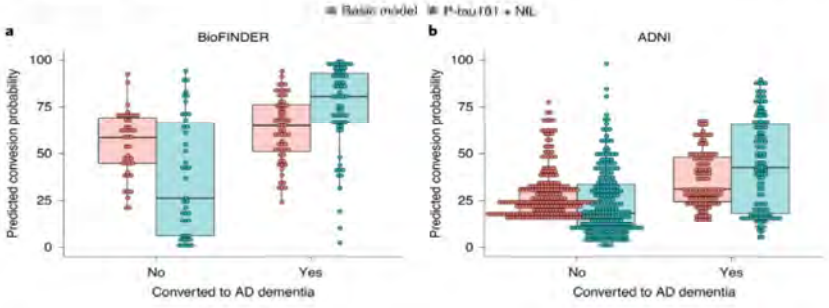
Blood-based Biomarkers

The combination of plasma p-tau181 and plasma neurofilament light chain levels predicts well, on an individual basis, which patients with MCI are likely to progress to Alzheimer's disease.

These findings make it increasingly likely that a combination of plasma biomarkers.



Cullen et al. Nature Aging 2021;1:114–123

Treatment options

치매 신약이 개발되었나요?

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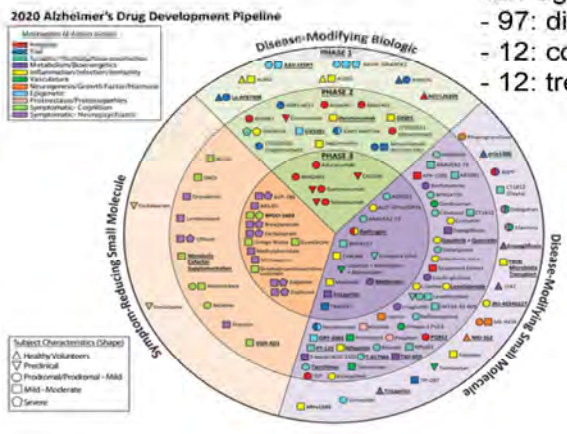
Pharmacological Treatments

Alzheimer's disease drug-development pipeline 2020



121 agents in clinical trials
- 97: disease-modifying agents
- 12: cognitive enhancing agents
- 12: treatment of neuropsychiatric symptoms

Cummings et al. *Alzheimer's Dement.* 2020;6:e12050

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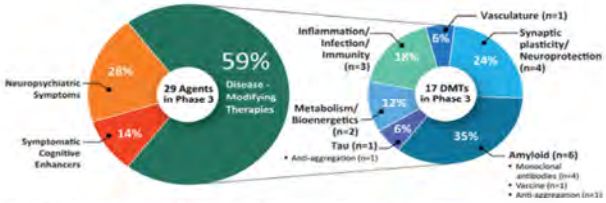
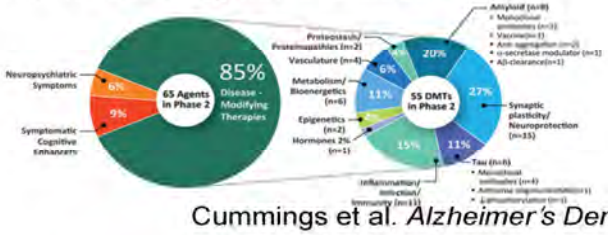
Pharmacological Treatments

Compared to the 2019 pipeline, there is an increase in the number of disease-modifying agents targeting pathways other than amyloid or tau.

- Mechanisms of action of agents in Phase 3



- Mechanisms of action of agents in Phase 2



Cummings et al. *Alzheimer's Dement.* 2020;6:e12050

Disease-modifying Treatments

Aducanumab (Biogen)

- FDA has extended the review period by three months for the Biologics License Application (BLA) for aducanumab. The updated Prescription Drug User Fee Act (PDUFA) action date is June 7, 2021.
- ENGAGE and EMERGE clinical trials has generated great controversy

	Low-dose aducanumab		High-dose aducanumab		PRIME
Diff vs Placebo (%)	ENGAGE N=547	EMERGE N=543	ENGAGE N=555	EMERGE N=547	10 mg/kg N=32
CDR-SB	-0.18 (-12%)	-0.26 (-15%)	0.03 (2%)	-0.39 (-22%)	-1.26 (-67%)
MMSE	0.2 (-6%)	-0.1 (3%)	-0.1 (3%)	0.6 (-18%)	1.9 (-76%)
ADAS-Cog 13	-0.58 (-11%)	-0.70 (-14%)	-0.59 (-11%)	-1.40 (-27%)	
ADCS-ADL-MCI	0.7 (-18%)	0.7 (-16%)	0.7 (-18%)	1.7 (-40%)	
Amyloid-PET* SUVR (centiloid unit)	-0.167 (-38.5)	-0.179 (-41.3)	-0.232 (-53.5)	-0.278 (-64.2)	-0.277 (-61.1)

p<0.05 favoring aducanumab

Numeric advantage favoring aducanumab

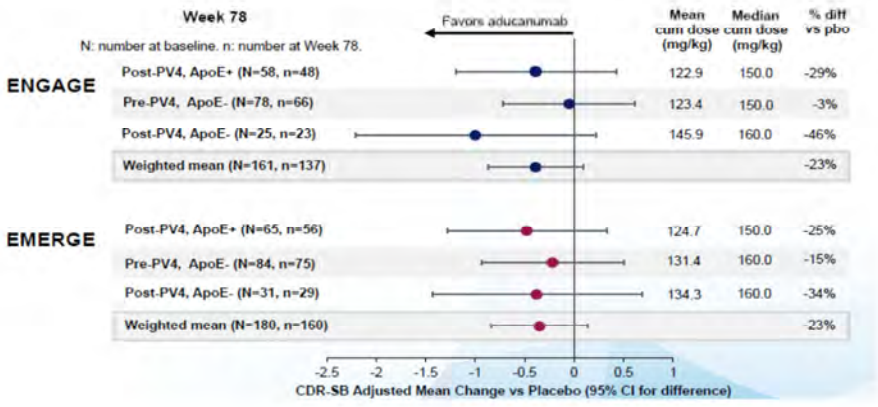
No numeric advantage favoring aducanumab

AD/PD 2021

Disease-modifying Treatments

Aducanumab (Biogen)

- Patients who had the opportunity for 14 doses of 10mg/kg had similar benefit in both studies.

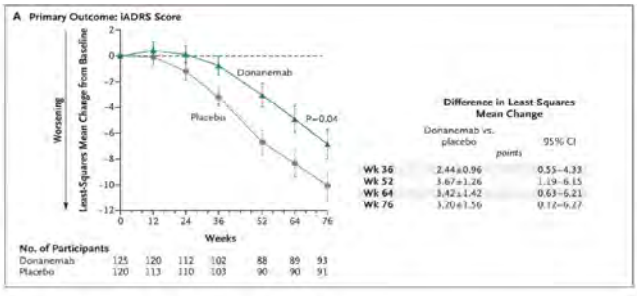


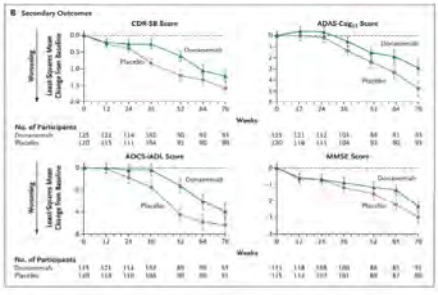
AD/PD 2021 13

Disease-modifying Treatments

Donanemab (Lilly)

- A recent phase 2 trial of donanemab suggests that this antibody directed against the pyroglutamate-modified form of amyloid β has promise as an amyloid-targeted treatment.
- The change from baseline in the iADRS score at 76 weeks was −6.86 with donanemab and −10.06 with placebo (difference, 3.20; 95% confidence interval, 0.12 to 6.27; P = 0.04).



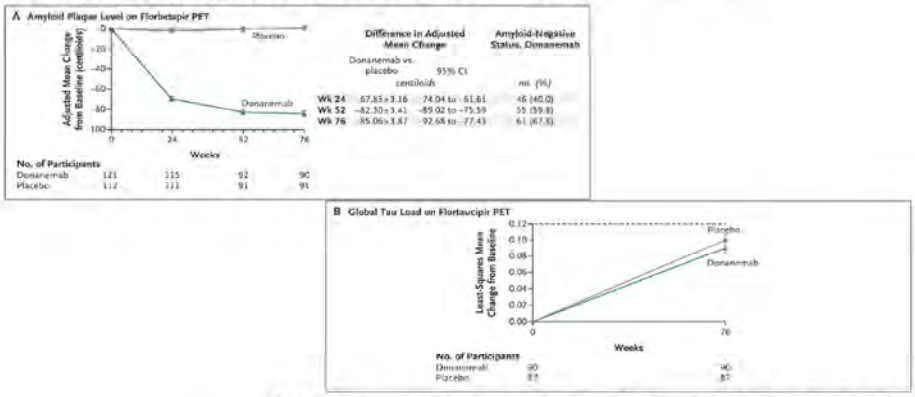


AD/PD 2021, Mintun et al. *N Engl J Med.* 2021 Mar 13

Disease-modifying Treatments

Donanemab (Lilly)

- At 76 weeks, the reductions in the amyloid plaque level and the global tau load were 85.06 centiloids and 0.01 greater, respectively, with donanemab than with placebo.
- New phase 3 trials of donanemab (NCT04437511 and NCT04640077) have since been initiated.

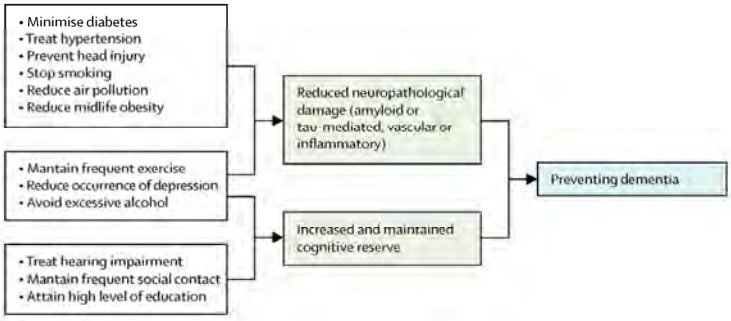


AD/PD 2021, Mintun et al. *N Engl J Med*. 2021 Mar 13

Non-pharmacological Interventions

The 2020 Lancet Commission on Dementia prevention, intervention, and care

- Three new modifiable risk factors for dementia
  - Excessive alcohol consumption, head injury, and air pollution
- Modifying 12 risk factors might prevent or delay up to 40% of dementias.



Livingston et al. *The Lancet* 2020; 396: 413-446

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Non-pharmacological Interventions

World-Wide FINGERS

The WW-FINGERS network aims to test and adapt the FINGER trial model in different settings and populations, to define effective and feasible preventive strategies.

Kivipelto et al. *Alzheimer's Dement* 2020;16:1078–1094

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Epidemiology and genetics

치매 현황 및 유전자

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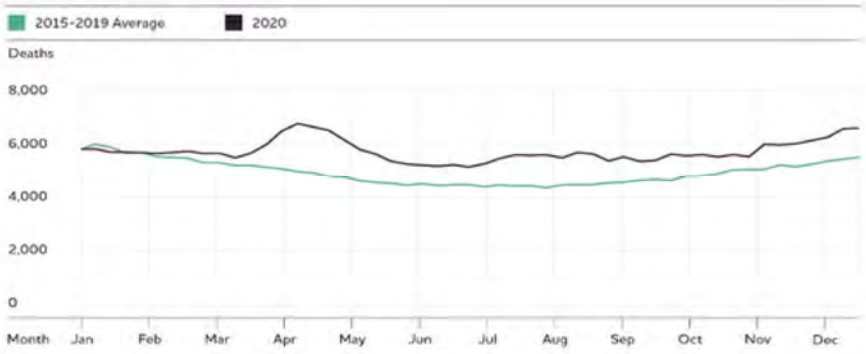
Epidemiology and genetics

The effect of COVID-19 on deaths from Alzheimer's disease

- Deaths due to Alzheimer's and other dementias in the United States in 2020 compared with previous years. Data for 2020 are current as of February 3, 2021.



Alzheimer's Dement. 2021;1–80.

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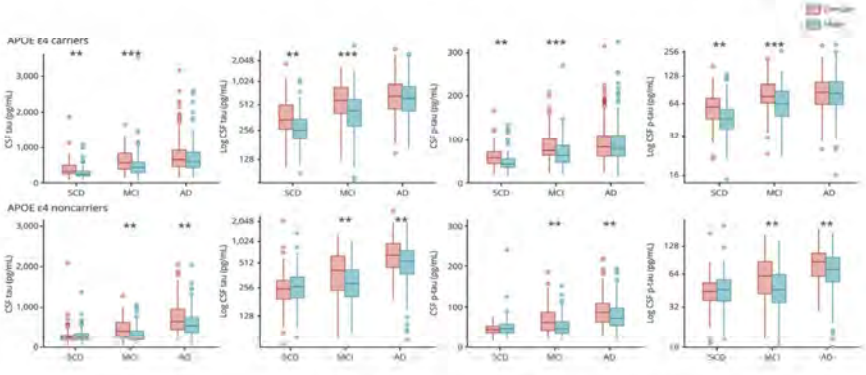
Epidemiology and genetics

Within *APOE* ε4 carriers, sex differences in CSF p-Tau are more evident in early disease stages, whereas for *APOE* ε4 noncarriers, sex differences are more evident in advanced disease stages.



Mofrad et al. *Neurology* 2020; 95: e2378–88.

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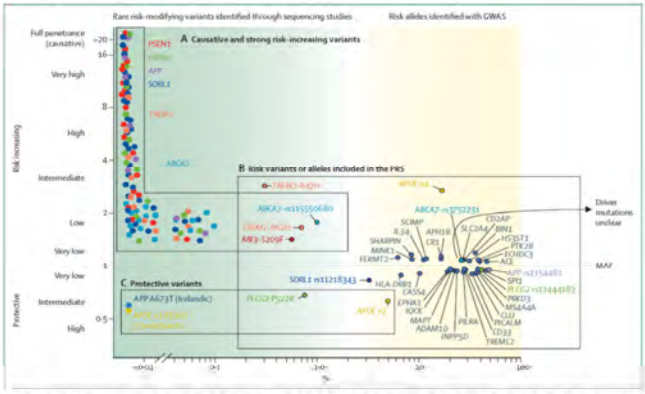
Epidemiology and genetics

The genetic landscape of Alzheimer's disease

- The identification of risk-increasing genetic variants has fuelled the interest in the detection of protective genetic variants.
- Protective genes: *APOE ε2*, rare mutations of *PLCG2*, *APP*, and *APOE ε3*



Scheltens et al. *Lancet* 2021 Mar 2:S0140-6736(20)32205-4.

Epidemiology and genetics

The 100-plus Study

- In Maintained Cognitive Health group, 18.6% carried at least 1 APOE-ε4allele, compared with 5.6% of the centenarians with declining cognitive performance.
- A rare Pro522Arg amino acid change in the *PLCG2* gene was associated with a near 2 times reduced risk of Alzheimer's disease and other types of dementia, and with a 2·3 times increased chance of reaching 100 years in cognitive health.

Beker et al. *JAMA Netw Open* 2020; **3:** e200094.
van der Lee et a. *Acta Neuropathol* 2019; **138:** 237–50.

Pathophysiology

치매는 왜 생기나요?

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Pathophysiology

- The core signature biochemical amyloid and tau pathology and the microglia response, which defines Alzheimer's disease.
- However, it is clear that the blood–brain barrier, the peripheral immune system, and potentially the gastrointestinal microbiome affect the clinical development of the disease.

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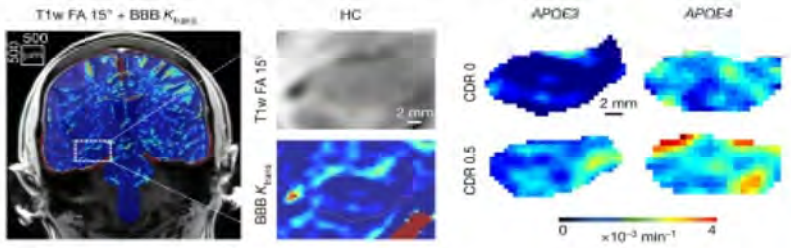
Pathophysiology

Breakdown of the blood–brain barrier (BBB) is an early biomarker of human cognitive dysfunction.

Leakage of the BBB causes dementia independently from amyloid β and tau pathology, especially in *APOE* ε4 carriers.



Montagne et al. *Nature* 2020; **581:** 71–76.

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Take Home Message

- Blood-based Biomarker의 신뢰도를 입증할 수 있는 연구결과들이 축적되고 있음. 특히 최근 p-tau 관련 연구가 활발함.
- Amyloid-β 를 target으로 하는 약제에 대한 연구가 지속되고 있으며 이외의 mechanism 관련 약제 개발 임상시험이 증가하고 있음.
- COVID-19 관련하여 사망률이 증가함.
- Risk 를 감소시키는 gene mutation도 있음.
- Amyloid, tau pathology 와 microglia response 이외에도 BBB breakdown 등 다양한 mechanism 이 치매 진행에 영향을 줄 수 있음.

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