Les marqueurs plasmatiques de la maladie d'Alzheimer. Le recommandations de la Task Force du CTAD

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CERPOP

En tant qu'investigateur, le Dr. ANGIONI a reçu ou reçoit des financements de recherche des compagnies suivantes:

Alector Inc., Alzheon Inc., Araclon Biotech S.L., Avanir Pharmaceuticals, Eisai Inc., Genentech, Inc., Hoffmann-La Roche, Janssen Research & Development, Medesis Parma, Novo Nordisk, Shanghai Greenvalley Pharmaceutical Co., UCB Biopharma.

Aucun avantage personnel direct n'est à déclarer.

Task force

- EU/US/CTAD Virtual Task Force Mai 2022
- **Blood Biomarkers from Research Use to Clinical Practice: What Must Be Done?**
- EU/US/CTAD Task Force Novembre 2022

- **Can We Use Blood Biomarkers as Entry Criteria and for Monitoring Drug Treatment Effects in Clinical Trials?**

Contexte

- Augmentation du nombre des troubles neurocognitifs attendue dans les prochaines décennies
- La Maladie d'Alzheimer est l'étiologie la plus fréquente
- Trois essais cliniques de phase III « positifs » sur (au moins) le critère de jugement principal
- Nécessité de démarches diagnostiques complètes et logiques

Contexte

Diagnostic **syndromique** vs. diagnostic **étiologique**

ANAMNESE

HETERO-ANAMNESE

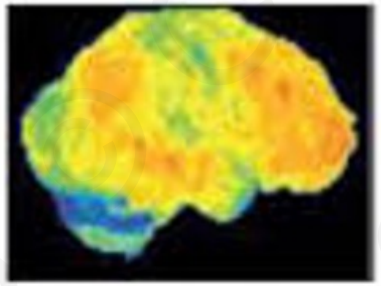
EXAMEN PHYSIQUE

TESTS NEUROPSYCHOLOGIQUES

PLAINTE COGNITIVE SUBJECTIVE

TROUBLE NEUROCOGNITIF MINEUR

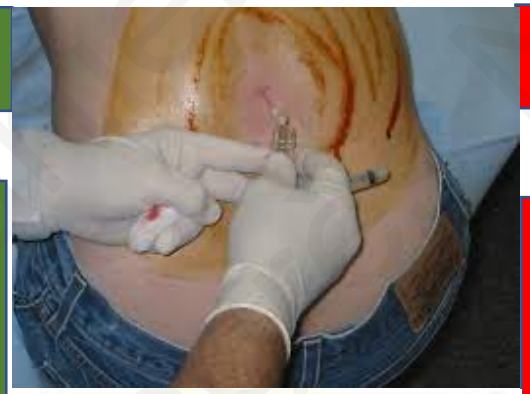
TROUBLE NEUROCOGNITIF MAJEUR

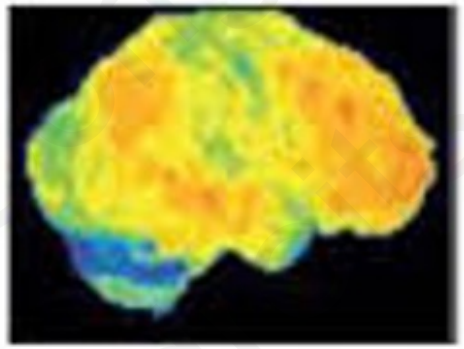


TEP-amyloïde

Contexte

Avantages	Inconvénients
Définir l'origine étiologique des troubles neurocognitifs Identification de la cible thérapeutique	Couteux Invasifs Disponibilité limitée aux centres spécialisés





TEP-amyloïde

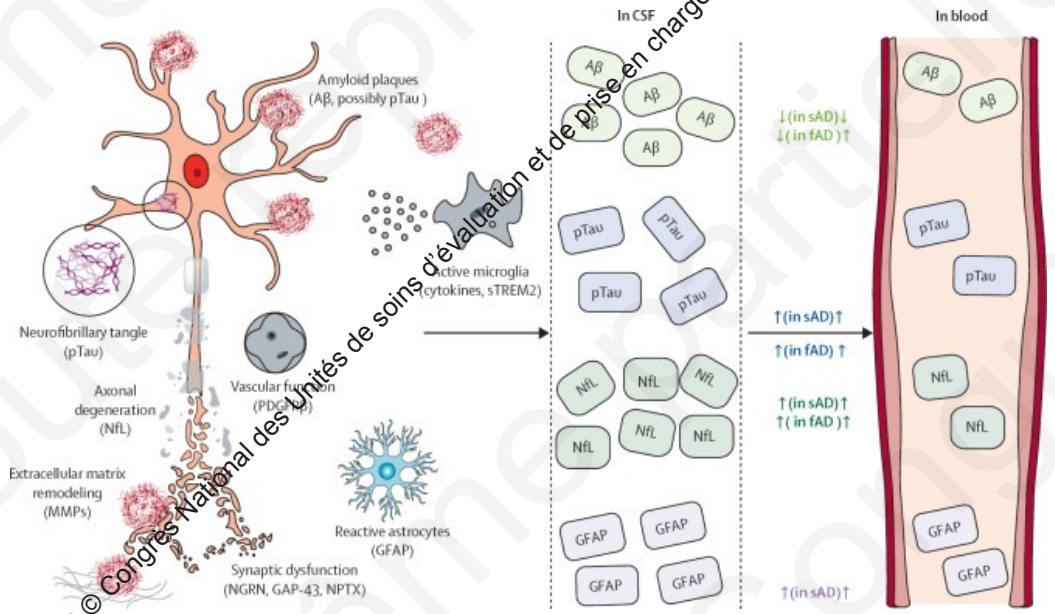
Task Force 1

Blood Biomarkers from Research Use to Clinical Practice: What Must Be Done?

D Angioni, J Delrieu, O Hansson, H Fillit, P Aisen, J Cummings, J R Sims, J B Braunstein, M Sabbagh, T Bittner, M Pontecorvo, S Bozeat, J L Dage, E Largent, S Mattke, O Correa, L M Gutierrez Robledo, V Bandivieso, D R Willis, A Atri, R J Bateman, P-J Ousset, B Vellas, M Weiner

1) L'état du développement des biomarqueurs plasmatiques
2) Les limites des biomarqueurs plasmatiques
3) L’usage des biomarqueurs dans la pratique clinique

Les biomarqueurs plasmatiques



Aβ40, Aβ42 et Aβ42/40

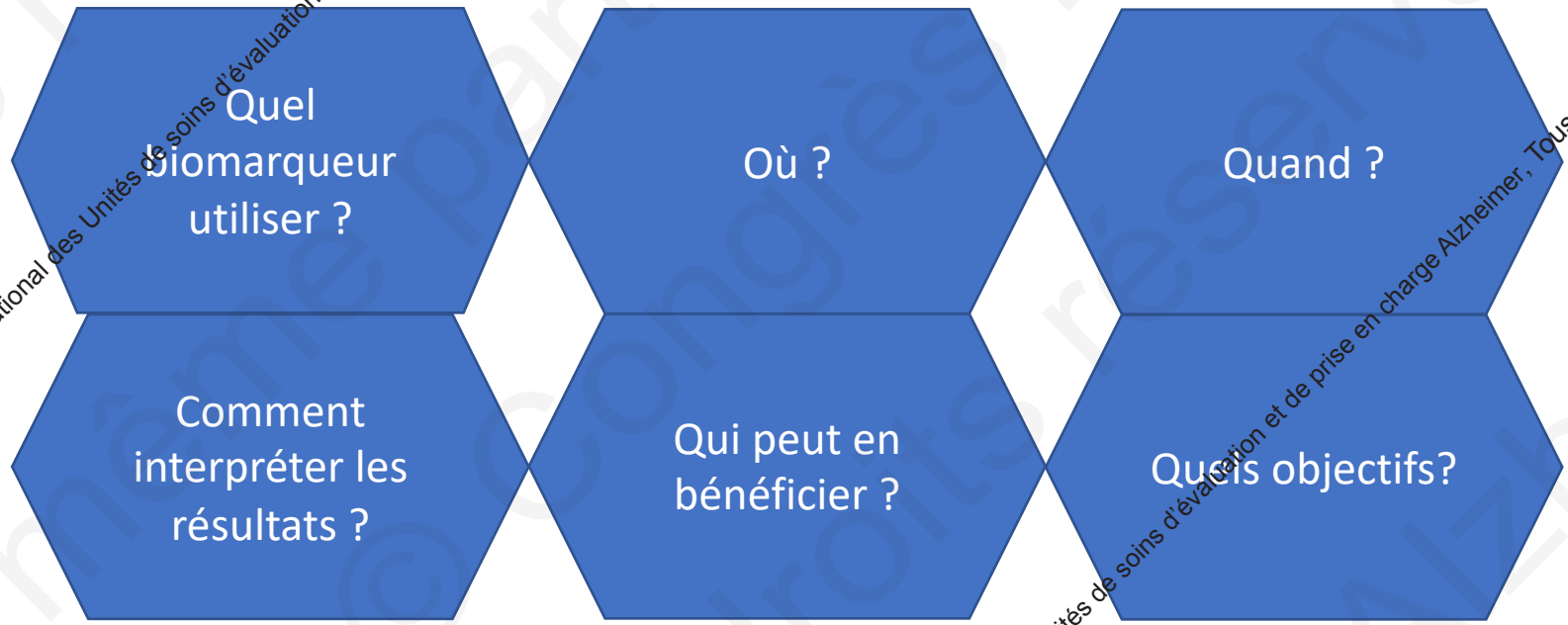
p-tau (181, 217, 231)

NfL

GFAP

- Performances diagnostiques vs. TEP amyloïde et tau
  - Performances diagnostiques vs. analyse LCR
  - Corrélation avec lésions anatomo-pathologiques

Usage des biomarqueurs en pratique clinique



Quel biomarqueur utiliser ?

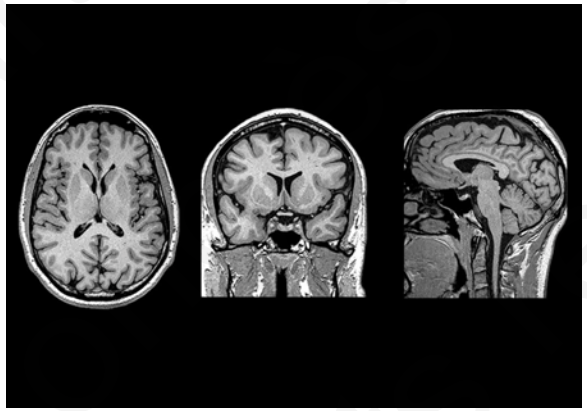
- Aβ42/40
- p-tau(s)

- Meilleures performances si association:

- plusieurs marqueurs plasmatiques (ex. Aβ42/40 + p-tau)
- marqueurs plasmatiques + Apoε4 génotypage
- marqueurs plasmatiques + variables cliniques (ex. âge)

Quand ?

- Histoire cognitive
- Antécédents
- Traitements médicamenteux
- Examen physique
- Examen neuropsychologique



EVALUATION CLINIQUE **IMAGERIE MORPHOLOGIQUE** **TESTS SANGUINS**

Choix du patient

Patient symptomatique +

Atteinte cognitive objectivée +

Suspicion de Maladie d'Alzheimer

	Appropriate use	Inappropriate use
When to use blood-based markers?	1. In individuals with objective cognitive impairment (possible or probable AD, MCI/dementia) 2. If suspicion of AD, as part of the initial diagnostic workup 3. If any contraindication or patient aversion to LP (CSF biomarkers)	1. Instead of the cognitive testing 2. In cognitively unimpaired individuals, except context of clinical research 3. Use to determine disease severity in patients having already received a diagnosis of AD 4. APOE4 carriers with no cognitive impairment

Comment interpréter les résultats ?

How to interpretate blood-based markers?	1. Holistic approach, model combining blood-based biomarkers and cognitive performance 2. Need to perform CSF biomarkers or PET if clinical presentation, structural imaging or other evaluative tests conflict with the blood-based biomarker test result	1. Interpretation of biomarkers without considering the history, clinical exam, cognitive testing, and patient autonomy

Où ?

- Soins primaires
- Consultation mémoire
- Essais thérapeutiques

Potential role		Where?
Risk/probability	To detect persons at risk for a disease or condition	Primary care
Diagnosis	To confirm the presence of a disease/condition	Primary care and specialists in memory disorders
Prognosis	To determine risk of worsening and/or progression from MCI to AD	Primary care and specialists in memory disorders
Monitoring	To assess changes in disease severity or the effect of a treatment	Specialists in memory disorders
Pharmacodynamic	To detect changes in response to treatment	Specialists in memory disorders and Clinical trials
Predictive	To predict a favorable or unfavorable effect of a treatment	Specialists in memory disorders and Clinical trials
Safety	To detect an adverse event	Specialists in memory disorders and Clinical trials

Avantages: Diagnostic et prise en charge plus rapide
Possibilité de combiner le dosage des biomarqueurs avec des évaluations digitales

Risques

- Sous-diagnostic de pathologies cognitives ≠ Maladie d'Alzheimer.
  - Test normal ≠ Absence de troubles cognitifs
- Mésusage
  - Usage à large échelle, ex. PSA pour le cancer de la prostate
- Interprétation incorrecte des résultats
  - nécessité absolue d'une consultation de synthèse des résultats

Task Force 2

EU/US/CTAD Task Force Novembre 2022

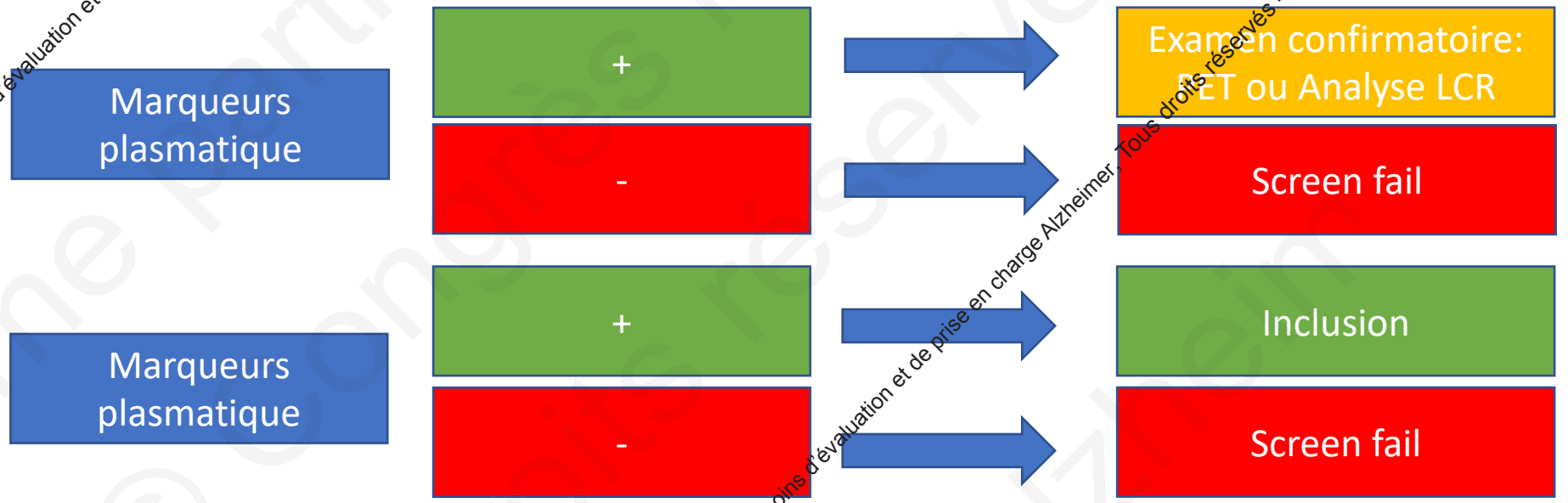
Can We Use Blood Biomarkers as Entry Criteria and for Monitoring Drug Treatment Effects in Clinical Trials?

D Angioni, O Hansson, R J Bateman, C Rabe, M Toloue, J B Braunstein, S Agus, J R Sims, T Bittner, M C Carrillo, H Fillit, C L Masters, S Salloway, P Aisen, M Weiner, B Vellas, S Gauthier

JPAD 2023

Marqueurs plasmatiques dans les essais thérapeutiques

- Pre-screening:
- Screening:
- Monitoring: évaluer la réponse au traitement



Marqueurs plasmatiques: critères d'entrée

Table 1. Some examples of BBMs used in clinical trials as entry criteria

PRE-SCREENING						
Study	**Clinicaltrial.gov Identifier**	**Phase**	**Population**	**Drug**	**BBM**	**Confirmatory Exam**
AUTONOMY	NCT04659420	II	Early symptomatic AD	JNJ-63733657	p-tau217	Tau PET
INVOKE-2	NCT04592874	II	Early symptomatic AD	AL002	PrecivityAD™ (algorithm derived from Aβ 42/40, ApoE and Age)	Amyloid PET or CSF
PROSPECT-ALZ	NCT05063539	II	Early symptomatic AD	LY3372689	p-tau217	Amyloid PET Tau PET
TRAILBLAZER-ALZ 2	NCT04437511	III	Early symptomatic AD	Donanemab	p-tau181	Amyloid PET Tau PET
AHEAD 3-45	NCT04468659	III	Preclinical AD	Lecanemab	Aβ42/40 ratio	Amyloid PET
SKYLINE	NCT05256134	III	Preclinical AD	Gantenerumab	p-tau181 and ApoE	Amyloid PET or CSF
SCREENING						
Study	**Clinicaltrial.gov Identifier**	**Phase**	**Population**	**Drug**	**BBM**	
TRAILBLAZER-ALZ 3	NCT05026866	III	Preclinical AD	Donanemab	p-tau217	

Marqueurs plasmatiques: critères d'entrée dans les essais thérapeutiques

Table 2. Key points about BBMs use as entry criteria for Alzheimer's trials

- Promising feedback for BBMs as pre-screeners but limited experience for BBMs as screening tools.
- Advantages of BBMs use
  - Lower costs for enrollment if pre-screening is done with BBMs, since less screening failures occur with amyloid PET or CSF analysis.
  - BBMs can promote enrollment speed and reduce burden for study participants
  - A blood sample for a BBM can be obtained in a home setting.
- Gaps to be resolved:
  - Limited knowledge of confounding factors, potentially able to modify BBMs values
  - Cut points established from previous repositories of plasma collected from research patients may not be applicable in more diverse populations.

Marqueurs plasmatiques: critères de monitoring dans les essais thérapeutiques

Table 3. Some examples of BBMs use in clinical trials as monitoring criteria

	Clarity AD	Emerge	Engage	Scarlet Road	Marguerite Road	Trailblazer ALZ	Trailblazer ALZ 4	ALZ-801-201-ADBM
	NCT03887455	NCT02484547	NCT02477800	NCT01224106	NCT02051608	NCT03367403	NCT05108922	NCT04693520
	Lecanemab	Aducanumab		Gantenerumab		Donanemab	Donanemab versus Aducanumab	ALZ-801
	Phase 3	Phase 3		Phase 3 OLE		Phase 2	Phase 3	Phase 2
Aβ 42/40	Increased ** from BL to mo18			+14% from OLE BL to mo36	+9% from OLE BL to mo36	+ 4 % * from BL to w76		
p-tau181	Reduced ** from BL to mo18	-13 % ** from BL to w78	- 16 % ** from BL to w78	-13 % from OLE BL to mo36	-7 % from OLE BL to mo36			-41% from BL to w52
p-tau181/ Aβ42								-37 % from BL to w52
p-tau217		-	-	-24% from OLE BL to mo36	-11% from OLE BL to mo36	-20% ** from BL to w76	Donanemab -25% Aducanumab+2.8% from BL to w24	
GFAP	Reduced ** from BL to mo18					-12% ** from BL to w76		

BL, baseline; mo, months; OLE, open label extension; w,week; * no significant difference with placebo arm; ** significant difference with placebo arm

Marqueurs plasmatiques: critères de monitoring dans les essais thérapeutiques

Table 4. Key points about BBMs use to monitor treatment effects in Alzheimer's trials

- BBMs can be performed more frequently than PET due to no radiation burden, permitting to improve the temporal resolution of monitoring.
- BBMs cannot inform about the neuroanatomic evolution of AD pathology.
- Multiple BBMs covering neurodegeneration, neuroinflammation and neuropathology, can be assessed based on one blood draw.
- BBMs have mainly been used as exploratory outcomes in AD clinical trials so far.
- More evidence that drug-induced changes in BBMs values are consistently correlated with beneficial changes in clinical outcomes is required to use BBMs as surrogate endpoints in clinical trials.
- Characteristics of an optimal monitoring BBM:
  - Longitudinal change of BBM concentration is associated with changes in underlying pathology
  - BBM values reflect the drug-induced changes in brain
  - At the individual level, changes in BBM could allow treatment to be tailored (e.g. lower/greater doses or frequency, decision to start/stop treatment).

Take home messages

- Marqueurs plasmatiques de la maladie d'Alzheimer: avancées importantes dans la dernière décennie
- Avantages des biomarqueurs plasmatiques: non invasifs, moins couteux, potentiellement utilisables en dehors des centres spécialisés
- Limites: techniques, valeurs seuils, facteurs confondants
- Les marqueurs plasmatiques peuvent faciliter les procédures de recrutement des essais thérapeutiques et limiter les coûts
- Les marqueurs plasmatiques ont le potentiel pour faciliter l'arrivée des nouvelles thérapies en pratique clinique.