

# **Implementation of a blood-based biomarker test for sporadic Creutzfeldt-Jakob in clinical practice**

## Objectives

1. The implementation in clinical grounds of blood-based (plasma) tests for the differential diagnosis of sCJD and other prion diseases.
2. Obtain a valuable tool for the early diagnosis, providing the possibility to intervene at initial stages of disease, assist in eligibility screening for clinical trials and assist in ruling out reversible (and treatable) causes of rapidly progressive dementia.
3. The development of a blood-based prognostic model for overall survival in sCJD.

## Summary of accomplishments to date

So far, we investigated and described the pre-analytical and analytical conditions under which Neurofilament light Chain (NfL) levels in blood-plasma may be used as a biomarker for prion diseases in the clinical setting. Further, we calculated the diagnostic accuracy of plasma NfL and Tau-Protein not only to differentiate prion disease from healthy controls but also from other neurological conditions that may mimic prion disease. We could show how these markers are associated with disease stage and survival time in sporadic Creutzfeldt-Jakob disease (sCJD) and Fatal Familial Insomnia (FFI) to pave the ground for an application as markers to estimate prognosis. We also investigated the evolution of NfL in an animal model for CJD, as well as in a human case study in FFI. In both diseases, we could show that the blood plasma levels of this marker do not increase before symptom onset but in the very early clinical phase. Finally, we have established a German registry and observational trial for healthy individuals with known Prion gene mutation. Blood and other fluid samples that have and will be obtain through this observation will be used to identify methods for non-invasive pre-clinical detection of prion disease.

## Key findings and implications for the prion disease field

1. Plasma NfL is a stable and consistent marker for sCJD. Variation of results between repeated tests and within one test assay is minimal. Concentrations remain stable at room

temperature and after freeze-thaw cycles. The marker is reliable, even after storage or shipment (Schmitz et al. 2022).

2. Plasma NfL and Tau showed good diagnostic accuracy for the differentiation of CJD from healthy individuals (HC), Alzheimer's disease (AD), and non-neurodegenerative causes of dementia (NND-Dem). Plasma Tau (but not NfL) was associated with CJD subtype and disease duration, offering a moderate survival prediction capacity.

Figure 1.

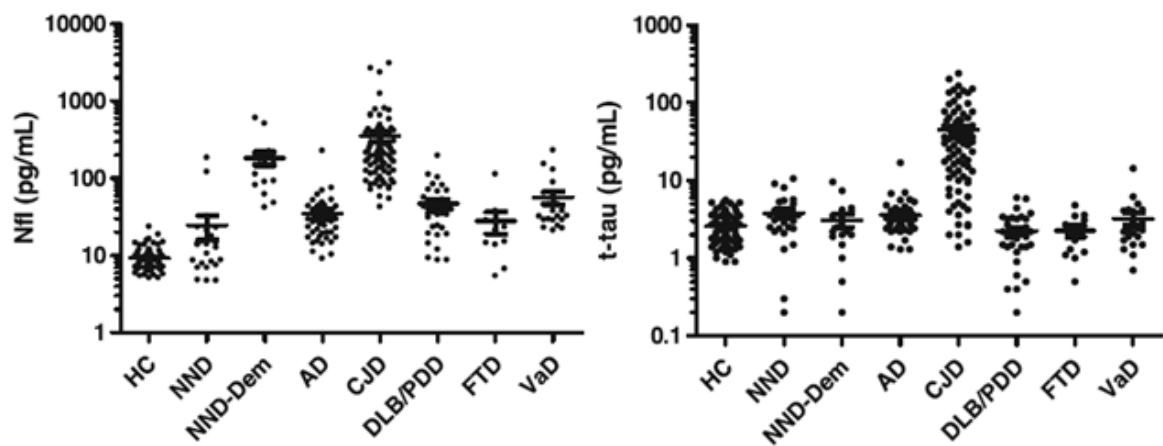


Figure 1 (Zerr et al. 2021) displays the biomarker levels in the different case groups like CJD, AD, HC, NND-Dem, and others. An important point was the variation of diagnostic accuracy among different control groups. NfL levels showed no overlap with HC, indicating 100% accuracy. On the other hand, NND-Dem showed similar levels to sCJD, warranting a thorough interpretation of results in the context of clinical characteristics. Combination of markers may also improve the diagnostic performance.

3. In validation studies, the diagnostic value of NfL for sCJD was confirmed and an optimal cut-off of plasma concentration levels for the clinical application was calculated (Schmitz et al. 2022). In addition, the diagnostic and prognostic value of plasma NfL was also confirmed in FFI (Hermann et al. 2022). This is very important, because early clinical signs of FFI may mimic affective disorders such as anxiety and depression and “classical” CJD biomarkers, even in cerebrospinal fluid and MRI, are negative in most FFI cases.
4. Plasma NfL was identified as an early or potentially even pre-clinical marker in CJD (Schmitz et al. 2022) and FFI (Hermann et al. 2022). Its application may significantly improve detection of sCJD in very early stages and early detection of disease in prion gene mutation carriers to determine time points for clinical interventions in the future.

Figure 2.

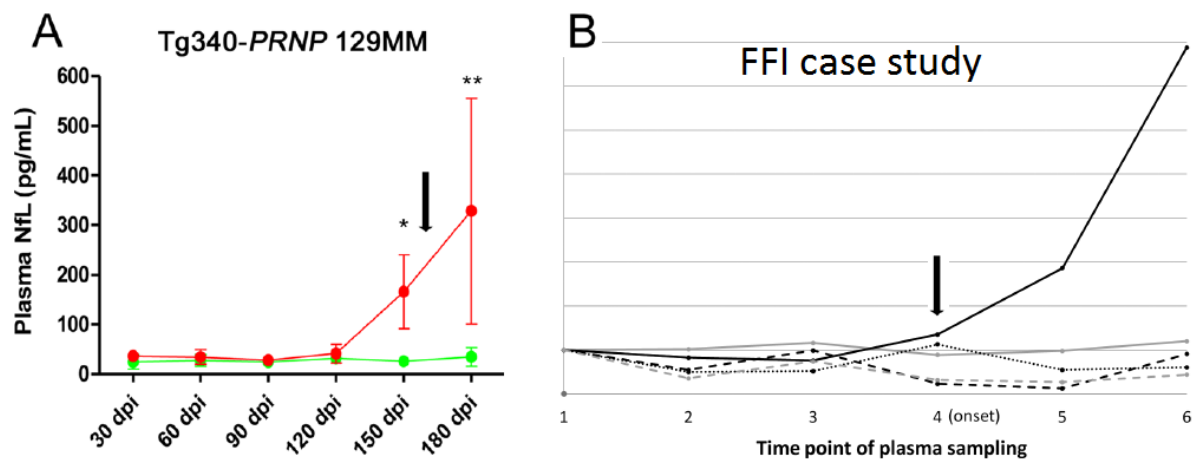


Figure 2 A (Schmitz et al. 2022) shows clear plasma NfL increase before symptom onset in a CJD animal model. Figure 2 B (Hermann et al. 2022) shows moderate increase at the exact time point of symptom onset in a patient with FFI. Here, other plasma biomarker candidates such Tau, GFAP, YKL-40, and S100b showed no consistent tendency during the disease course.

### Next steps

The performed analyses have opened the field for further investigations:

- Biomarker combinations involving plasma glial fibrillary acidic protein, phosphorylated Tau, and others will be investigated for their potential to improve diagnostic accuracy.
- More consecutive blood samples from healthy prion gene mutation carriers will be collected through a recently established longitudinal observational trial in Göttingen and through an international consortium of research centers. Analyses of these samples may provide further insight into potential pre-clinical diagnostic and trial surrogate markers.

### **Related Publications**

1. Zerr I, Villar-Piqué A, Hermann P, et al. Diagnostic and prognostic value of plasma neurofilament light and total-tau in sporadic Creutzfeldt-Jakob disease. *Alzheimers Res Ther.* 2021;13(1):86.
2. Schmitz M, Canaslan S, Espinosa JC, et al. Validation of Plasma and CSF Neurofilament Light Chain as an Early Marker for Sporadic Creutzfeldt-Jakob Disease. *Mol Neurobiol.* 2022;59(9):1-9. doi:10.1007/s12035-022-02891-7
3. Hermann P, Canaslan S, Villar-Piqué A, et al. Plasma neurofilament light chain as a biomarker for fatal familial insomnia. *Eur J Neurol.* 2022;29(6):1841-1846. doi:10.1111/ene.15302