Information Sheet for Plasma testing for Alzheimer's disease

Scottish Brain Sciences
Better brain health for all.

Laboratory Information

NAME AND ADDRESS OF LABORATORY:	Scottish Brain Sciences Building 1 Eden Campus Guardbridge KY16 0US
OPENING HOURS:	9:00am-5:00pm Monday -Friday
CONTACT INFORMATION:	Tel no: 07745 520319 Email: labenquiries@brainsciences.scot
DIRECTOR OF LABORATORY:	Dr Lewis K Penny
PLASMA TESTS:	Phosphorylated tau $_{181}$ (pT181P / pTau181) Phosphorylated tau $_{217}$ (pT217P / pTau217)
TURNAROUND TIME:	5-20 working days

Purpose of Plasma Biomarker Testing:

Over the last five years there has been increasing evidence that blood-based biomarkers (BBB) have a role to play in the detection of the very earliest signs of Alzheimer's disease (AD). Of all the BBB investigated, phosphorylated tau $_{181}$ (pTau181) and phosphorylated tau $_{217}$ (pTau217) have shown the most promise.[1,2]

Plasma pTau217

The Elecsys Phospho-Tau (217P) Plasma assay is an in vitro diagnostic immunoassay for the quantitative determination of the phospho-tau (217P) (pTau217) protein in human plasma from individuals aged 55 years and older. The assay is intended for use as an aid in identifying patients with amyloid pathology presenting with signs, symptoms, or complaints of cognitive decline associated with Alzheimer's disease.

- A positive Elecsys Phospho-Tau (217P) Plasma assay result indicates a high likelihood of amyloid pathology. This result, in the absence of clinical evaluation, does not establish a diagnosis of Alzheimer's disease.

- An intermediate Elecsys Phospho-Tau (217P) Plasma assay result is indeterminate for the presence of amyloid pathology. It is recommended to consider these patients for further testing.
- A negative Elecsys Phospho-Tau (217P) Plasma assay result indicates a low likelihood of amyloid pathology. Further clinical investigation into other causes of cognitive decline is recommended for these patients.

Plasma pTau181

The Elecsys Phospho-Tau (181P) Plasma assay result is intended as a 'rule-out' test for amyloid pathology be used as an aid in the initial assessment for Alzheimer's disease and other causes of cognitive decline in adult patients aged 55 years and older, presenting with signs, symptoms, or complaints of cognitive decline. The result should be interpreted in conjunction with other clinical information.

- A negative test result is consistent with a negative amyloid positron emission tomography (PET) scan result and reduced likelihood that a patient's cognitive impairment is due to amyloid pathology. These patients should be investigated for other causes of cognitive decline.
- A positive test result may not be consistent with a positive amyloid PET scan result. Patients with an initial positive result should be further investigated to determine whether the amyloid pathology can be a cause of cognitive impairment.

Procedure Overview:

- **Informed Consent:** It's essential to understand the purpose, benefits, and potential risks of the test. Clinicians should provide clear information, considering the patient's cognitive status, and may need to repeat explanations to ensure comprehension. It is the responsibility of the external client to obtain informed consent.
- **Role in Diagnosis:** Understand that plasma biomarker results complement other assessments, such as cognitive tests, CSF testing and imaging studies, and are not standalone. Plasma pTau181 and pTau217 concentrations may be influenced by renal function. Results should be interpreted with caution in patients with significantly impaired renal function (e.g., CKD) or history of traumatic brain injury (TBI).
- **Plasma collection tubes:** Only K2 and K3 EDTA plasma is suitable for phosphorylated tau $_{181}$ and phosphorylated tau $_{217}$ analysis. Plasma tubes containing separating gel can be used.
- **Plasma Storage and transportation**: We recommend that blood samples are separated within 1 hour of being collected and the plasma is stored in a screwtop low-bind polypropylene tube (0.5 to 2 mL) at -20°C/-80°C before being sent to us frozen at -20°C/-80°C. We recommend screw cap micro tube 0.5 ml (SARSTEDT, 72.730.007)

All samples must be sent in UN 3373 biological substance category B compliant packaging. We recommend using a same/next day delivery.

It is recommended that referring laboratories retain an aliquot of sample as risk mitigation in the event of damage or loss en route.

- **Plasma sample shipment:** The plasma sample must be sent to:

  Scottish Brain Sciences
  Building 1
  Eden Campus
  Guardbridge KY16 0US

- **Plasma Request Information:** A Request form can be found at the Scottish Brain Sciences website under Laboratory Services. Complete the request form fully, print and send with the sample shipment. It is important that the request form is completed as fully as possible to avoid a delay in processing the samples due to missing essential information.

  Any deviation from the guidance provided in this document, particularly relating to sample collection and sample storage, must be recorded on the request form so the potential impact to any results and the patient can be assessed.

  Each sample must be accompanied by a request form with the following information:

  Patient Name
  Patient Date of Birth
  Hospital number
  CHI/NHS number, if known
  Sex
  Date and time of sample collection
  Name and contact information of Requesting Doctor
  Address for result report
  Clinical Information

- **Acceptance/Rejection Criteria:** To be accepted by the laboratory for analysis. Plasma samples must meet the criteria below:
  - The sample must be clearly labelled with patient name, date of birth, date of collection
  - Have a volume of at least 0.5 mL plasma
  - Be collected into a screwtop low-bind polypropylene tube as described above
  - Must NOT be visibly haemolysed

- **Plasma analysis:** Each plasma sample is analysed for pT181P and/or pT217P using Roche Elecsys® on a Roche Cobas Core e801 autoanalyzer. The SBS Biomarker Laboratory participates in the Alzheimer's Association EQA Scheme (European).

- **Additional Tests:** To request an additional test, email the laboratory at labenquiries@brainsciences.scot with the following information:

    - Patient Name
    - Second patient identifier (eg CHI number, date of birth)
    - Date of sample collection
    - Additional Test requested

    Additional tests can only be fulfilled if received within time limits listed below, and if there is sufficient sample volume.

    1. Within 12 weeks of sample collection if sample sent to lab at -20°C / -80°C.

- **Price:** Please contact labenquiries@brainsciences.scot for further information.

Result Interpretation

Elevated plasma phosphorylated tau $_{181}$ and phosphorylated tau $_{217}$ levels are associated with increased likelihood of having abnormal CSF AD testing or evidence of abnormal β-amyloid PET imaging. Plasma pTau181 and pTau217 concentrations may be influenced by renal function. Results should be interpreted with caution in patients with significantly impaired renal function (e.g. CKD) or with history of traumatic brain injury.

Each result report will have an interpretative comment and further information regarding the interpretation of these results can be provided by contacting Dr Alison Green, Clinical Biochemist (a.green@brainsciences.scot), Dr Meher Lad, Academic Cognitive Neurologist (m.lad@brainsciences.scot) or Prof Craig Ritchie, Professor of Psychiatry (C.Ritchie@brainsciences.scot).

Internal clinical validation has been conducted using data from over 900 participants, with paired plasma (blood) and cerebrospinal fluid (CSF) samples analysed to evaluate the clinical suitability and performance of plasma pTau181 and pTau217 assays. CSF biomarker analysis using the Roche Elecsys® cobas® platform was used as the reference standard for determining amyloid pathology consistent with Alzheimer's disease. A CSF pTau181/Aβ42 ratio >0.023 was applied as the threshold indicative of amyloid-positive pathology. This comprehensive clinical validation has enabled the establishment of optimised assay cut-offs that maximise diagnostic performance while ensuring the assays are suitable for clinical use.

Plasma pTau217

The validated cut-offs and their corresponding clinical interpretation for the plasma pTau217 assay are presented in the table below.

Internal clinical validation demonstrated predictive values of 92% and approximately 91% for positive and negative pTau217 classifications for amyloid pathology, respectively. Only 8% of participants had an indeterminate result. Suggested further testing for indeterminate results for amyloid pathology may include CSF testing that is offered by Scottish Brain Sciences.

Elecsys Phospho-Tau (217p) Plasma	**Interpretation**
Result > 0.503 pg/mL = positive	A positive result indicates a high likelihood of amyloid pathology. This result, in the absence of clinical evaluation, does not establish a diagnosis of Alzheimer's disease.
0.354 pg/mL < result ≤ 0.503 pg/mL = intermediate	An intermediate result is indeterminate for the presence of amyloid pathology. It is recommended to consider these patients for further testing.
Result ≤ 0.354 pg/mL = negative	A negative result indicates a low likelihood of amyloid pathology. Further clinical investigation into other causes of cognitive decline is recommended for these patients.

Plasma pTau181

The validated cut-offs and their corresponding clinical interpretation for the plasma pTau181 assay are presented in the table below. Internal clinical validation demonstrated a negative predictive value of 92 % for amyloid pathology and fit-for-use as a “rule-out” test.

Elecsys Phospho-Tau (181p) Plasma	**Interpretation**
Negative (≤ 0.934 pg/mL)	A negative result is consistent with a negative amyloid PET scan result. These patients should be investigated for causes of cognitive decline other than amyloid pathology.
Positive (> 0.934 pg/mL)	A positive result may not be consistent with a positive amyloid PET scan result. Patients with an initial positive result should be further investigated to determine whether amyloid pathology can be a cause of cognitive impairment.

Expression of Dissatisfaction: If you wish to express dissatisfaction with any of the services provided, you can do so by completing with form found on the Scottish Brain Sciences Website under Laboratory Services.

References:

1. Rodriguez et al., Plasma ptau 181 accurately predicts Alzheimer's disease pathology at least 8 years prior to post-mortem and improves the clinical characterisation of cognitive decline *Acta Neuropathological* (2020) **140:**267-278.
2. Ashton et al., Diagnostic accuracy of a plasma phosphorylated Tau 217 immunoassay for Alzheimer's Disease Pathology**.** *JAMA Neurol* (2024) **81(3)**: 255-263