This is a summary of the American Academy of Neurology (AAN) guideline regarding diagnostic accuracy of CSF 14-3-3 protein in sporadic Creutzfeldt-Jakob disease (sCJD).

Please refer to the full guideline at www.aan.com for more information, including definitions of the classifications of evidence and recommendations.

For patients with rapidly progressive dementia does the presence of CSF 14-3-3 protein accurately identify patients who have sCJD?

**Moderate evidence**

For patients who have rapidly progressive dementia and are strongly suspected of having sCJD, and for whom diagnosis remains uncertain (pretest probability ~20%–90%), clinicians should order CSF 14-3-3 assays to reduce the uncertainty of the diagnosis (Level B).

Figure 1 shows the sensitivity and specificity derived from each of the Class II studies. Figure 2 shows the relationship of pretest probability of having Creutzfeldt-Jakob disease (CJD) and the implications of a CSF 14-3-3 result.

**Figure 1: Sensitivities and specificities for testing for presence of 14-3-3 for CJD**

![ROC CSF 14-3-3 for CJD](image)

**Figure 2: Relationship of pretest probability of having CJD and the implications of a CSF 14-3-3 result**

![Posttest probability vs Pretest probability](image)
CLINICAL CONTEXT

The 14-3-3 assay, although of moderately high diagnostic accuracy, is an imperfect test. The test lacks the diagnostic accuracy either to include a CJD diagnosis as a possibility or to rule out CJD. It is important to realize that the test will not importantly change the probability of CJD in patients who are unlikely to have CJD to begin with. A positive result in such patients should not distract the investigator from considering a different dementing illness, or more important, a reversible cause of dementia. The relationship of this pretest probability of having CJD and the implications of a CSF 14-3-3 result are illustrated in figure 2. The upper curve in figure 2 indicates the degree to which the probability of sCJD will change if the CSF 14-3-3 result is positive. The lower curve indicates the degree to which the probability of sCJD will change if the CSF 14-3-3 analysis is negative.

The method by which the pretest probability is determined is usually implicit, and as an example, can be based on the specialist’s experience or knowledge about the incidence of the disease among individuals presenting with a suggestive clinical picture in a particular population. The dependence of the usefulness of CSF 14-3-3 assay on the pretest probability of sCJD can be illustrated by considering the case of a 72-year-old with dementia progressing over 18 months. Such a patient would appropriately be judged to have a very low pretest probability of CJD (< 1%). A positive 14-3-3 test for this patient would most likely represent a false-positive result (posttest probability of CJD < 5%). Likewise, the 14-3-3 assay would provide minimal information for patients with a high probability of having the disease. In the case of a 54-year-old with dementia progressing rapidly over 3 months and with symmetric MRI diffusion-weighted imaging (DWI) changes in the basal ganglia, the person is very likely to have CJD (>95%). A negative 14-3-3 test in this situation would most likely represent a false-negative result (posttest probability of CJD >80%).

The usefulness of the 14-3-3 assay will thus largely depend on a clinician’s judgment of the pretest probability of CJD for a given patient. Such judgments will reasonably consider the rarity of CJD (incidence 1 per million per year), the practice setting (community hospital versus tertiary referral center), the patient’s clinical presentation, and the results of already obtained ancillary tests such as head MRI. Figure 2 illustrates that the test is most useful when the pretest probability of CJD ranges from 20% to 90%. The use of other ancillary tests may affect this pretest probability. Periodic sharp and slow wave complexes (PSWC) on EEG testing have a sensitivity of 66% and specificity of 74%. PSWC tend to occur in older patients, and in half of the patients 6 months or more into the disease course, and then to decrease as the condition progresses. Despite the low sensitivity, in the right clinical setting EEG can be highly suggestive of sCJD; however, it is not entirely specific and is seen in various toxic or metabolic conditions or even during the late stages of Alzheimer disease or Lewy body dementia.

Imaging studies are emerging as valuable tools in diagnosing CJD. DWI and FLAIR MRI sequences are more useful than EEG. The sensitivity and specificity of DWI and FLAIR in diagnosing CJD were found to be 91%–92.3% and 93.8%–95%, respectively. Reduced diffusivity of ADC images in the basal ganglia and cortical regions has been demonstrated and can last as long as 2 months.

Finally, when considering the results of this analysis, it is important to highlight that there is significant variation in the way the 14-3-3 protein assays are performed. Most of the earlier studies used the Western blot technique, which is subjective and interpreted qualitatively. Later studies started to employ the quantitative ELISA technique, where sensitivity and specificity may vary according to the laboratory’s determined cutoff. There also are various isoforms of the 14-3-3 protein, and tests have been conducted on the beta isoform mostly; newer studies have started to test for the gamma isoforms. The time in the course of the illness when the test is carried out and the disease subtype are also important factors that can contribute to variation in test results.

This is an educational service of the American Academy of Neurology. It is designed to provide members with evidence-based guideline recommendations to assist the decision making in patient care. It is based on an assessment of current scientific and clinical information and is not intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, and are based on the circumstances involved. Physicians are encouraged to carefully review the full AAN guidelines so they understand all recommendations associated with care of these patients.