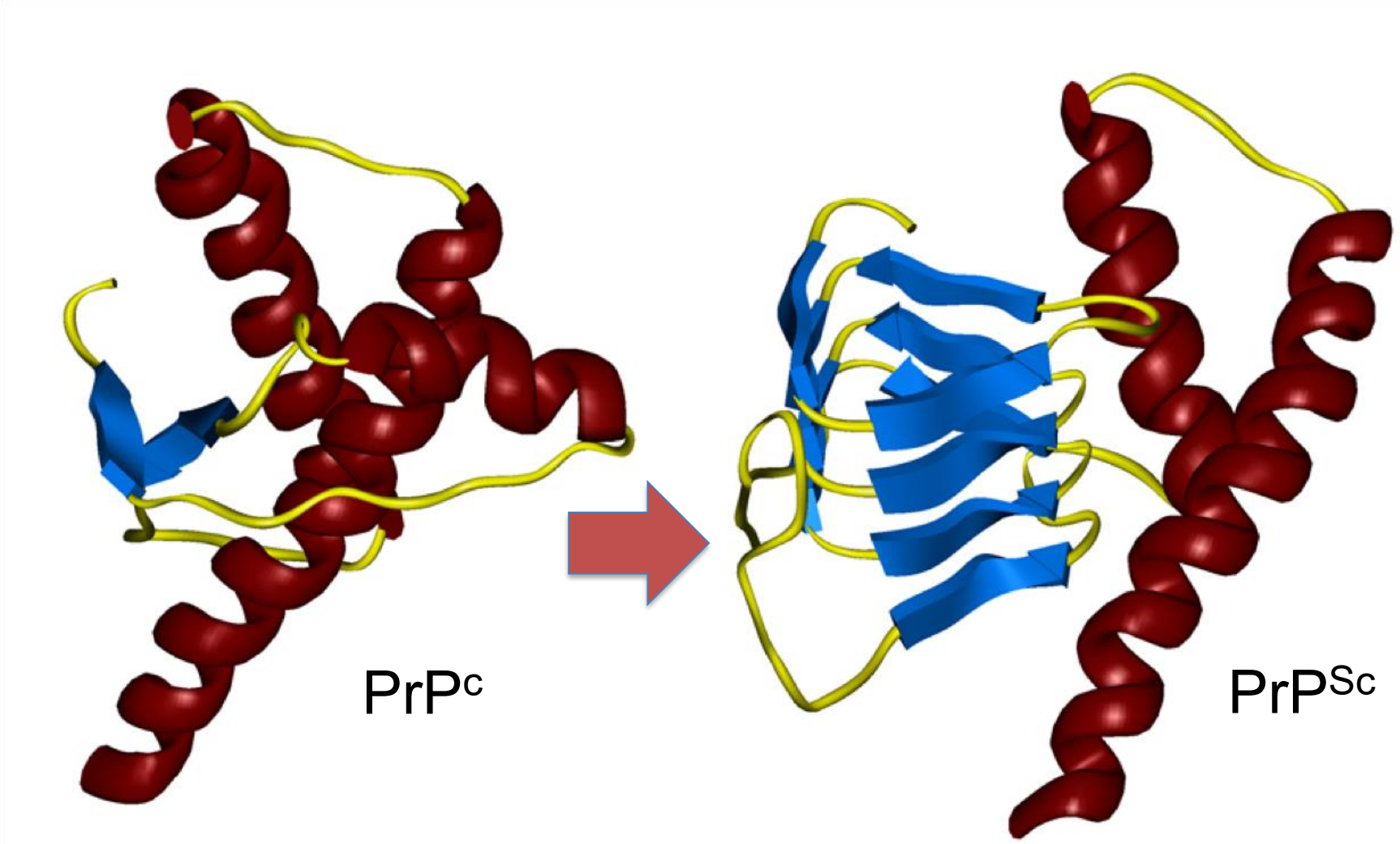
Prion Disease Basics – Clinical

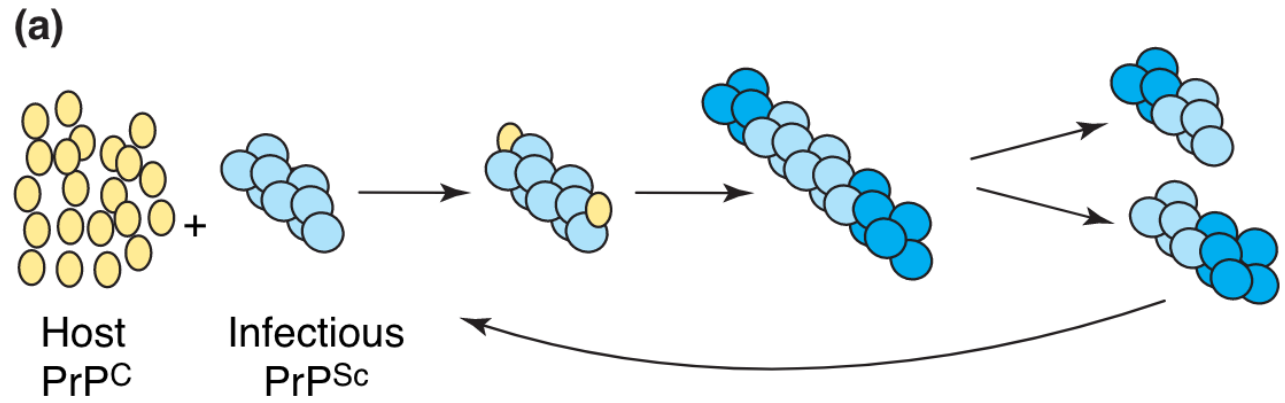
Brian Appleby, MD

Overview

- What is a prion?
- Review demographic features of prion disease
- Review the diagnostic process for prion disease
- Why is there so much clinical variability?

What is a prion?





Soto C, Trends Biochem Sci 2006

Causes of Prion Disease

<u>Sporadic Prion Diseases</u>
Sporadic CJD
Variably protease sensitive prionopathy
Sporadic fatal insomnia

<u>Acquired Prion Diseases</u>
Kuru
Iatrogenic CJD
Variant CJD

<u>Genetic Prion Diseases</u>
Genetic CJD
Gerstmann-Straussler Scheinker disease
Fatal familial insomnia

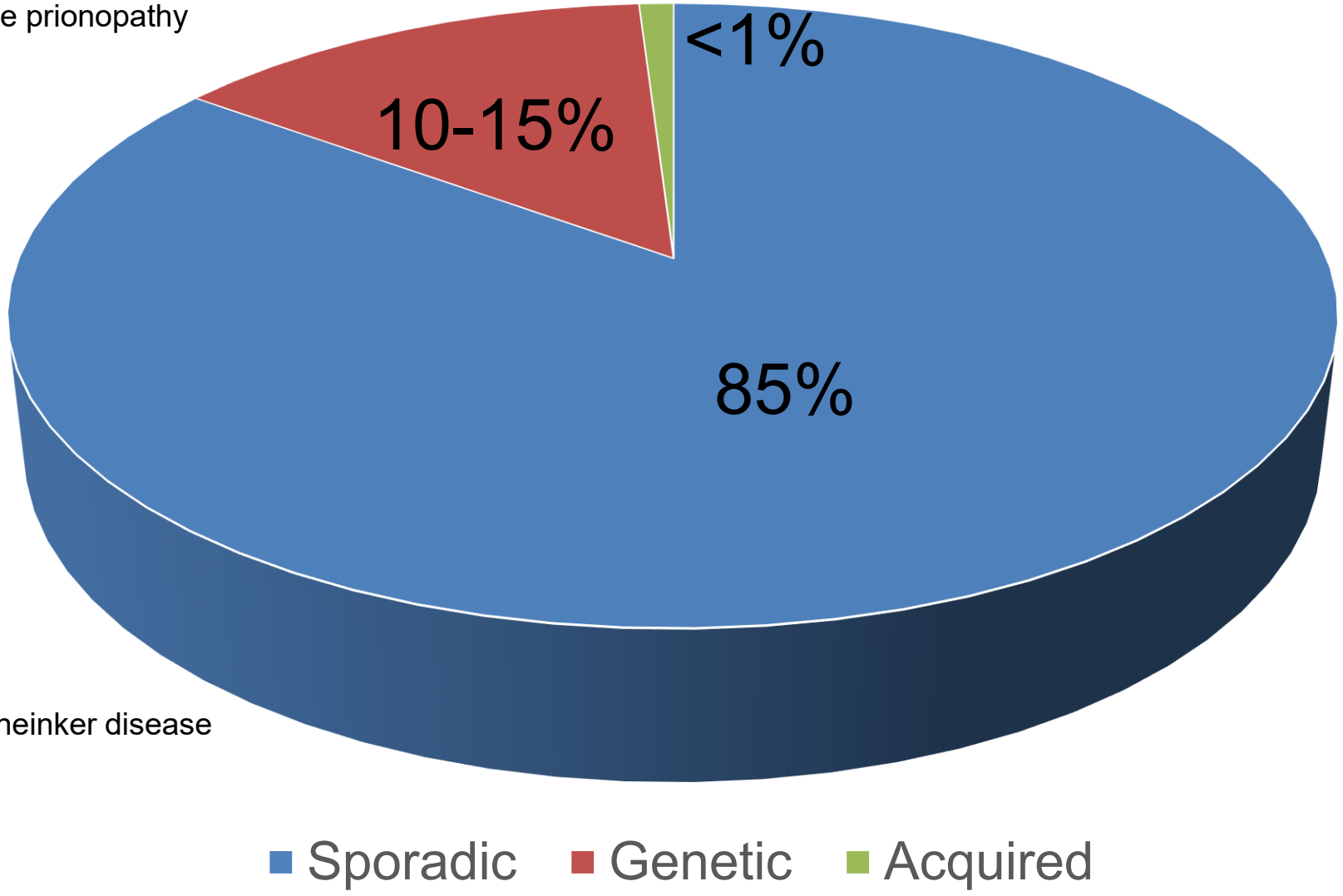
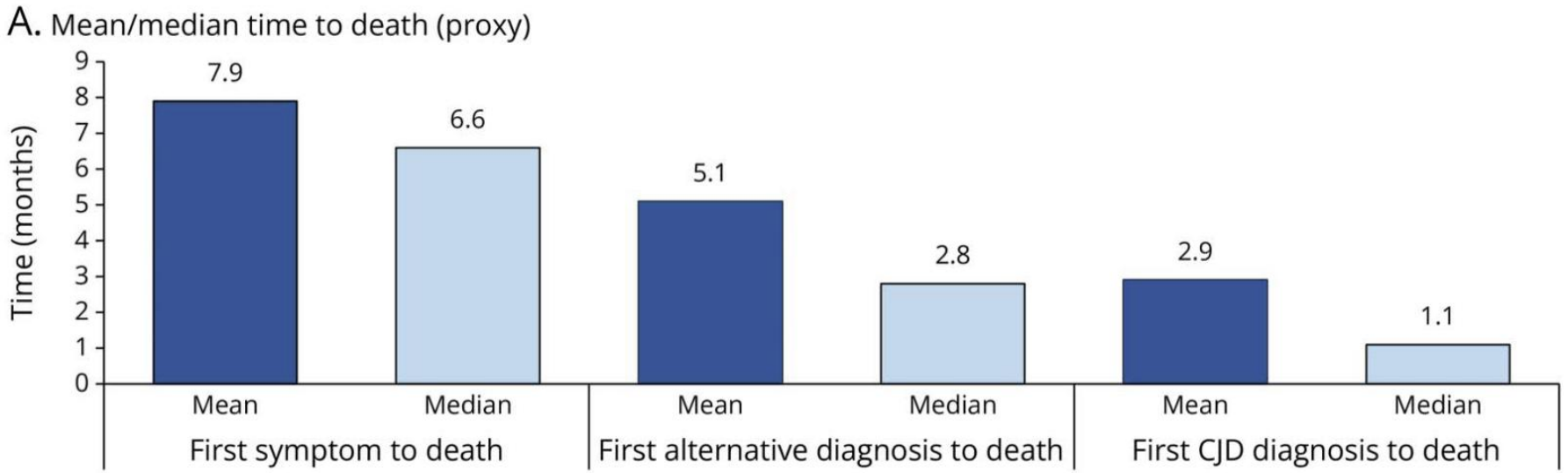
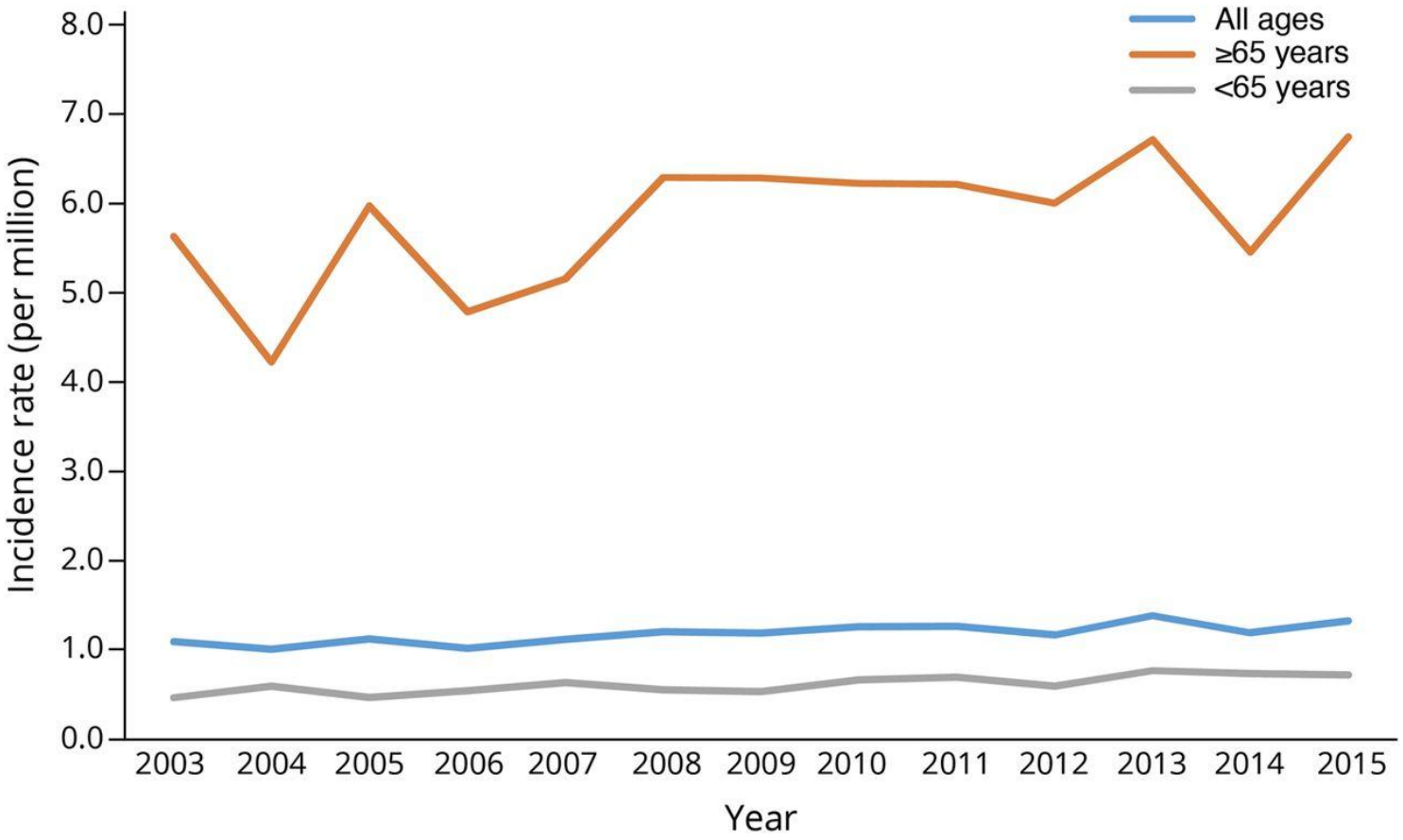


Figure 1 Time From First Symptom, Alternative Diagnosis, and CJD Diagnosis to Death (Proxy) Among Patients With CJD



CJD = Creutzfeldt-Jakob disease; Dx = diagnosis.

Epidemiology



1/6,239 US deaths per year

Maddox RA, *Neurology* 2019

As Rare as a Brown's Touchdown

- Capacity: 70,000 people
- About 12 people will get prion disease at some point

Clusters

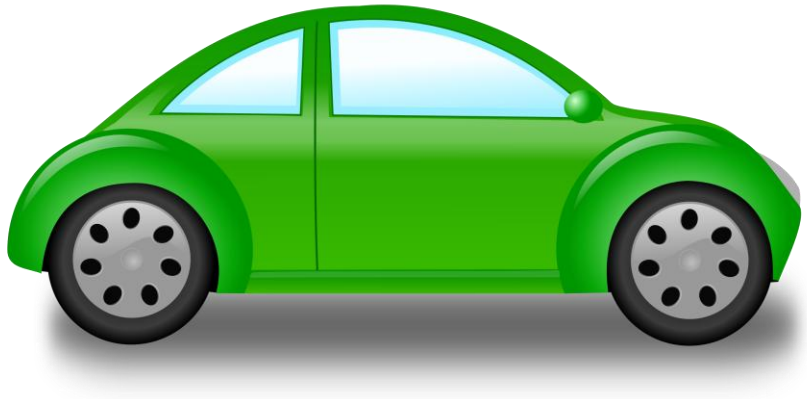
- Primarily investigated by CDC and local health depts with NPDPSC assistance
- Steps taken to investigate the cluster:
  - Verify that they are prion disease
  - Verify the type of prion disease
  - Verify the the numbers being investigated higher than what is expected
  - Verify the likelihood of a common exposure
  - Verify that incubation periods make sense

Prion Clusters in My Life

- I've seen 5 cases of prion disease within my community (~30,000 people) in the last 10 years
- My research nurse was in the son's wedding of one of them
- My daughter's dentist brother-in-law had CJD
  - My social worker went to him for physical therapy
- A person at a friend's funeral had a grandmother that just died of CJD
- A daughter of one of my Alzheimer's patients got CJD
  - A prion center staff member's husband was friends with her daughter
- A former departmental chairman's mother died of CJD
- A beloved teacher in my daughter's school community died of CJD

How is prion disease diagnosed and why does it take so long?

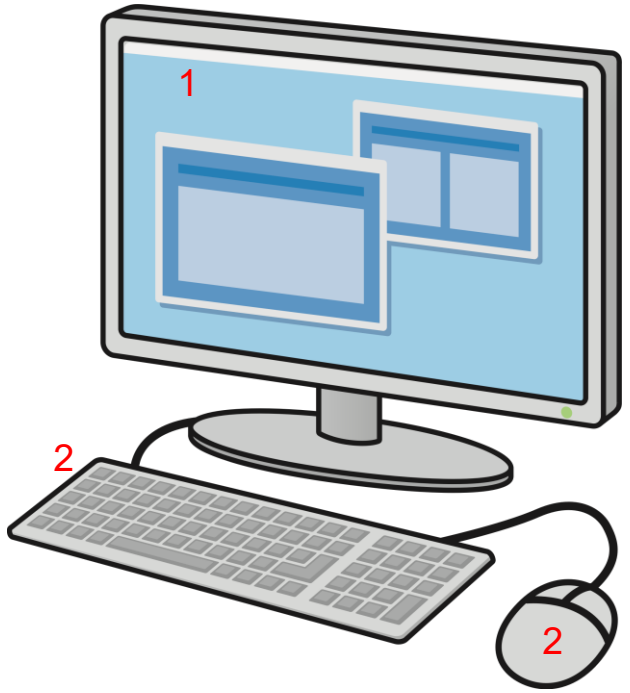
The diagnostic process is not unique to medicine



Medical diagnoses typically start with recognizing syndromes

A syndrome is a collection of signs and symptoms that help point to the underlying cause of a problem

Recognizing syndromes helps the clinician know what to do next (e.g., what tests to order)

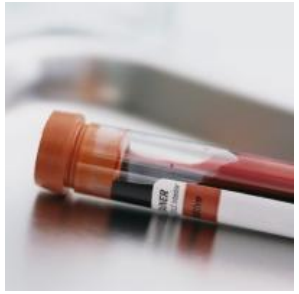


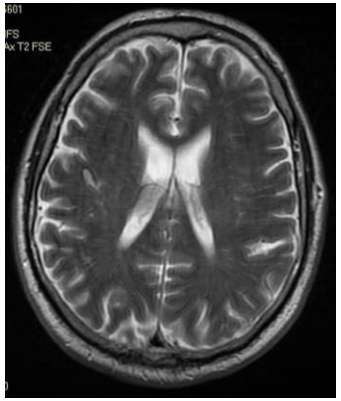
3-hard drive

4-software

Prion Disease (CJD), Initial Evaluation

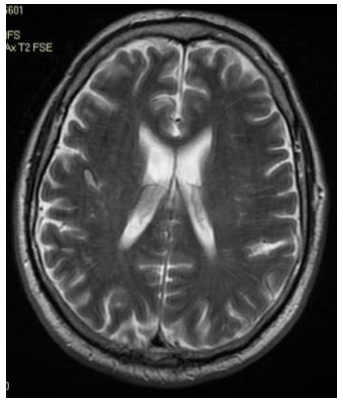
List of Possible Diagnoses
(Differential Diagnoses)
Alzheimer's disease
Vitamin Deficiency
Thyroid Problem
Depression

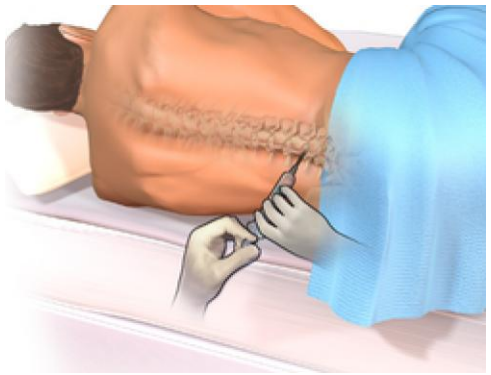




Prion Disease (CJD), Second Visit

List of Possible Causes
Blood vessel disease
Infections
Inflammation



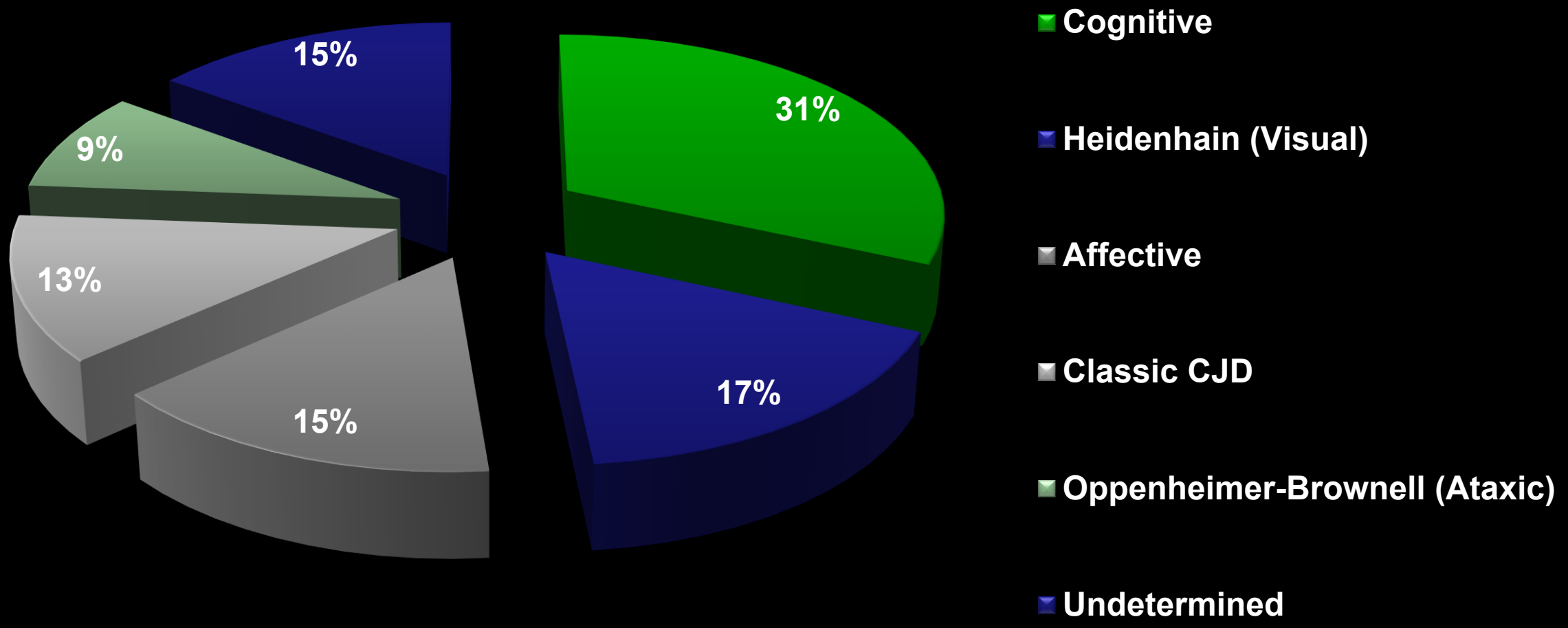


- Rule-out potential causes
- Look for results that suggest a cause

Typical Symptoms of Human Prion Disease

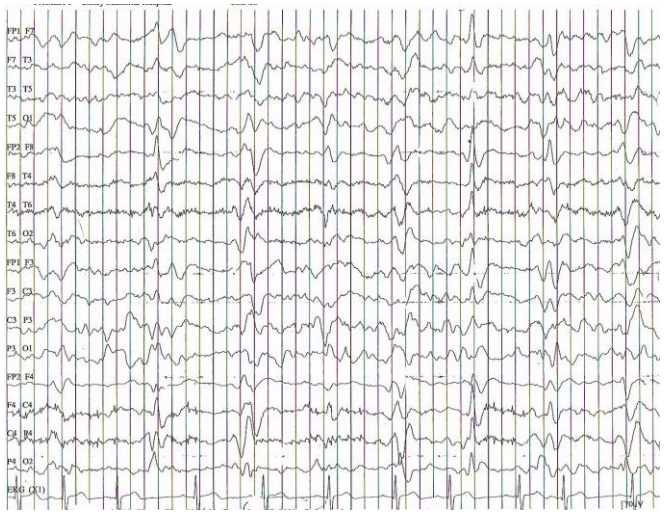
- Cognitive impairment
- Gait impairment
- Abnormal movements
- Visual disturbances
- Muscle weakness
- Psychiatric symptoms

Sporadic CJD Initial Clinical Symptoms

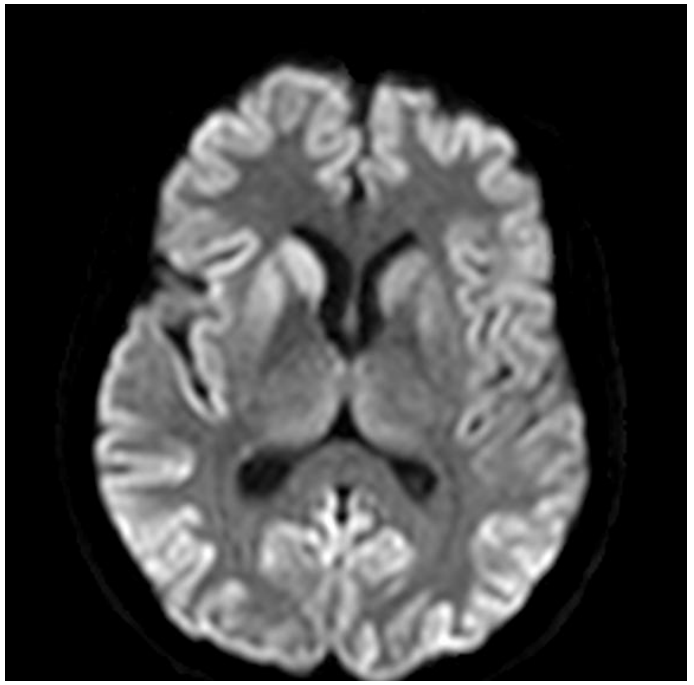


Adapted from Appleby BS *et al.*, *Arch Neurol* 2009

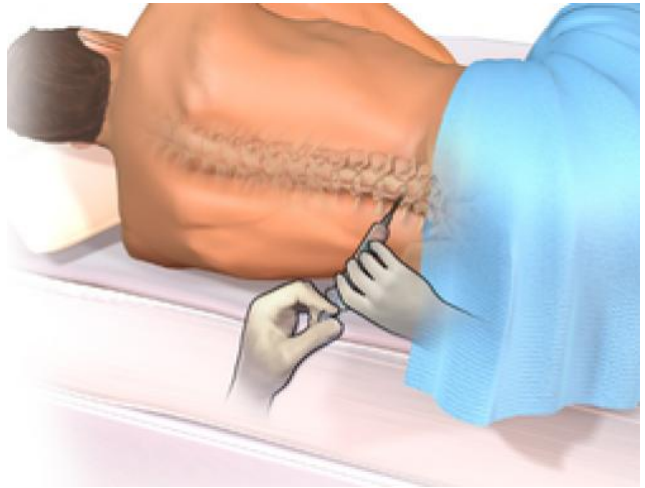
Prion Disease Tests



- More helpful for ruling out other causes
- Occasionally can be suggestive of CJD



- Present in most cases
- Narrows down possibilities
- May be the first thing that suggests CJD



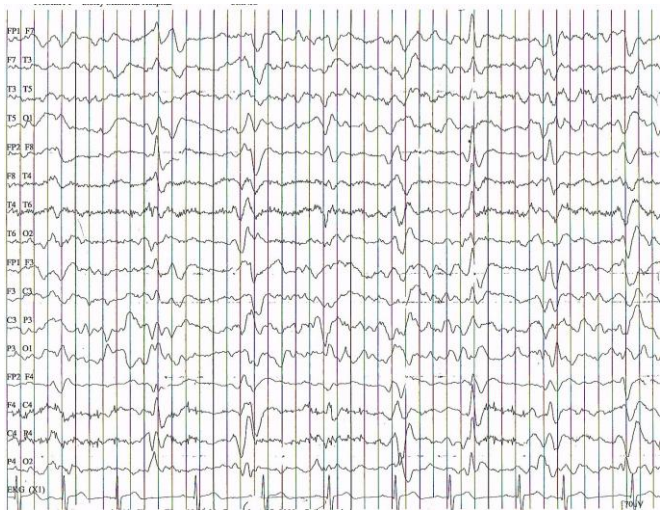
- Helps rule-out other causes
- Some markers that suggest CJD
- One marker that is almost only seen in CJD

Diagnostic Test Characteristics

Sensitivity: How well does the test find the disease that we are looking for? (Broad)

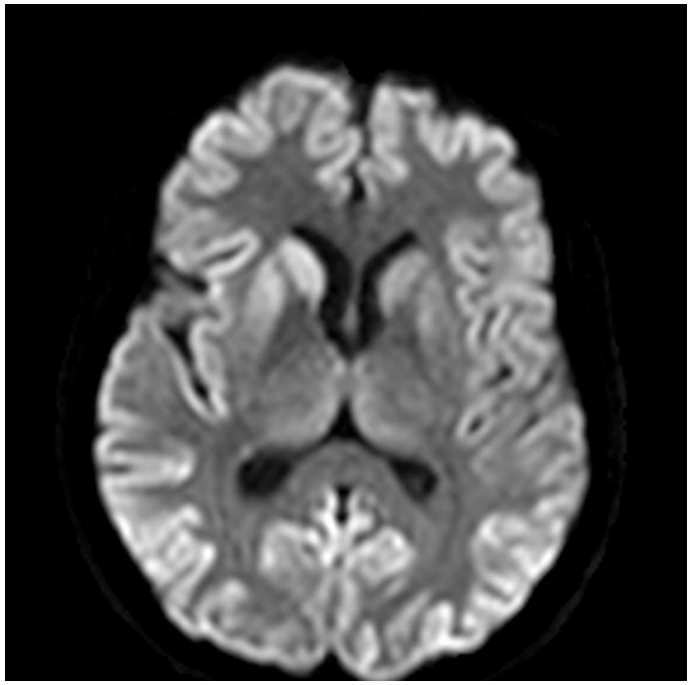
Specificity: How well does the test ONLY find the disease that we are looking for? (Narrow)

CJD Diagnostic Test Characteristics



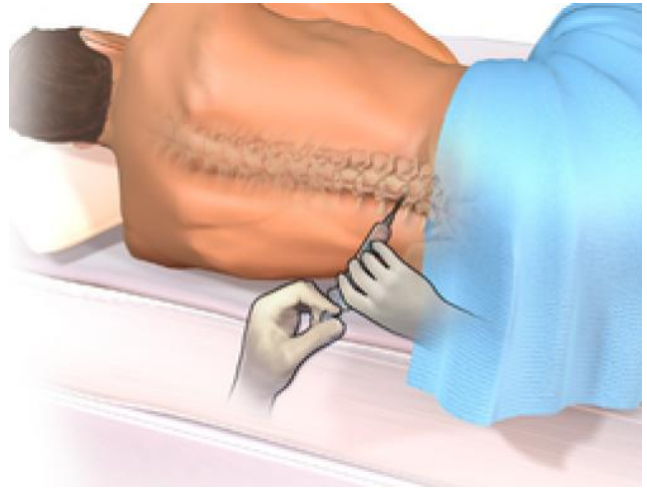
Not very sensitive
Fairly specific

Requires some local expertise



Very sensitive
Pretty specific

Requires local expertise
or expert consultation



Very sensitive
Some tests are somewhat specific
One test is extremely specific

Doctor must know to order
Done in a specialty lab

Cerebrospinal Fluid Tests

Markers of brain cell injury:

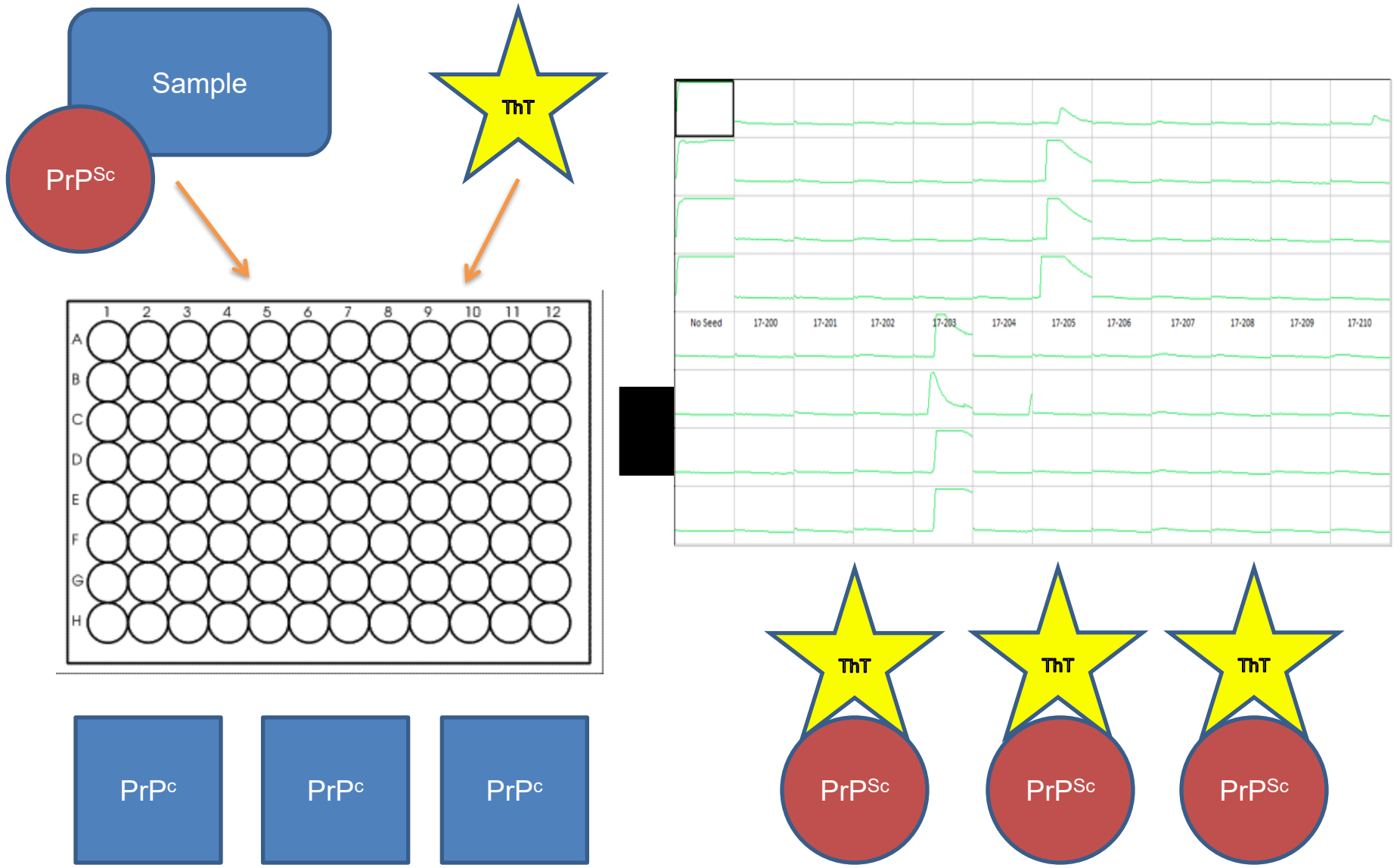
- 14-3-3
- Total tau

Disease specific test:

- RT-QuIC: detects abnormal prion protein (highly specific)

Hamlin C, Neurology 2012

Real-Time Quaking-Induced Conversion (RT-QuIC)



Main Limitations for Diagnosing Prion Disease

- Variability within prion diseases
- Some knowledge of prion disease is required
- CJD needs to be on the list of possible causes to get the tests
- Confidence in giving diagnosis

What about Artificial Intelligence (v2)?

This 79-year-old white woman initially started having changes of her speech and would frequently drop things starting 4 months ago. What is the possible list of diagnoses in order of likely diagnosis?

1. **Amyotrophic Lateral Sclerosis (ALS)**
2. **Stroke (subacute or chronic ischemic, including small vessel disease)**
3. **Primary Progressive Aphasia (nonfluent/agrammatic variant)**
4. **Normal Pressure Hydrocephalus (NPH)**
5. **Corticobasal Syndrome (CBS)**
6. **Alzheimer's Disease (logopenic or atypical presentation)**
7. **Parkinson's Disease or Parkinson-plus syndromes (e.g., PSP, MSA)**
8. **Myasthenia Gravis (late-onset, bulbar-predominant)**
9. **Brain Tumor or Mass Lesion**
10. **Functional Neurological Disorder (FND)**

Most Likely Diagnosis

1. Sporadic Creutzfeldt-Jakob Disease (sCJD)

Recommended work-up:

1. **Neurological Exam**
   - Assess for UMN/LMN signs, speech type, apraxia, gait, cognitive function
2. **MRI Brain (with and without contrast)**
   - Rule out stroke, tumor, neurodegeneration (look for DWI cortical changes)
3. **EMG/NCS**
   - If ALS or other neuromuscular disorder suspected
4. **Neuropsychological Testing**
   - Evaluate for PPA, CBS, Alzheimer's, or other cognitive syndromes
5. **Speech-Language Pathology Evaluation**
   - Characterize speech changes (aphasia vs apraxia vs dysarthria)
6. **Lumbar Puncture (CSF Studies)**
   - 14-3-3 protein, tau, RT-QuIC (for prion), cell count, glucose, protein
7. **EEG**
   - Evaluate for seizures or periodic sharp wave complexes (sCJD)
8. **Laboratory Tests**
   - B12, folate, TSH, HIV, RPR, CMP, CBC, inflammatory markers
9. **Optional Imaging/Tests** (case-dependent)
   - DaTscan (Parkinsonism), PET scan (atypical dementia), SPECT, autoimmune panel

ChatGPT4o

Comparison

2024

Problems:
- Initial suggested work-up was not economically practical
- No mention of RT-QuIC
- Diagnosed at the same time point as her human doctors

Potential:
- Potential for AI to properly diagnose MRI and result in earlier diagnosis

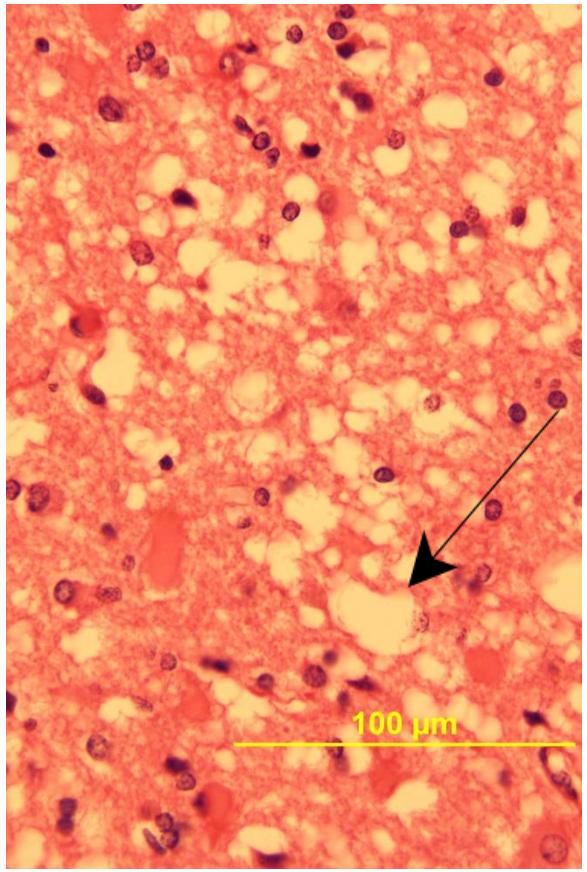
2025

Problems:
- Some initial work-up was unnecessary and left some testing up to the clinician's discretion.
- Diagnosed at the same time point as her human doctors
- Assumed a sporadic etiology

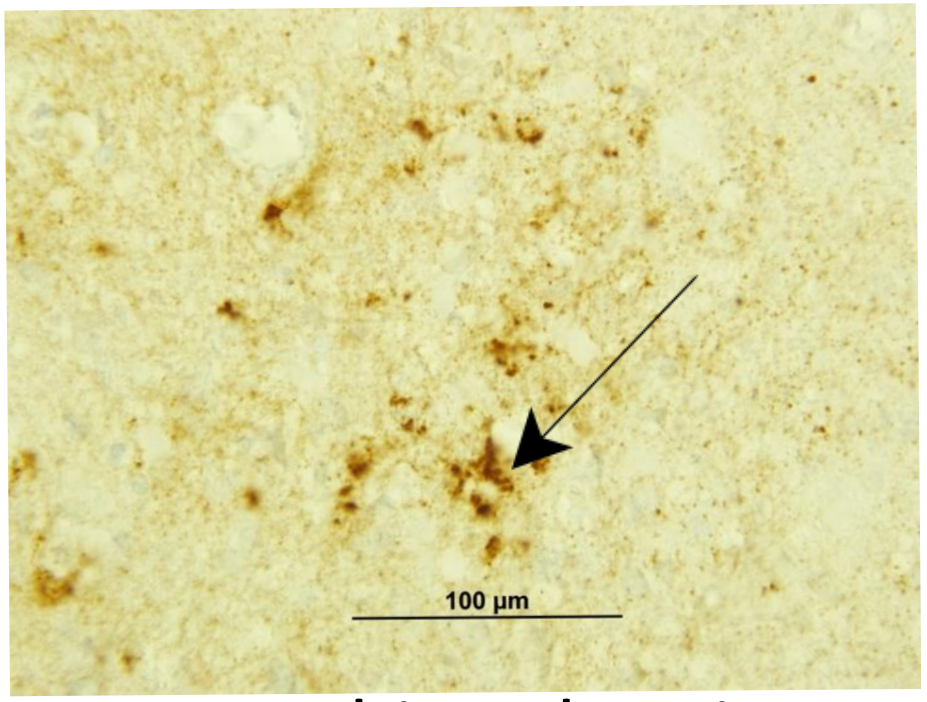
Potential:
- Potential for AI to properly diagnose MRI and result in earlier diagnosis
- More practical as a clinician's assistant/brainstorm tool
- Did a good job at recommending management approaches

Why is there so much clinical variability in prion disease?

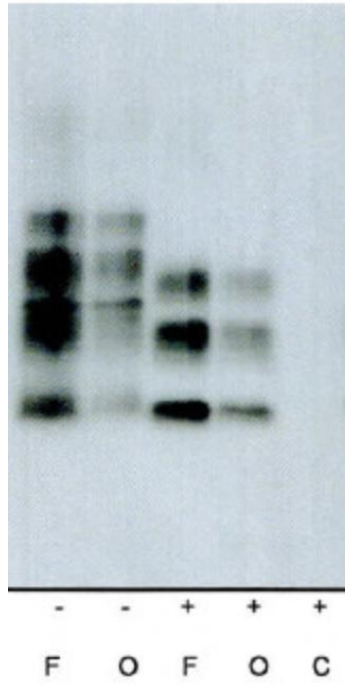
Information Obtained at Autopsy



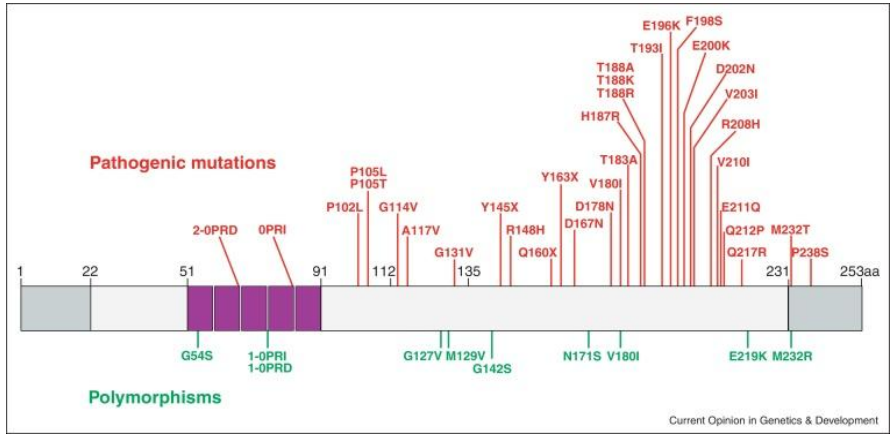
H & E Staining



Immunohistochemistry

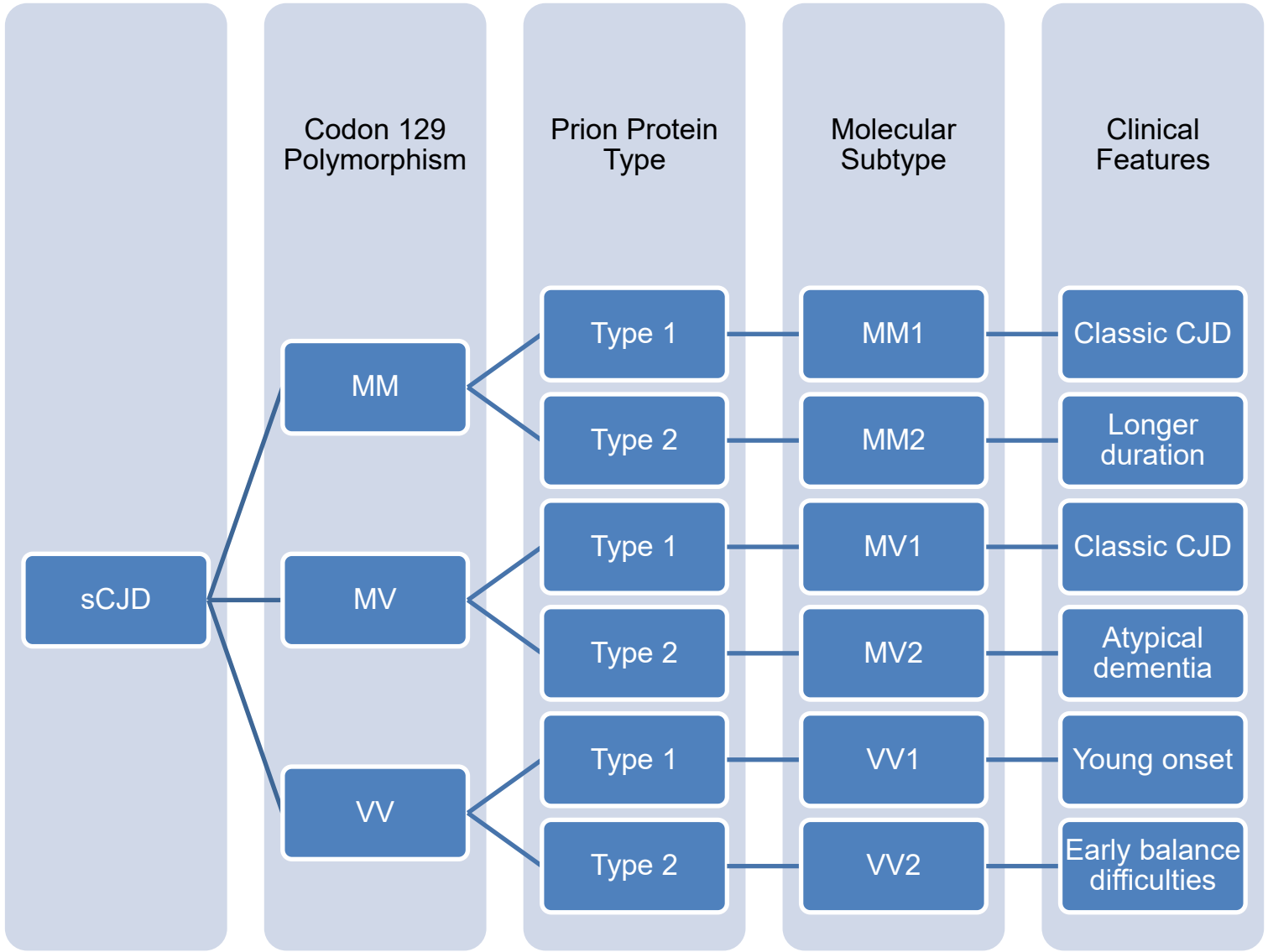


Western Blot



Prion protein gene genetic testing

sCJD Molecular Subtypes

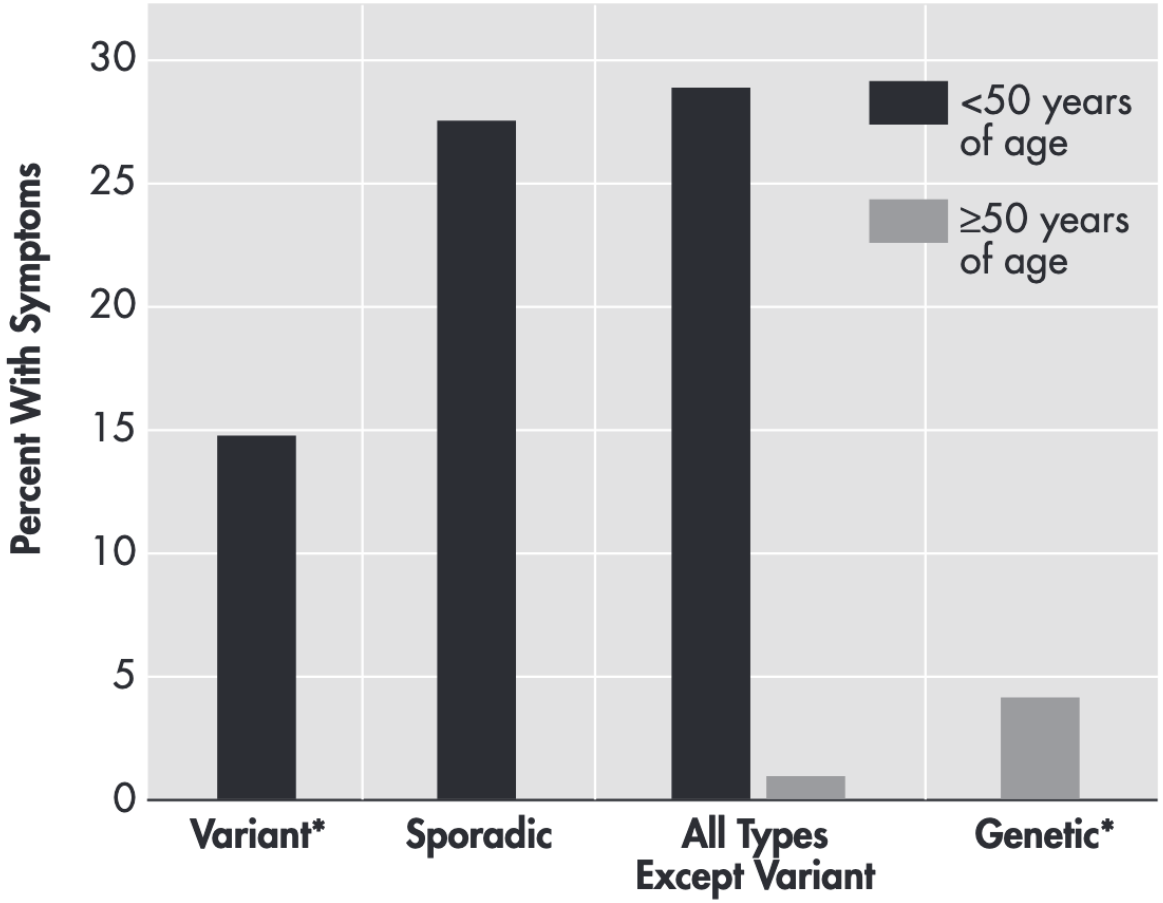


Variability in other prion diseases

- Genetic prion diseases often differ by genetic mutation (>50)
- Variant CJD often differs from other prion diseases
- ? New prion diseases

Age

FIGURE 3. Affective illness Across CJD Type and Age



* There were 2 variant cases >50 years and 16 genetic cases <50 years.

Appleby BS, J Neuropsychiatry Clin Neurosci 2007

Thank You!