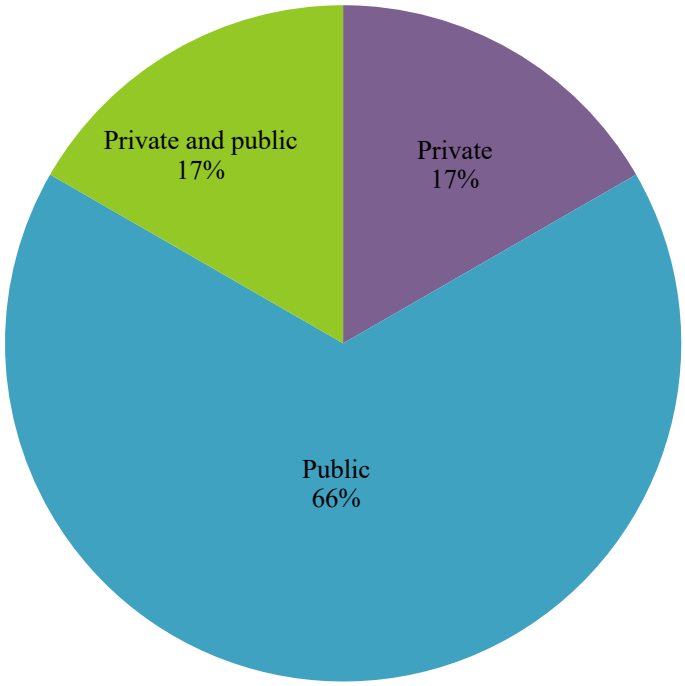
Supplementary Material

Current and future trends in biomarkers for the early detection of Alzheimer's disease in Asia: expert opinion

Asia Region Alzheimer's Disease Virtual Meeting 2021: Pre-meeting Survey Report

What is your clinical practice setting?



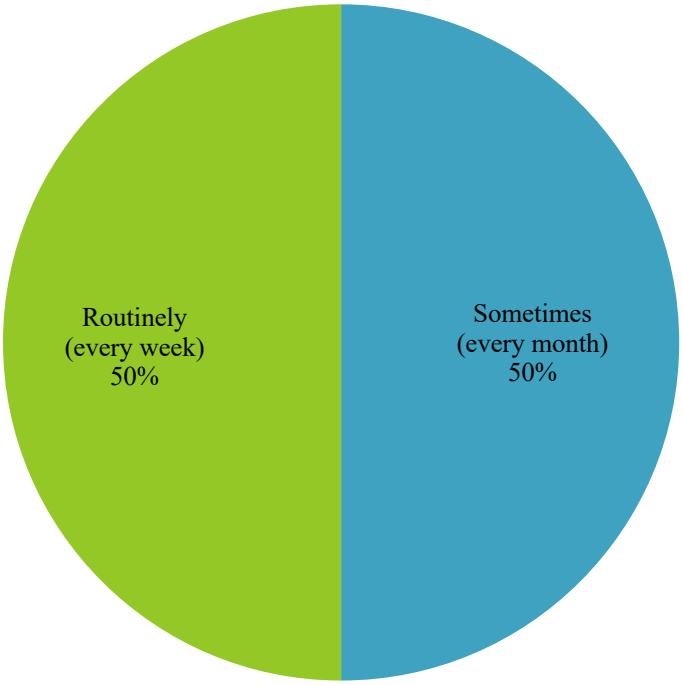
Value	Percentage	Count
Private	16.7%	1
Public	66.7%	4
Private and public	16.7%	1
	Total	6

Of the patients you see per month, approximately what proportion (%) are in the following stages of Alzheimer's disease (AD)?

Item	Average	Min	Max	StdDev	Sum	Total responses
Mild cognitive impairment/prodromal AD	45.0	30	70	13.8	270.0	6
Mild AD	30.8	20	40	7.3	185.0	6
Moderate to severe AD	24.2	10	30	7.3	145.0	6

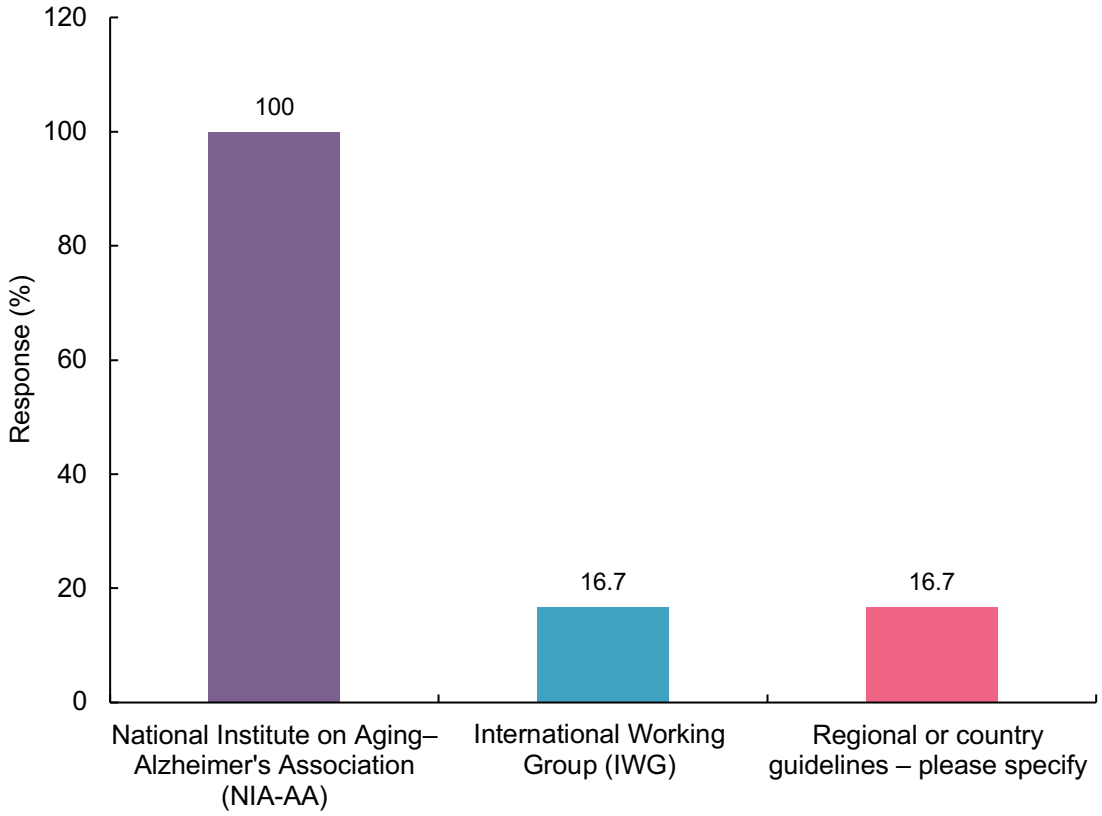
Max, maximum; Min, minimum, StdDev, standard deviation.

How often do you make a diagnosis of prodromal AD or MCI due to AD?



Value	Percentage	Count
Sometimes (every month)	50.0%	3
Routinely (every week)	50.0%	3
	Total	6

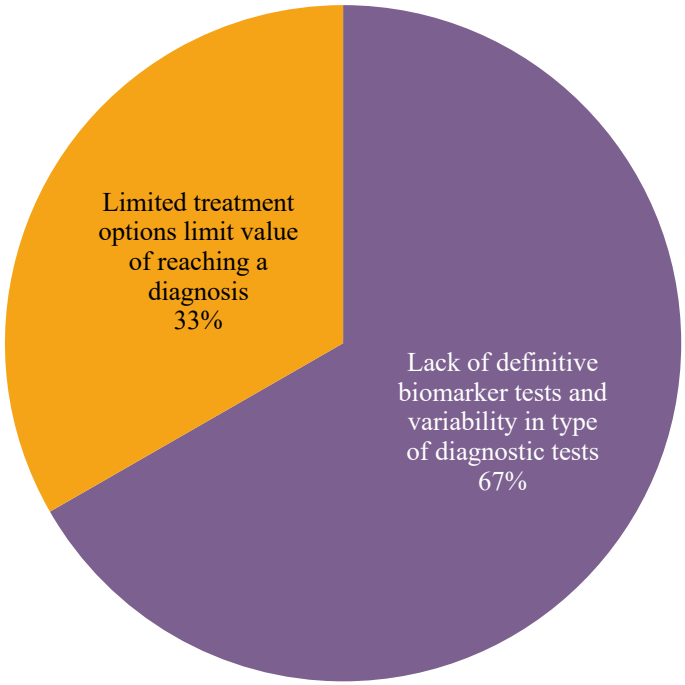
In your locality, which guidelines do neurologists/psychiatrists tend to refer to when making decisions about AD diagnosis/screening? [You may select more than one answer option]



Value	Percentage	Count
National Institute on Aging–Alzheimer's Association (NIA-AA)	100.0%	6
International Working Group (IWG)	16.7%	1
Regional or country guidelines – please specify	16.7%	1
	• The ATN research framework, even though it is not recommended for clinical use • Guidelines published by the Taiwan Dementia Society • Peterson's criteria as a diagnostic criterion for MCI • Japanese Society of Neurology guidelines, in which the procedures are covered by standard medical insurance. If the patient's symptoms are atypical or young onset and require further investigation, biomarker studies (PET/CSF) are added in research settings on agreement, and the results would be interpreted based on NIA-AA guidelines	

ATN, amyloid, tau, and neurodegeneration; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; PET, positron emission tomography.

What do you think is the most important clinical barrier to the prompt diagnosis of MCI and AD?



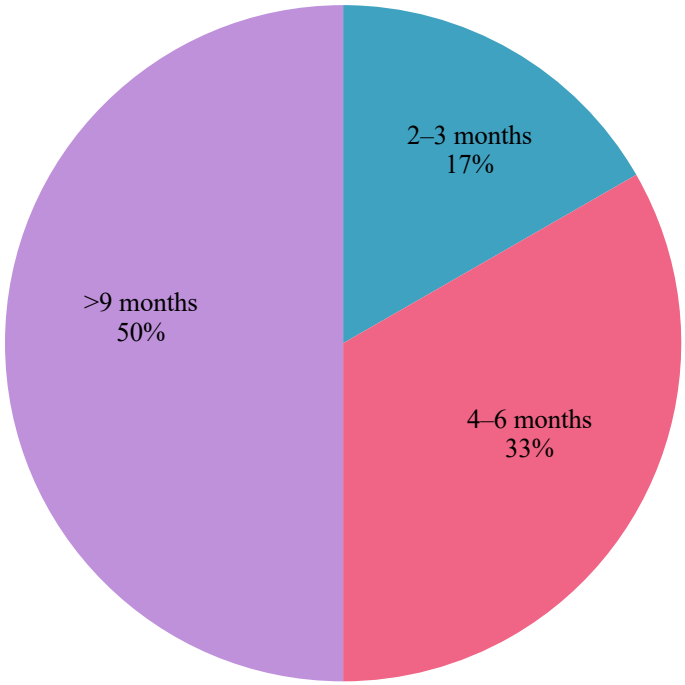
Value	Percentage	Count
Lack of definitive biomarker tests and variability in type of diagnostic tests	66.7%	4
Limited treatment options limit value of reaching a diagnosis	33.3%	2
	Total	6

How often do you prescribe the following medications when a patient meets the criteria for prodromal AD/MCI due to AD?

	Not at all	Count	Seldom	Count	Frequently	Count
ChEIs	33.3%	2	33.3%	2	33.3%	2
Memantine	50.0%	3	16.7%	1	33.3%	2
Both ChEIs and memantine	66.7%	4	16.7%	1	16.7%	1
Others	0	0	16.7% (Mood stabilizers)	1	16.7% (Dihydroergotoxine)	1

ChEI, cholinesterase inhibitor.

Typically, in your practice, what is the estimated time from AD symptom complaints to AD diagnosis?



Value	Percentage	Count
2–3 months	16.7%	1
4–6 months	33.3%	2
>9 months	50.0%	3
	Total	6

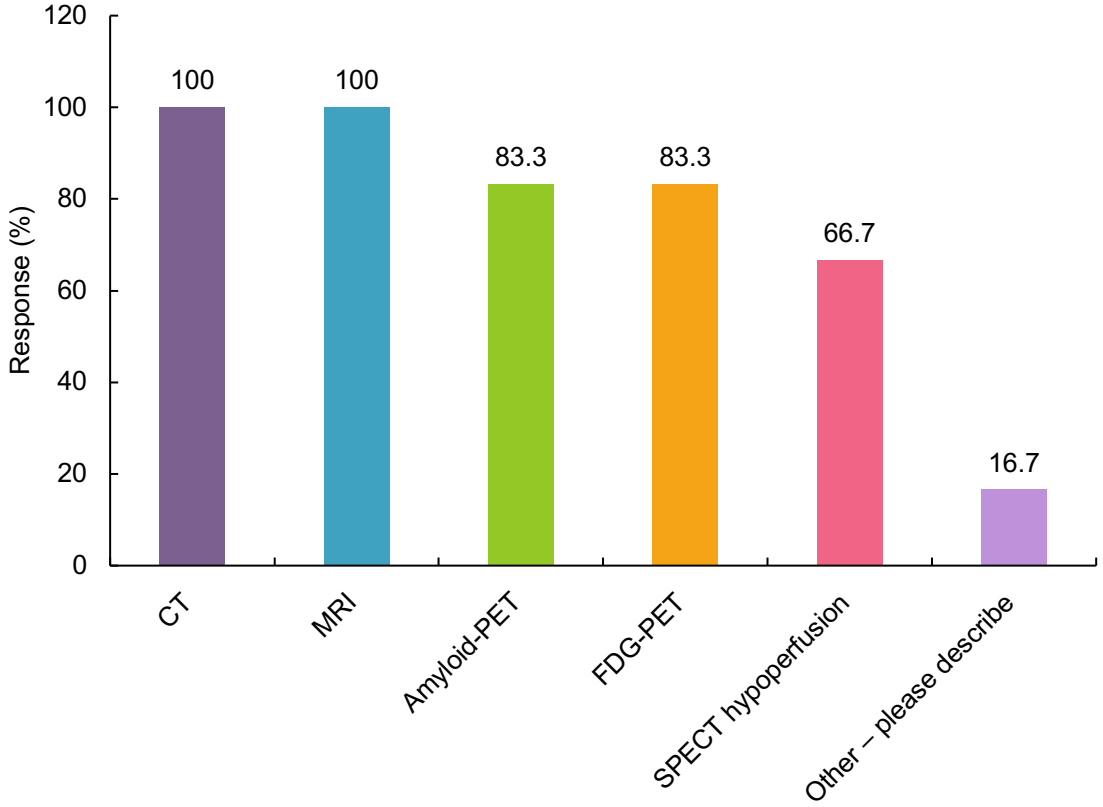
Please rank the following criteria of ideal biomarkers in the clinical setting.
[1 = most important; 6 = least important]

	Total rank score *(the lower the value, the more important the criterion)*					
	High specificity	**Reliable sensitivity**	**Detectable in early AD**	**Inexpensive and user friendly**	**Non-invasive/ easily accessible**	**Available for monitoring disease progression**
Diagnostic biomarker	11	16	17	24	20	25
Disease activity biomarker	22	21	26	20	19	11
Treatment response biomarker	17	17	26	25	20	14

Please provide any further comments that will help supplement your response regarding criteria of an ideal biomarker in clinical practice.

- Two important criteria: high specificity in diagnosis of AD and high sensitivity in detection of disease progression.
- Biomarkers for treatment response for MCI and dementia need not have attributes.

Which of the following neuroimaging tests for AD diagnosis are available in your clinic/institution?



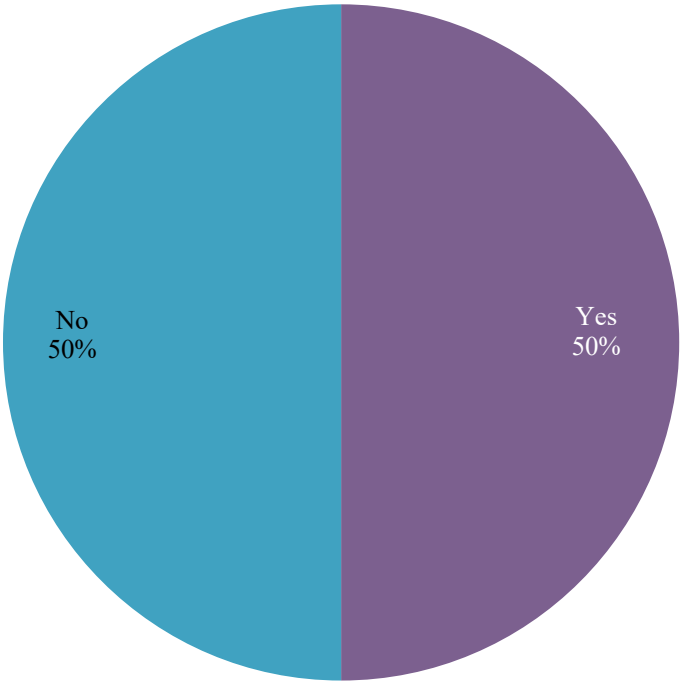
Value	Percentage	Count
CT	100.0%	6
MRI	100.0%	6
Amyloid-PET	83.3%	5
FDG-PET	83.3%	5
SPECT hypoperfusion	66.7%	4
Other – please describe	16.7%	1
	• CSF (Aβ, P-tau, T-tau) • DAT-SPECT, MIBG	

Aβ, amyloid-β; CT, computed tomography; DAT, dopamine transporter; FDG, fluorodeoxyglucose; MIBG, iodine-131-meta-iodobenzylguanidine; MRI, magnetic resonance imaging; P-tau, phosphorylated tau; SPECT, single-photon emission tomography; T-tau, total tau.

Which biomarkers do you use for scoring the criteria in clinical practice?

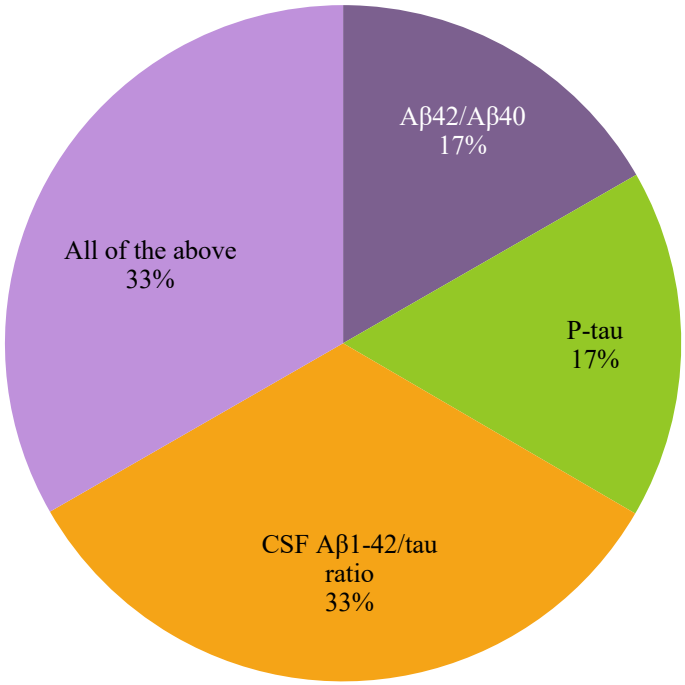
- MRI.
- SPECT, but only sometimes.
- Amyloid-PET.
- MRI, perfusion SPECT, CSF P-tau, DAT-SPECT, MIBG for routine clinical practice. For further investigation, we would use CSF Aβ, FDG-PET, amyloid-PET, and tau-PET.

Are there any guidelines for amyloid-PET in your clinic/institution?



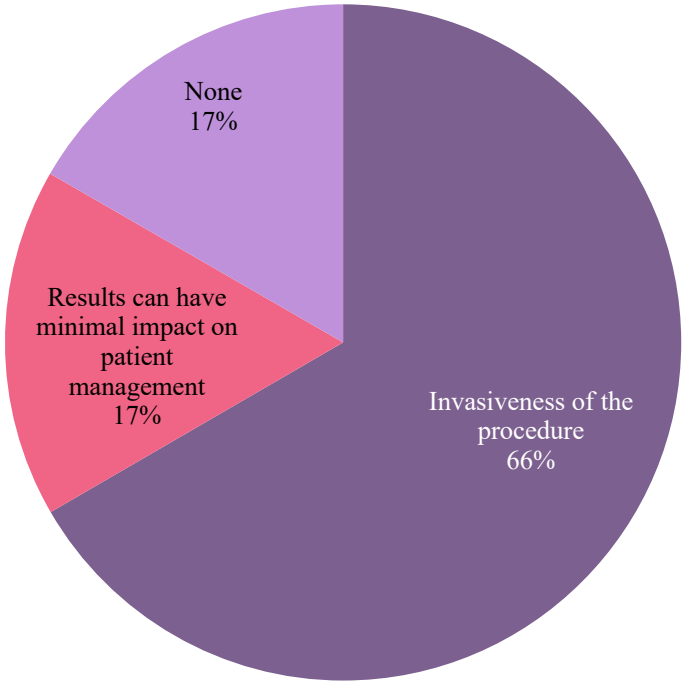
Value	Percentage	Count
Yes	50.0%	3
No	50.0%	3
	Total	6

Which of the following CSF AD biomarkers do you think has the highest level of clinical utility?



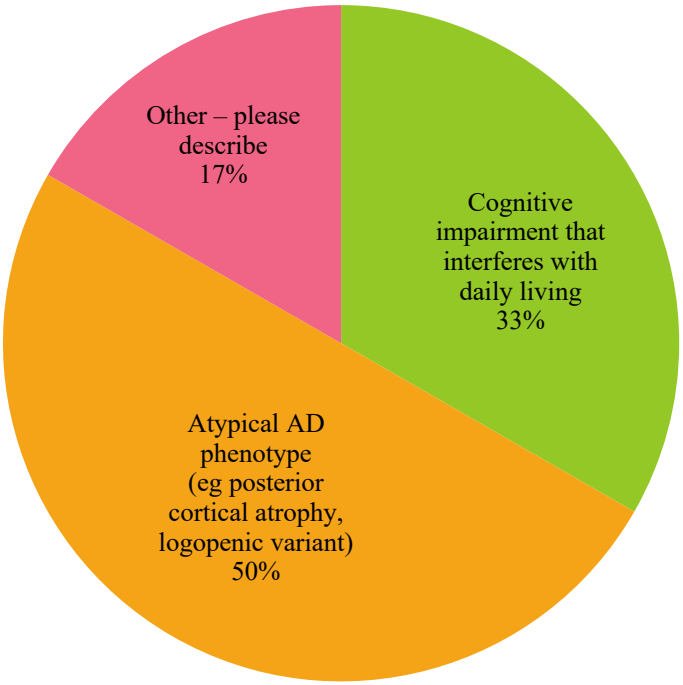
Value	Percentage	Count
$A\beta_{42}/A\beta_{40}$	16.7%	1
P-tau	16.7%	1
CSF $A\beta_{1\text{-}42}$/tau ratio	33.3%	2
All of the above	33.3%	2
	Total	6

What is your key concern when ordering/conducting a CSF biomarker test?



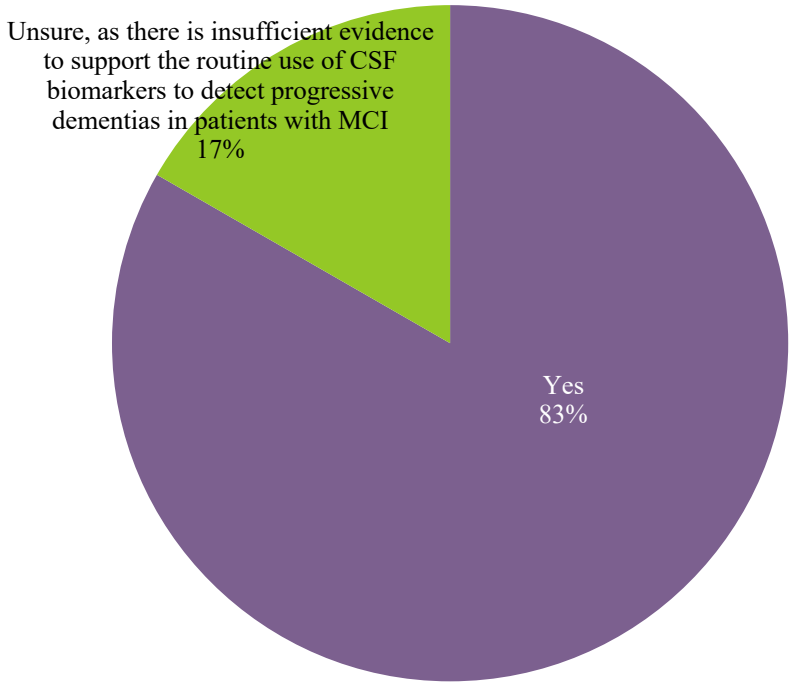
Value	Percentage	Count
Invasiveness of the procedure	66.7%	4
Results can have minimal impact on patient management	16.7%	1
None	16.7%	1
	Total	6

Which clinical criteria would most likely lead you to recommend Aβ biomarker testing by CSF analysis or amyloid-PET?



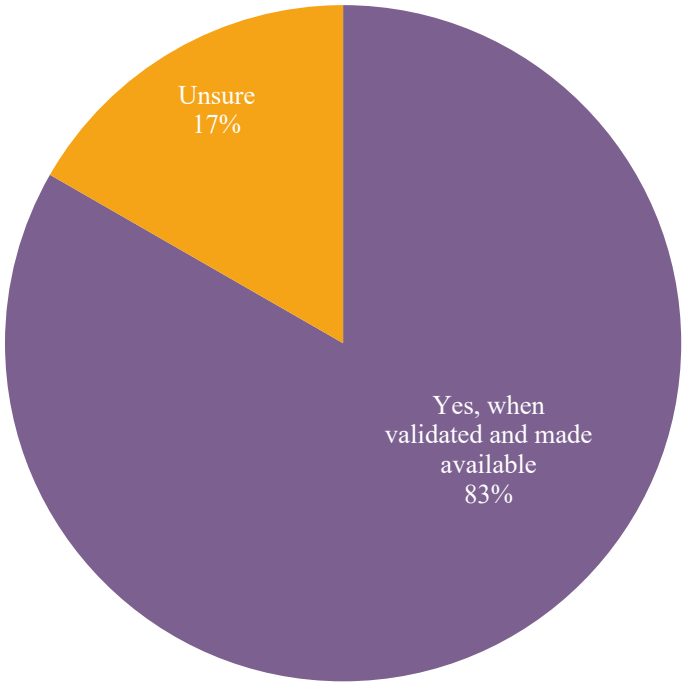
Value	Percentage	Count
Cognitive impairment that interferes with daily living	33.3%	2
Atypical AD phenotype (e.g., posterior cortical atrophy, logopenic variant)	50.0%	3
Other – please describe	16.7%	1
	• Early/young-onset cases	
	Total	6

Do you think CSF tau and Aβ biomarkers are accurate tests for predicting which patients with MCI will develop AD or other forms of dementia?



Value	Percentage	Count
Yes	83.3%	5
Unsure, as there is insufficient evidence to support the routine use of CSF biomarkers to detect progressive dementias in patients with MCI	16.7%	1
	Total	6

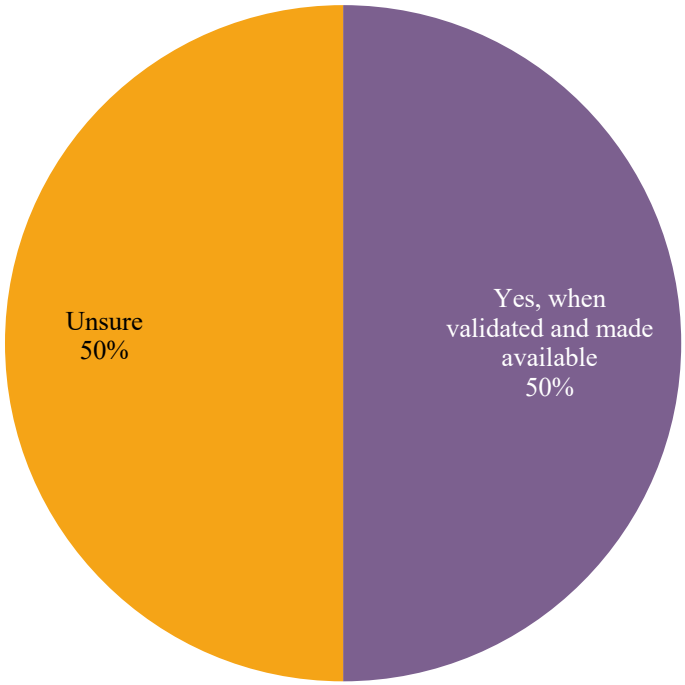
Do you think non-Aβ and non-tau fluid biomarkers (e.g., NfL, neurogranin, VILIP-1) would be useful in clinical practice to monitor treatment response?



Value	Percentage	Count
Yes, when validated and made available	83.3%	5
Unsure	16.7%	1
	Total	6

NfL, neurofilament light protein; VILIP-1, visinin-like protein 1.

Do you think non-Aβ and non-tau fluid biomarkers (e.g., NfL, neurogranin, VILIP-1) would be useful in clinical practice to track clinical severity?

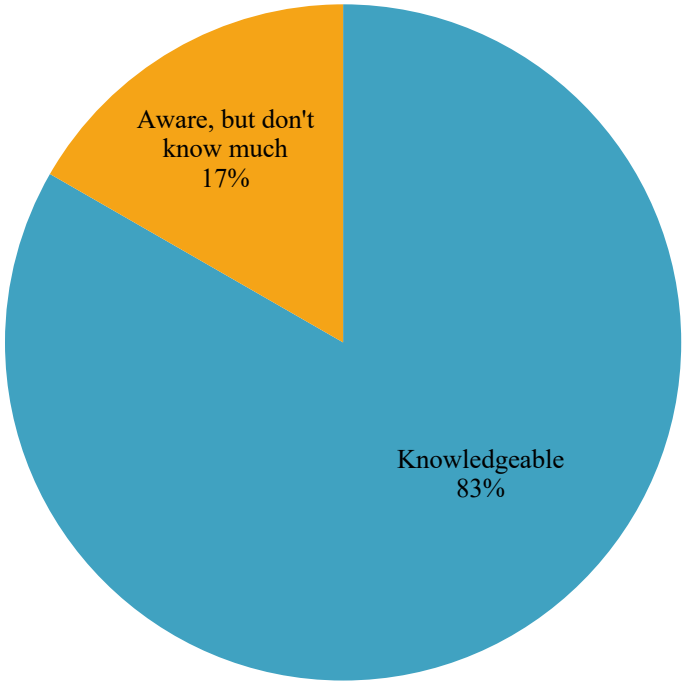


Value	Percentage	Count
Yes, when validated and made available	50.0%	3
Unsure	50.0%	3
	Total	6

What do you think are potential/future CSF biomarkers? Please explain.

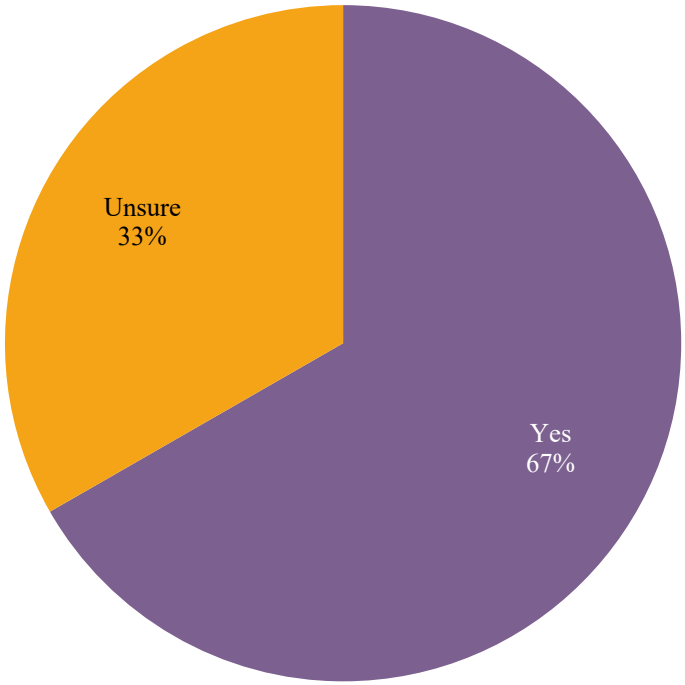
- CSF biomarkers are an important alternative to pathological diagnosis.
- CSF biomarkers are useful mainly for diagnosis but not follow-up. They will be more popular after disease-modifying treatments are made available.
- The place of some CSF biomarkers will be taken by blood-based biomarkers. However, several essential CSF biomarkers will remain in use.
- CSF biomarkers are important markers of vascular activity and blood–brain barrier integrity.
- CSF biomarkers still have potential as they are still easily accessible to neurologists and are relatively cheap compared with PET.

What is your level of knowledge about blood-based biomarkers in AD?



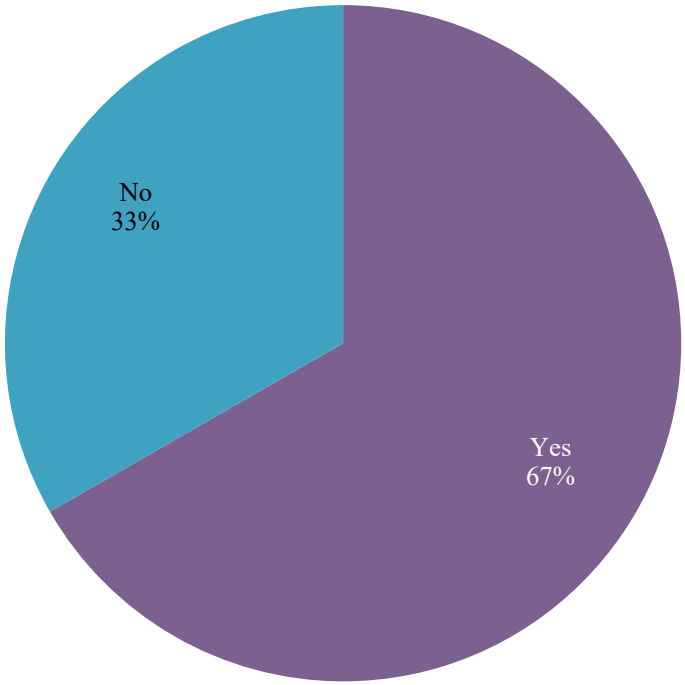
Value	Percentage	Count
Knowledgeable	83.3%	5
Aware, but don't know much	16.7%	1
	Total	6

Do you think the advent of blood-based biomarkers for AD diagnosis in the clinical setting would limit the use of CSF-based biomarkers?



Value	Percentage	Count
Yes	66.7%	4
Unsure	33.3%	2
	Total	6

Do you think that blood-based biomarkers can be used not only for AD screening but also for AD diagnosis and symptom monitoring?



Value	Percentage	Count
Yes	66.7%	4
No	33.3%	2
	• Blood-based biomarkers would be useful to screen AD patients, but not for AD diagnosis • There is still insufficient evidence on the role of blood-based biomarkers for AD diagnosis	
	Total	6

In your opinion, what is the biggest unanswered question/key barrier surrounding the use of blood-based biomarkers in screening and diagnosing AD?

- Variation in measured values between facilities and between measurement methods.
- The cost of blood-based biomarkers is still too high for it to be used as a screening or diagnostic tool. The specificity and sensitivity of blood-based biomarkers still need to be improved on.
- Blood-based biomarkers can reflect some pathological processes in the brain and may be useful for diagnostic and/or monitoring markers. However, it would be difficult to reflect precise information about where in the brain and what amount of the brain is injured.
- Specificity and fluctuations related to diurnal variation with blood-based biomarkers.
- Cut-off values of blood-based biomarkers.

What do you think is the potential/future of blood-based biomarkers?

- Blood-based biomarkers are the best candidate for AD screening in both clinical and research settings because of their ease of use and cost effectiveness. For precise diagnosis and evaluation, neuroimaging biomarkers may be the preferred modality.
- With blood or plasma sampling being easier than CSF collection, there is potential for blood-based biomarkers to be used routinely in the future.

Do you have any recommendations for digital biomarkers? Please specify.

- Digital biomarkers may be useful for dementia diagnosis but not for differential diagnosis.
- Digital biomarkers are potentially compensation for neuropsychological tests and physical examinations in the hospital. With artificial intelligence, there will be a wide range of uses for digital biomarkers in future dementia clinical practice.
- Digital biomarkers have potential to be used in future clinical practice but would need to meet the requirements of local communities.