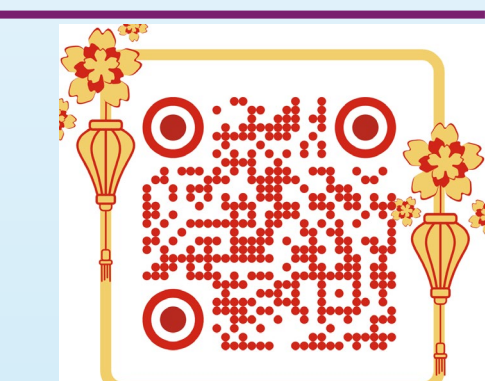




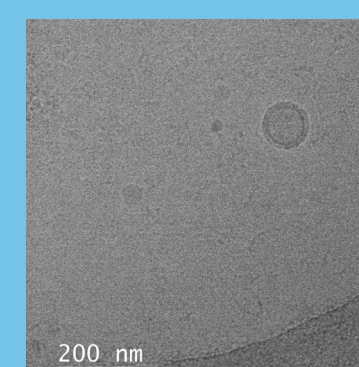
We have developed the first prototype plasma small extracellular vesicle (SEV) RNA diagnostic biomarker assay for DLB

INTRODUCTION

- ❖ There is an **urgent clinical need** for identifying blood-based biomarkers that aid distinguishing Dementia with Lewy Bodies (DLB) from dementia in Alzheimer's Disease (AD), especially in the UK NHS mental health memory assessment services (MAS)¹.
- ❖ People with DLB have high risk for developing antipsychotics induced serious adverse effects².
- ❖ New anti-amyloid monoclonal antibodies that can treat AD do not have evidence for treating DLB³.
- ❖ Dopamine SPECT is the only DLB biomarker, available to most MAS. It is not widely used because of several feasibility issues. Most MAS cannot access CSF analysis.
- ❖ We have identified DLB associated **miRNA** that are differentially expressed in both post-mortem DLB brains and in blood-based SEV from people living with DLB^{4,5}.
- ❖ We **aimed** to develop a multiplex RNA biomarker assay using the identified DLB associated miRNA.

METHODS

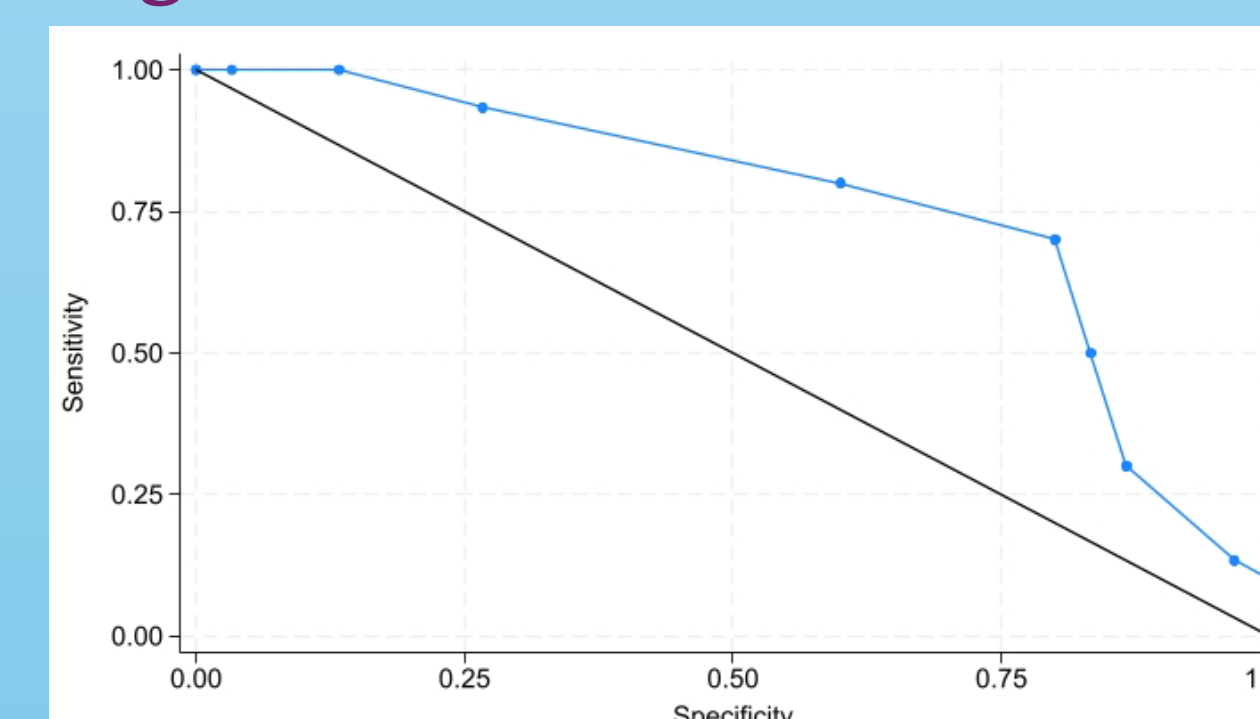
- ❖ We designed the customised BBDLB miRNA assay using the **nCounter®** (Bruker Spatial Biology, USA) technology that can detect SEV RNA as low as 200pg input⁶.
- ❖ The BBDLB assay includes 18 DLB associated miRNA probes, two reference miRNA, and 20 inbuilt probes for quality control and inter-plate calibration.
- ❖ We recruited people with DLB, AD, and people without cognitive impairment (N=90; n=30/group) from four UK NHS sites.
- ❖ We separated SEV from platelet-poor plasma using **size exclusion chromatography** and characterised the SEV using **cryo-transmission electron microscopy**.
- ❖ Considering the **reference standard** of DLB clinical diagnoses⁷, confirmed by consultant Old Age Psychiatrists with DLB expertise, we estimated the diagnostic accuracy of the BBDLB assay.



RESULTS

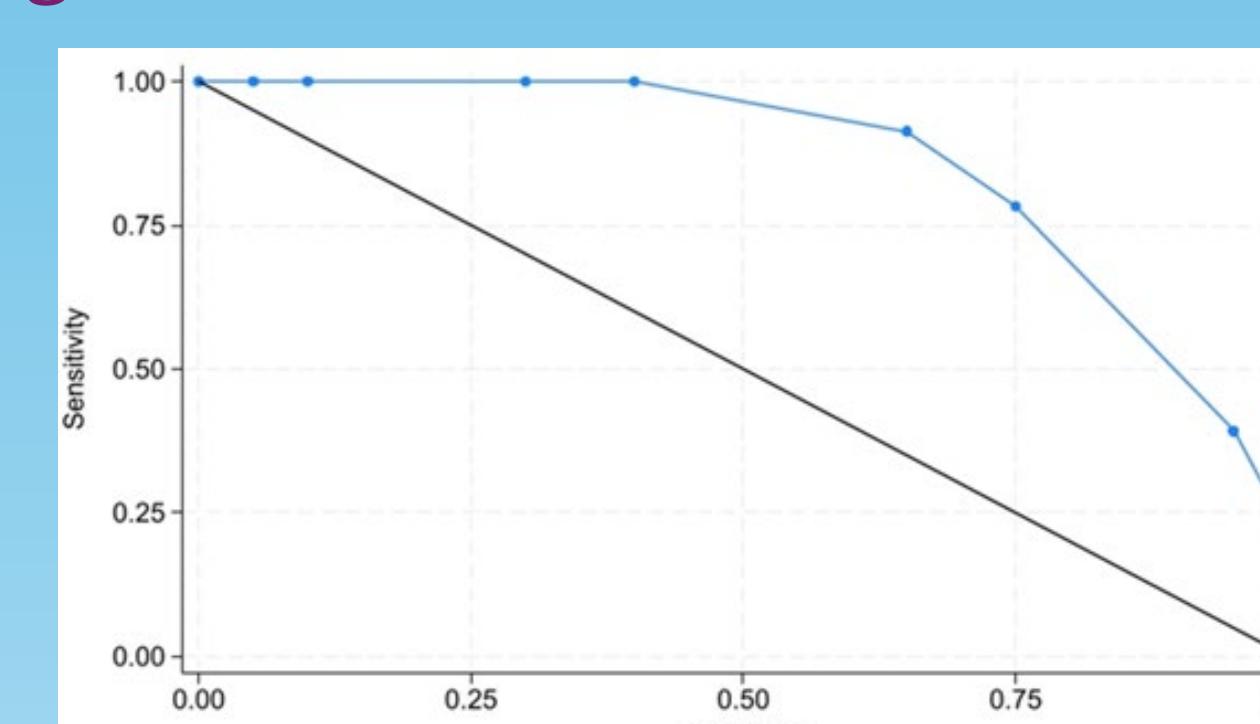
- ❖ We demonstrated the feasibility of measuring low input plasma SEV miRNA levels from clinically collected blood samples.
- ❖ The BBDLB assay **could correctly classify 78.4% of people with DLB from AD** with 70% sensitivity, 80% specificity, as well as 3.5 positive (PLR) and 0.38 negative (NLR) likelihood ratios (AUC=0.760).

Fig.1: DLB Vs AD ROC curve



- ❖ The biomarker assay could distinguish DLB from people without cognitive impairment with 79.1% accuracy (Sensitivity 91%, Specificity 65%, PLR 2.6, NLR 0.14 and AUC 0.857).

Fig.2: DLB Vs Controls ROC curve



CONCLUSIONS

- ❖ The BBDLB assay is the first blood-based SEV RNA diagnostic biomarker assay for DLB that has shown its potential for adaptation in the UK NHS MAS.
- ❖ **Enriching plasma SEV for neuronal and microglial origin** by immunoprecipitation can improve its signal-to-noise ratio.
- ❖ Thanks to a major project grant from the **Alzheimer's Research UK**, we are working on improving the diagnostic accuracy of BBDLB assay and on evaluating its performance in an independent clinical cohort.

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