Relative incremental value of ^{18}F-FDG-PET and CSF biomarkers in suspected Alzheimer's disease

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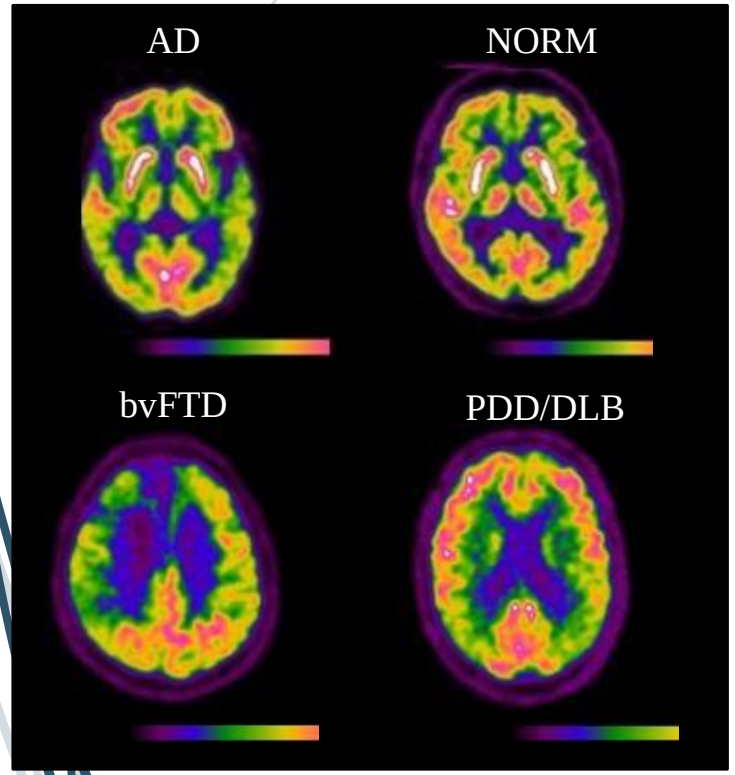
Background

In Alzheimer's disease (AD) a validated decision-tree algorithm about supportive biomarkers is still lacking. Consequently, in memory clinics their use is mainly guided by local expertise. Few studies assessed the utility of **combined use** of CSF with other biomarkers, such as ^{18}F-FDG-PET, to improve diagnosis accuracy in AD.

Our aim is to evaluate the **relative incremental value** of either CSF biomarker or ^{18}F-FDG-PET, used subsequently and in an alternate order, in differential diagnosis between **AD and non-AD conditions** in patients with uncertain diagnosis after standard clinical-neuropsychological assessment and brain MRI.

Materials and Methods

The study was performed in two Italian tertiary memory clinics, with alternative expertise in biomarkers: as per clinical routine, in uncertain diagnoses **CSF is performed first in Perugia, and ^{18}F-FDG-PET in** Genoa. We retrospectively selected only those cases submitted to the second biomarker evaluation because the first one gave uncertain results.



CRITERIA OF INTERPRETATION

GE →

← **PG**

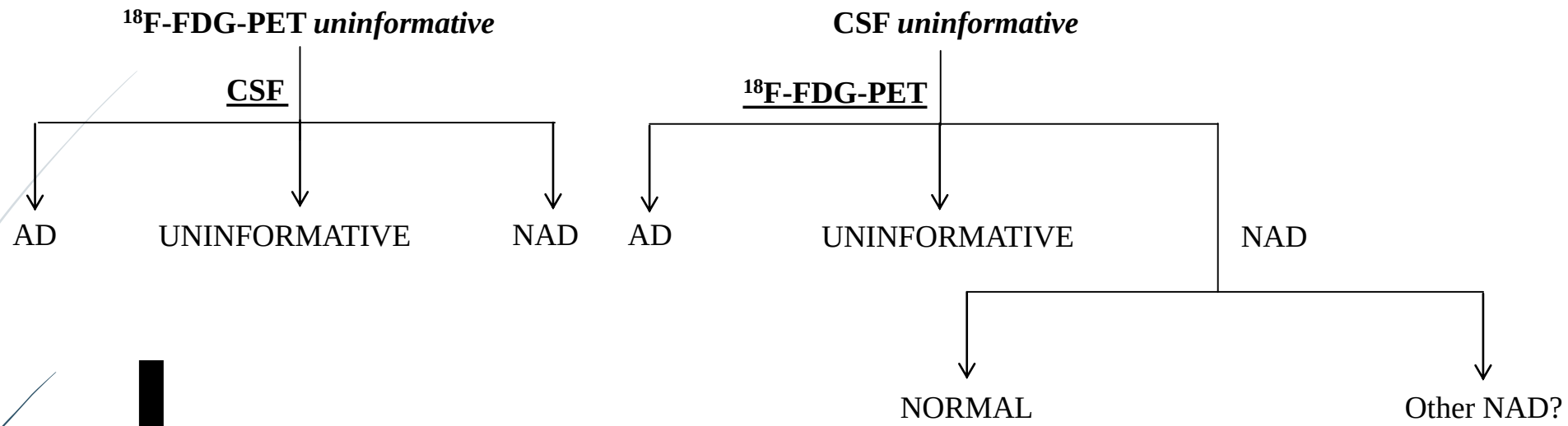
CSF markers cutoffs	Uninformative CSF profile
$A\beta_{42}$> 550 pg/ml: normal (-) $A\beta_{42}$ 495-550 pg/ml: uninformative (+*) $A\beta_{42}$ < 495 pg/ml: abnormal (+) **t-Tau < 400 pg/ml: normal (-)** t-Tau 400-440 pg/ml: uninformative (+*) t-Tau > 440 pg/ml: abnormal (+) **p-Tau < 65 pg/ml: normal (-)** p-Tau 65-72 pg/ml: uninformative (+*) p-Tau > 72 pg/ml: abnormal (+)	$A\beta_{42}$ (+ or +*)/ p-Tau (-) / t-Tau (-) $A\beta_{42}$ (+ or +*) / p-Tau (+ or +*) / t-Tau (-) $A\beta_{42}$ (+ or +*) / p-Tau (-) / t-Tau (+ or +*) $A\beta_{42}$ (-) / p-Tau (+ or +*) / t-Tau (-) $A\beta_{42}$ (-) / p-Tau (-) / t-Tau (+ or +*) $A\beta_{42}$ (-) / p-Tau (+ or +*) / t-Tau (+ or +*) $A\beta_{42}$ (+*) / p-Tau (+*) / t-Tau (+*)

*A “grey zone” including +10% of t-Tau and p-Tau values and -10% of $A\beta_{42}$ value was considered as uncertain (Molinuevo et al.)

**All images were evaluated by two independent experts, blinded to clinical data; interpretation of metabolic patterns was discussed until agreement.

Typical AD pattern: hypometabolism in at least one among precuneus, posterior cingulate or temporo-parietal ctx, MTL.

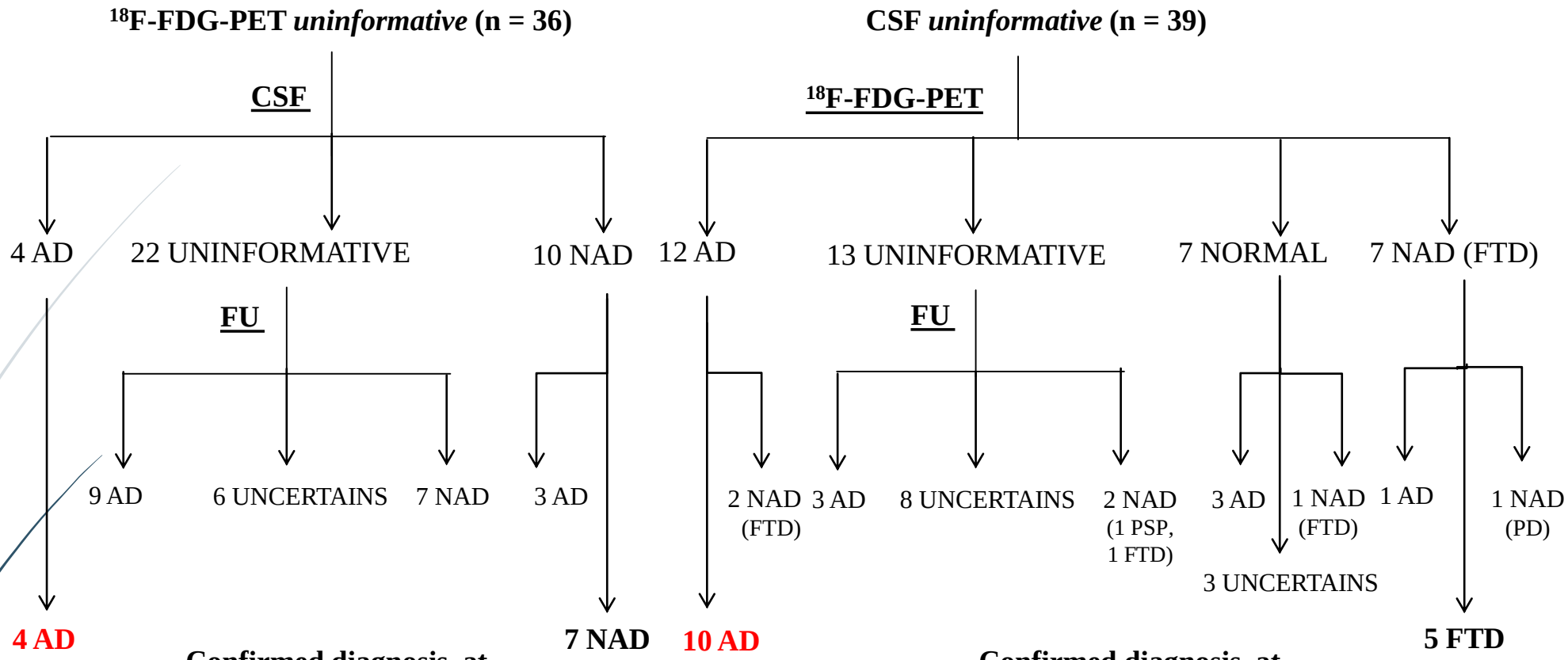
DIAGNOSTIC PATHWAYS



> 1-year FU

Relative incremental value (RIV%) = $\frac{\text{diagnosis suggested by the second biomarker and clinically confirmed at FU}}{\text{all patients with } \textit{uninformative} \text{ first biomarker}}$ x 100

Results



TOT confirmed diagnosis at follow-up: 26/75

+ 34.7%

Highlights

- RIV of CSF biomarkers and FDG-PET over one another was **30.6%** and **38.5%,** respectively (average 34.7% in the whole cohort), with a small advantage for FDG-PET.
- The majority (65%) of diagnoses suggested by an **informative** second-line biomarker were confirmed at follow-up, in this case with an advantage of CSF biomarkers (78.6%) over FDG-PET (57.7%).
- As for FDG-PET, the main advantage seems that an alternative diagnosis can be suggested when an AD-like hypometabolic pattern is not found, as in the case of FTD.

Conclusions

- Using biomarkers with a step-wise approach allows to increase the diagnostic accuracy although a non-trivial part of patients remains undiagnosed.
- Efforts should be directed to define a **diagnostic-tree** that considers either the main features of each biomarker, alone or in sequential combination, and a **cost-effective** approach to identify those patients in which adding a second biomarker could be really useful.