Prion Disease Basics – Clinical

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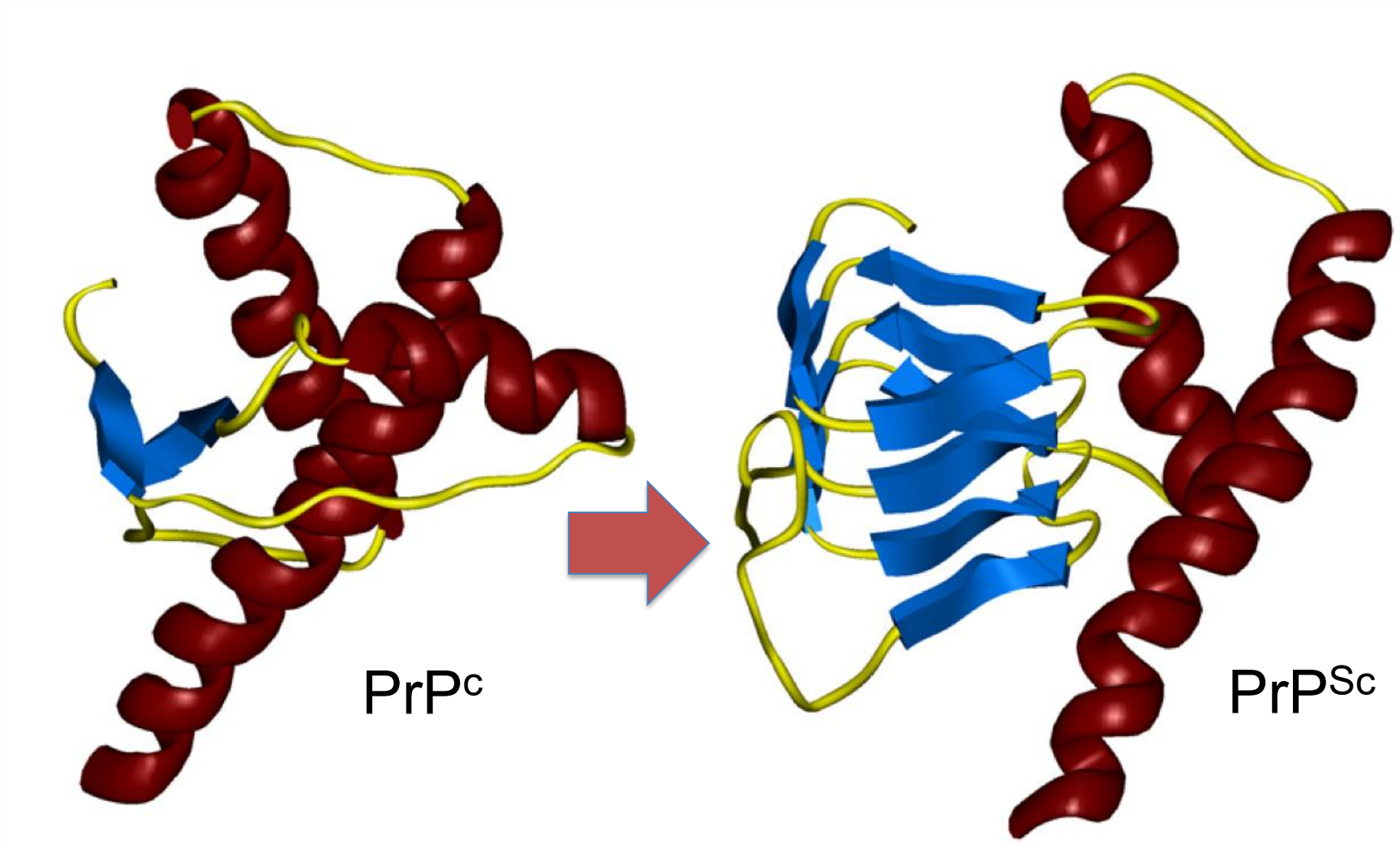
Overview

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

Prion Protein



What is a Prion?

Prions are misfolded proteins that can change normal proteins into misfolded proteins—spreading the problem.

1 The good kids (PrP^{c})

Normal proteins (PrP^{c}) are good kids—healthy, happy, and doing their job.

2 The bad kid (PrP^{sc})

A misfolded prion (PrP^{sc}) is like a bad kid in the schoolyard.

3 Recruiting others ("Join our gang!")

The bad kid convinces a good kid to join in—and when the good kid agrees, he changes and becomes bad too.

4 The gang grows (Spreading the problem)

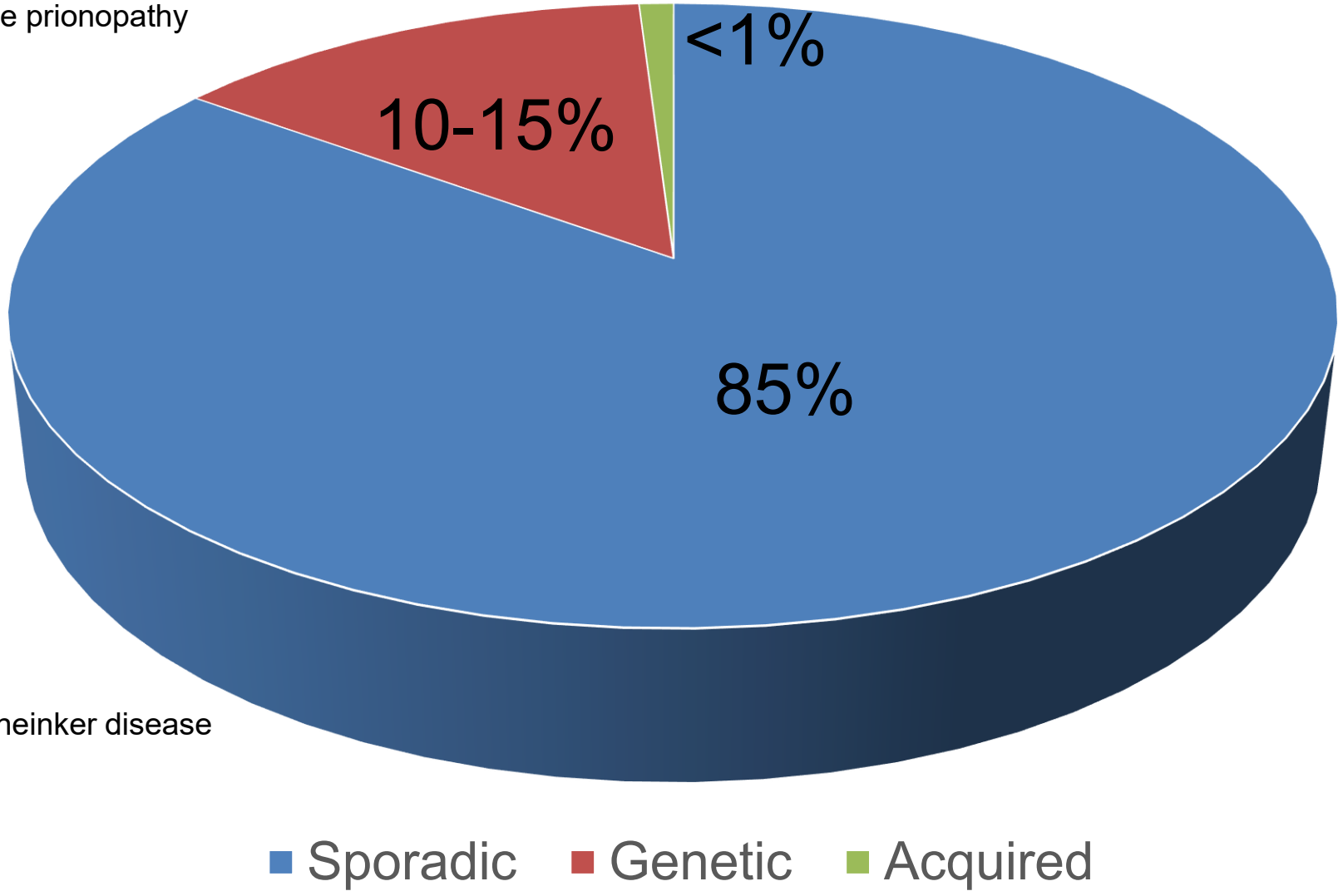
Over time, more good kids join the gang. The bad influence spreads, and the problem gets worse.

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

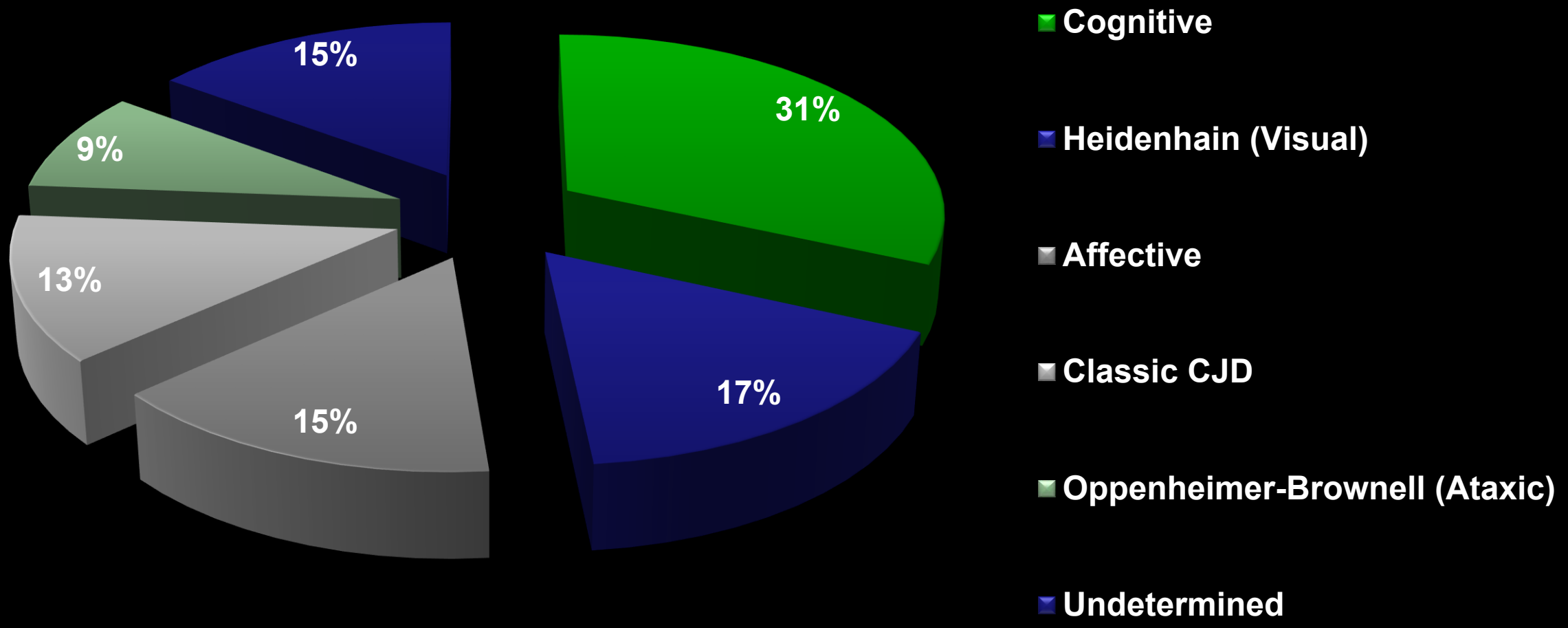
<u>Genetic Prion Diseases</u>
Genetic CJD
Gerstmann-Straussler Scheinker disease
Fatal familial insomnia



Typical Symptoms of Human Prion Disease

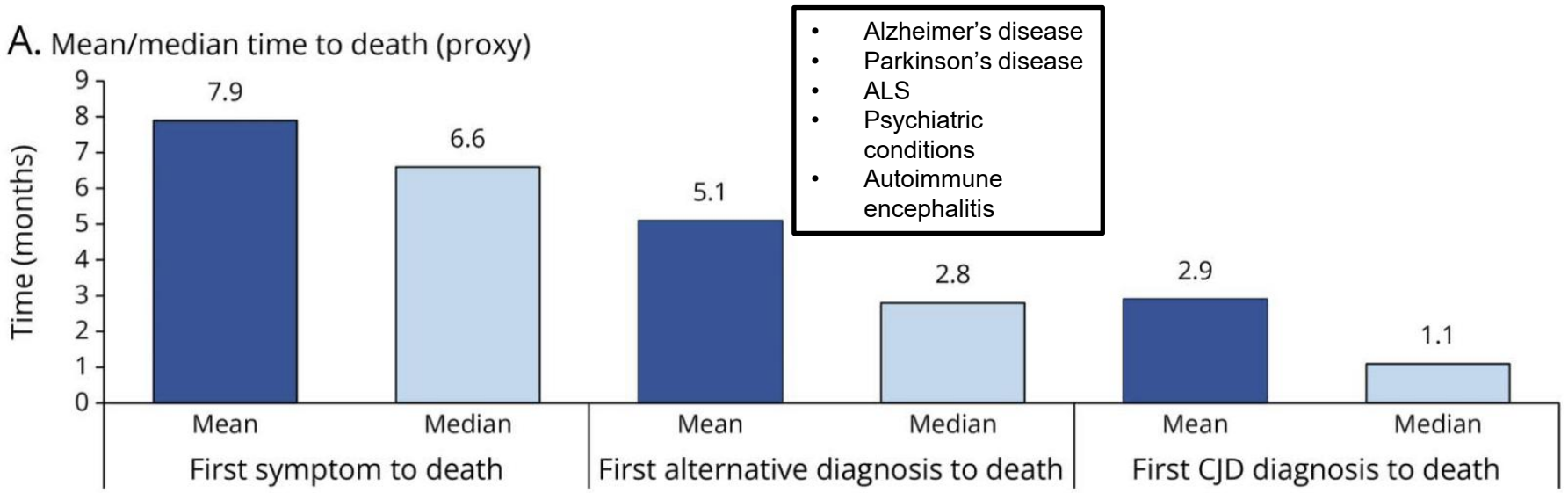
- Cognitive impairment
- Gait impairment
- Abnormal movements
- Visual disturbances
- Muscle weakness
- Psychiatric symptoms

Sporadic CJD Initial Clinical Symptoms



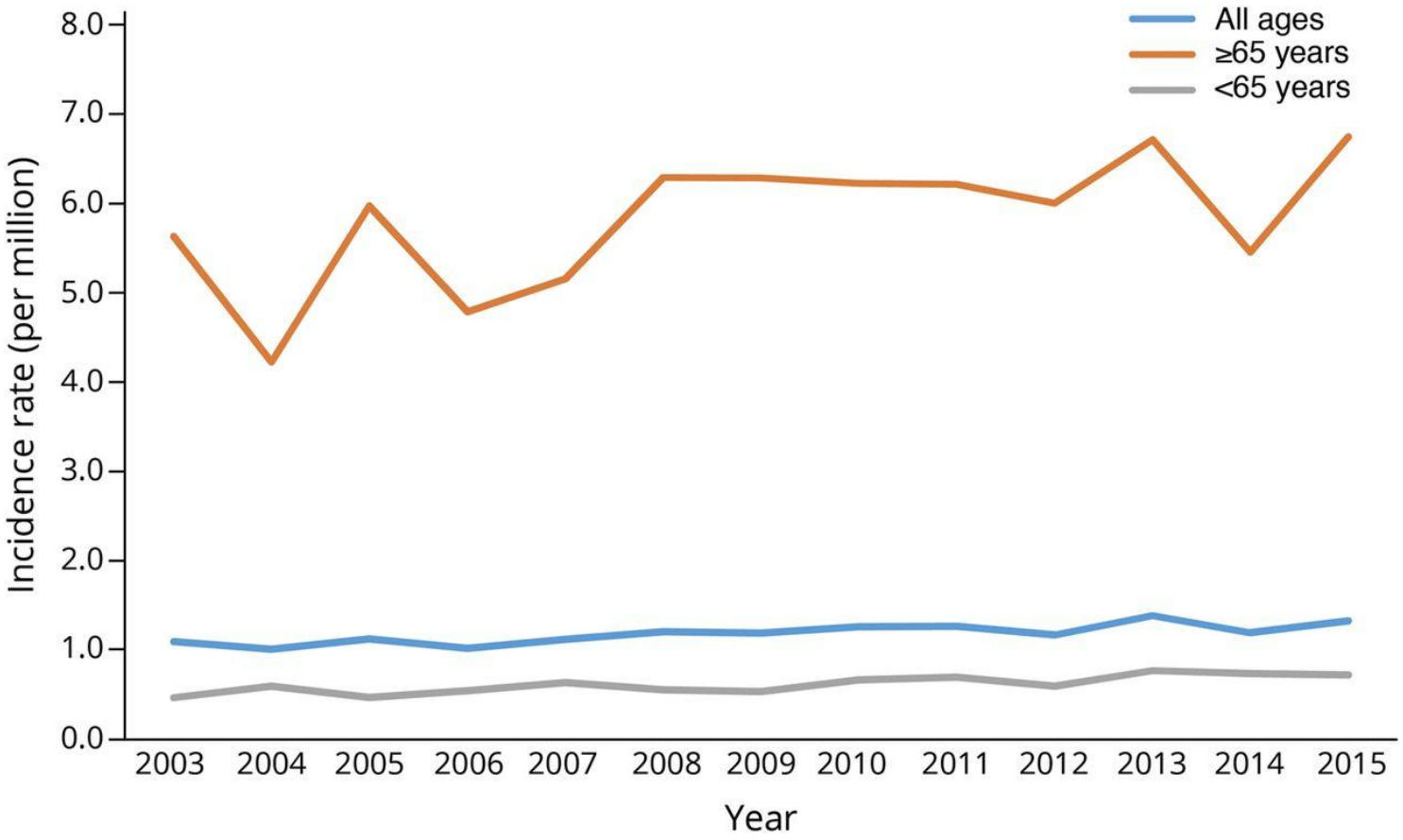
Adapted from Appleby BS *et al.*, *Arch Neurol* 2009

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

ChatGPT Commentary: "Your Browns analogy is funny, but it may age poorly depending on the season."

Clusters

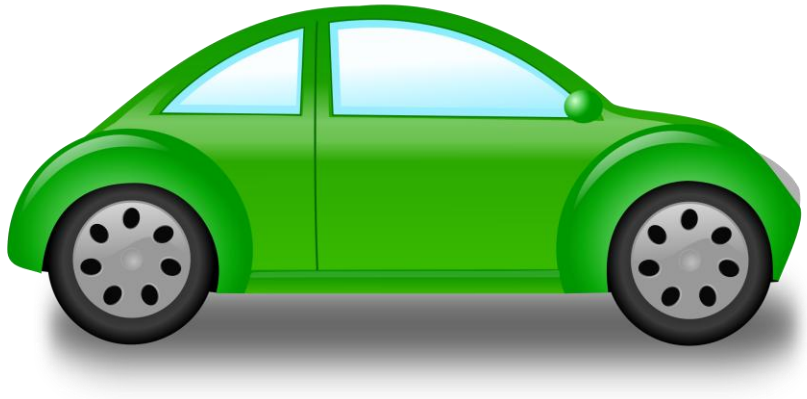
- Primarily investigated by CDC and local health depts with NPDPSC assistance
- Steps taken to investigate the cluster:
  - Verify that they are prion disease
  - Verify the type of prion disease
  - Verify the the numbers being investigated higher than what is expected
  - Verify the likelihood of a 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
- My daughter's friend's grandfather died of CJD

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

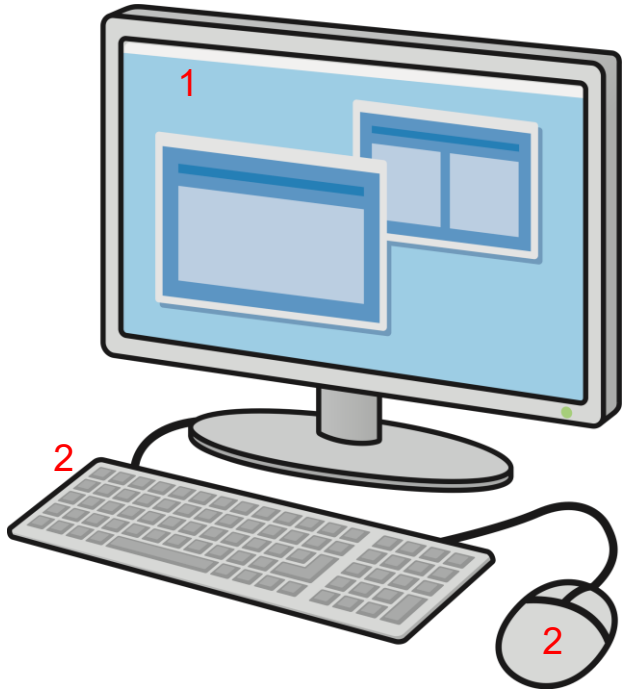
The diagnostic process is not unique to medicine



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)

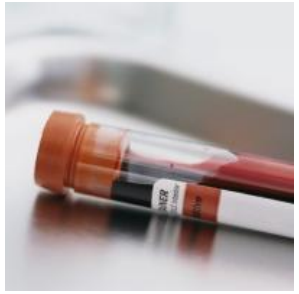


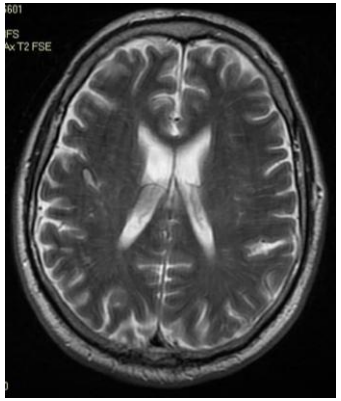
3-hard drive

4-software

Prion Disease (CJD), Initial Evaluation

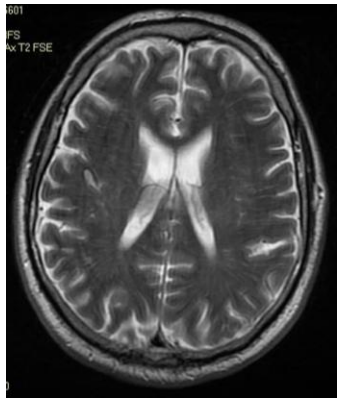
List of Possible Diagnoses
(Differential Diagnoses)
Alzheimer's disease
Vitamin Deficiency
Thyroid Problem
Depression

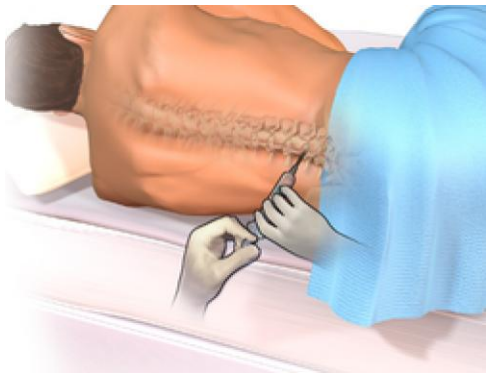




Prion Disease (CJD), Second Visit

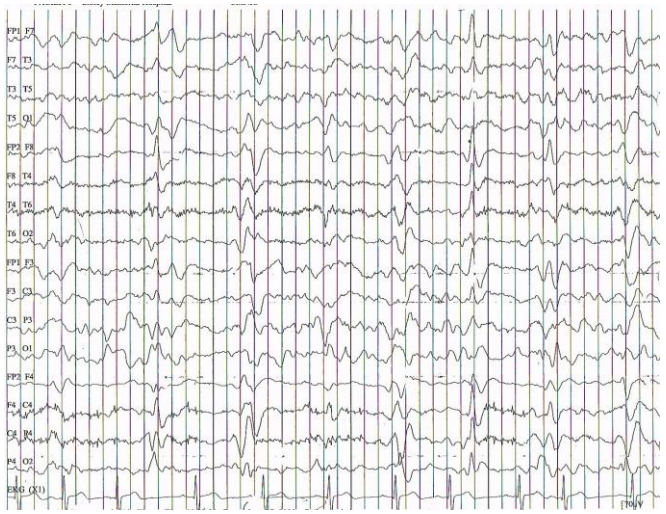
List of Possible Causes
Blood vessel disease
Infections
Inflammation



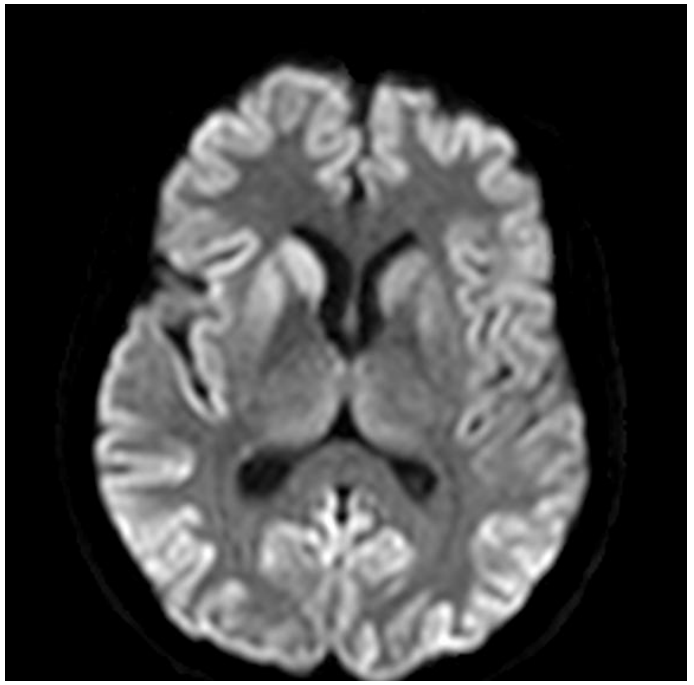


- Rule-out potential causes
- Look for results that suggest a cause

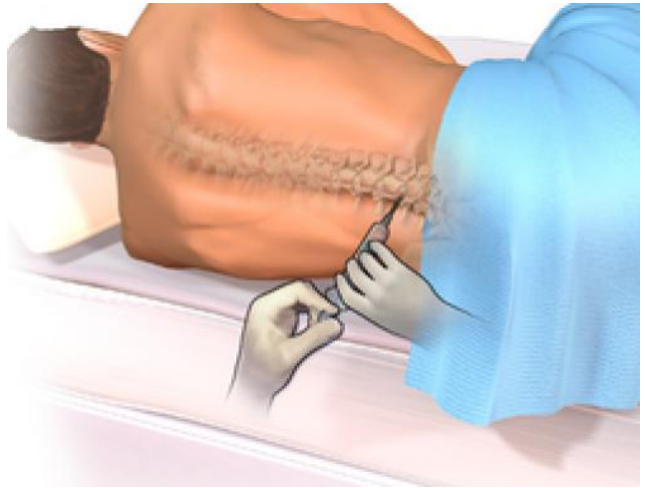
Prion Disease Tests



- 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



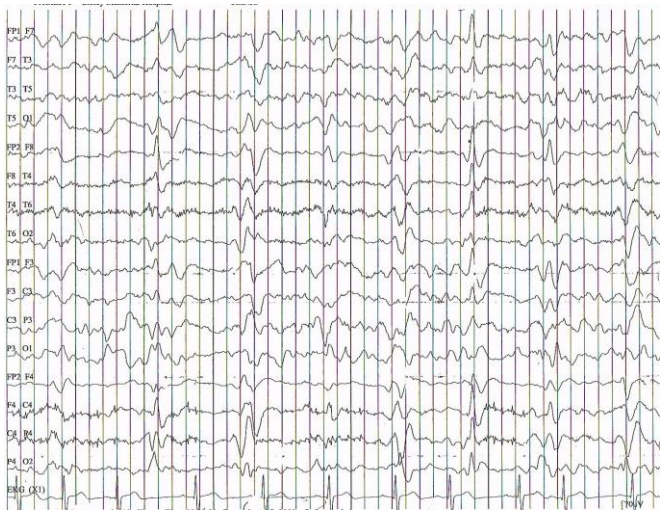
- Helps rule-out other causes
- Some markers that suggest CJD
- One marker that is almost only seen in CJD

Diagnostic Test Characteristics

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

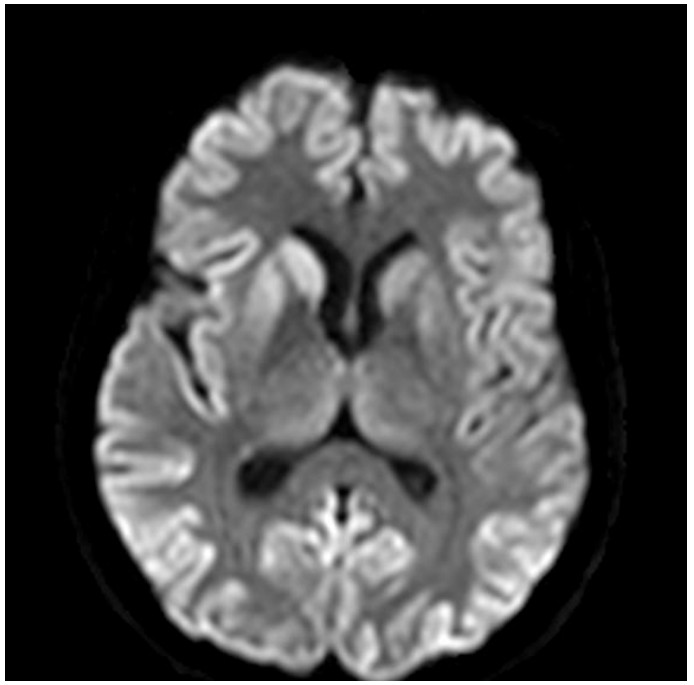
Specificity: How well does the test ONLY find the disease that we are looking for? (Narrow)

CJD Diagnostic Test Characteristics



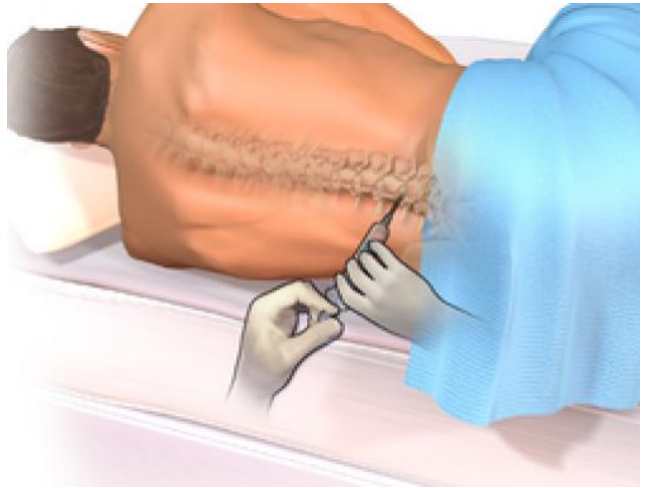
Not very sensitive
Fairly specific

Requires some local expertise



Very sensitive
Pretty specific

May require local expertise or expert consultation



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

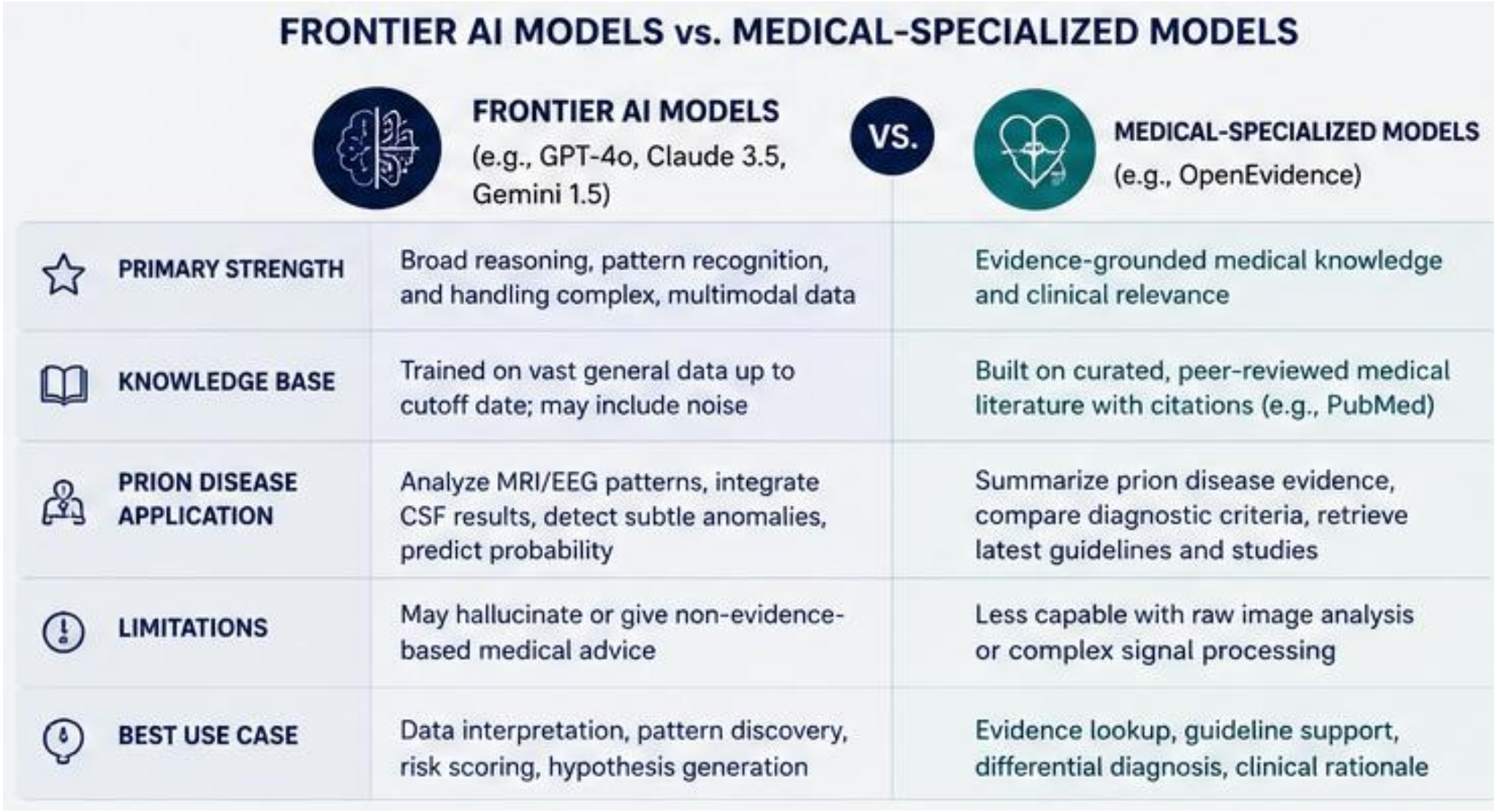
Doctor must know to order
Done in a specialty lab

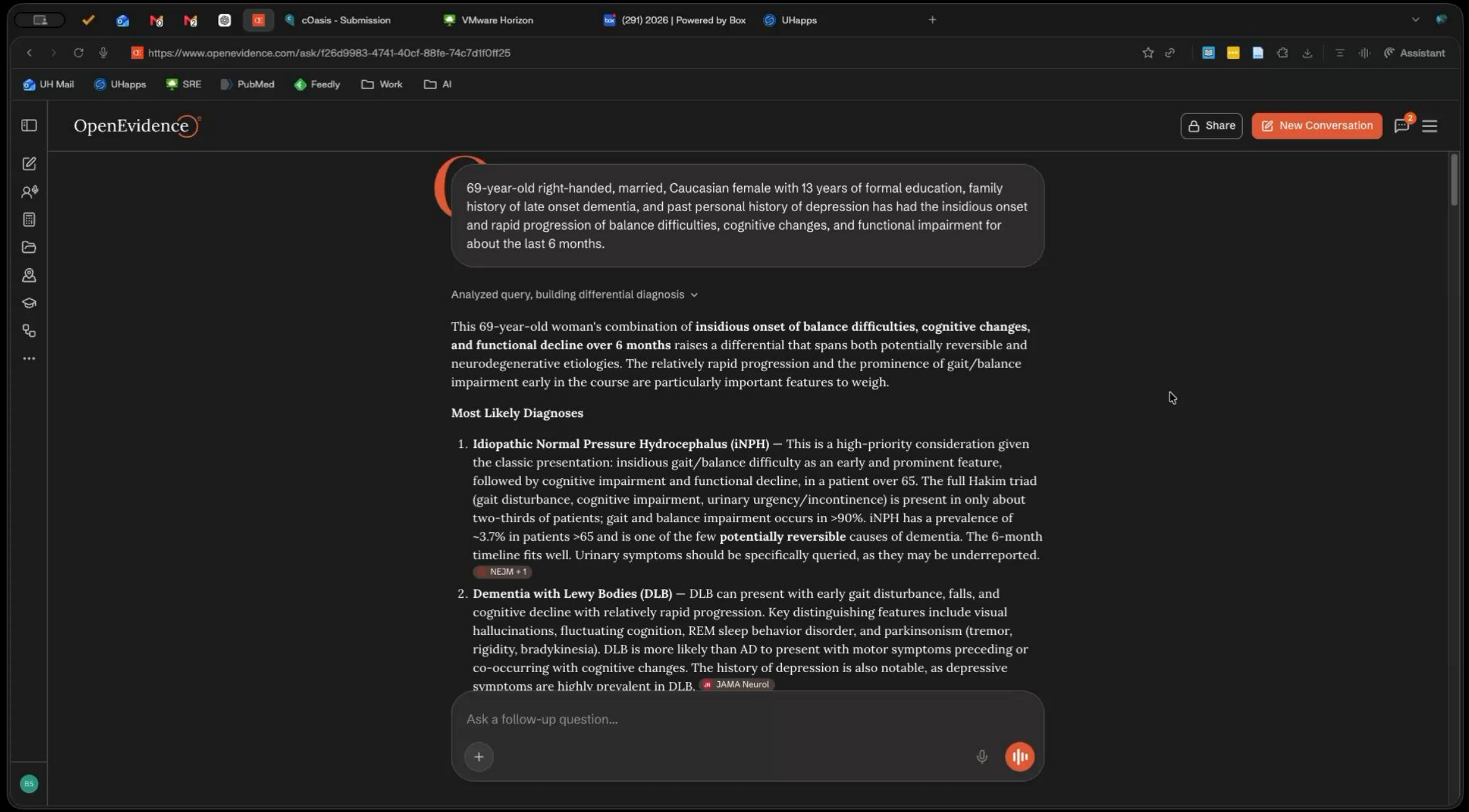
Main Limitations for Diagnosing Prion Disease

- 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

Can AI help diagnose prion disease faster (v3)?

Absolutely

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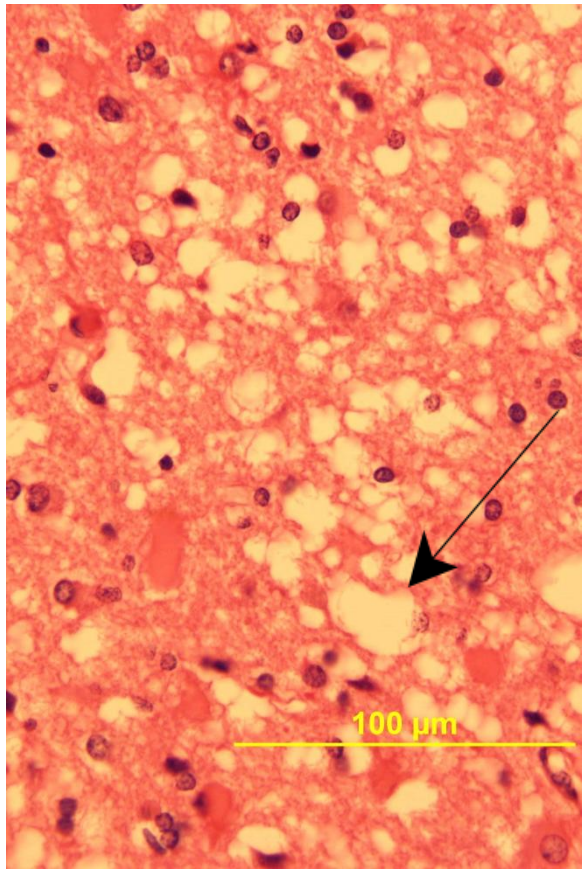
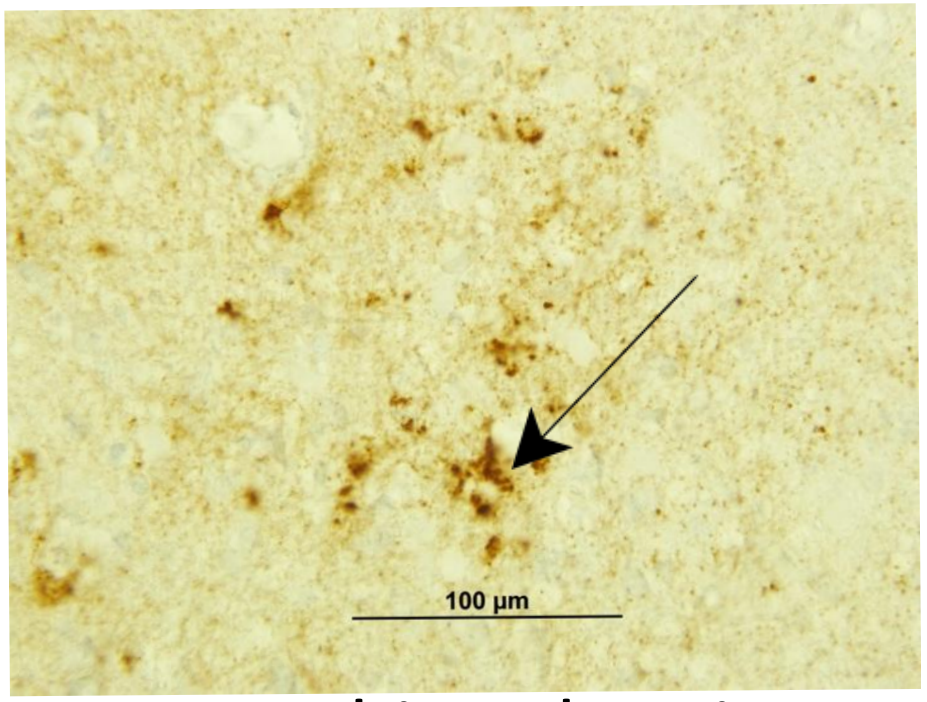
New Conversation
69-year-old right-handed, married, Caucasian female with 13 years of formal education, family history of late onset dementia, and past personal history of depression has had the insidious onset and rapid progression of balance difficulties, cognitive changes, and functional impairment for about the last 6 months.
Analyzed query, building differential diagnosis
This 69-year-old woman's combination of **insidious onset of balance difficulties, cognitive changes, and functional decline over 6 months** raises a differential that spans both potentially reversible and neurodegenerative etiologies. The relatively rapid progression and the prominence of gait/balance impairment early in the course are particularly important features to weigh.
Most Likely Diagnoses
1. **Idiopathic Normal Pressure Hydrocephalus (iNPH)** — This is a high-priority consideration given the classic presentation: insidious gait/balance difficulty as an early and prominent feature, followed by cognitive impairment and functional decline, in a patient over 65. The full Hakim triad (gait disturbance, cognitive impairment, urinary urgency/incontinence) is present in only about two-thirds of patients; gait and balance impairment occurs in >90%. iNPH has a prevalence of ~3.7% in patients >65 and is one of the few **potentially reversible** causes of dementia. The 6-month timeline fits well. Urinary symptoms should be specifically queried, as they may be underreported. NEJM + 1
2. **Dementia with Lewy Bodies (DLB)** — DLB can present with early gait disturbance, falls, and cognitive decline with relatively rapid progression. Key distinguishing features include visual hallucinations, fluctuating cognition, REM sleep behavior disorder, and parkinsonism (tremor, rigidity, bradykinesia). DLB is more likely than AD to present with motor symptoms preceding or co-occurring with cognitive changes. The history of depression is also notable, as depressive symptoms are highly prevalent in DLB. JAMA Neurol
Ask a follow-up question...

Why is there so much clinical variability in prion disease?

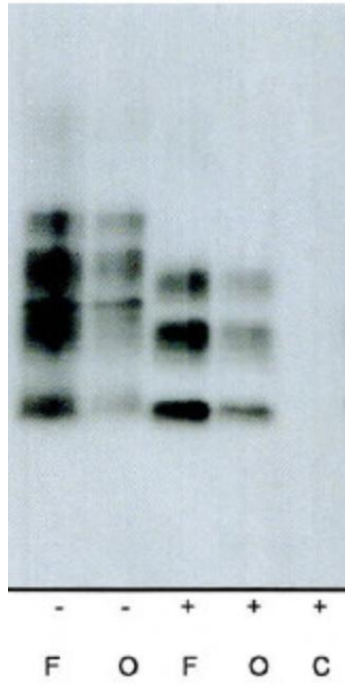
Information Obtained at Autopsy



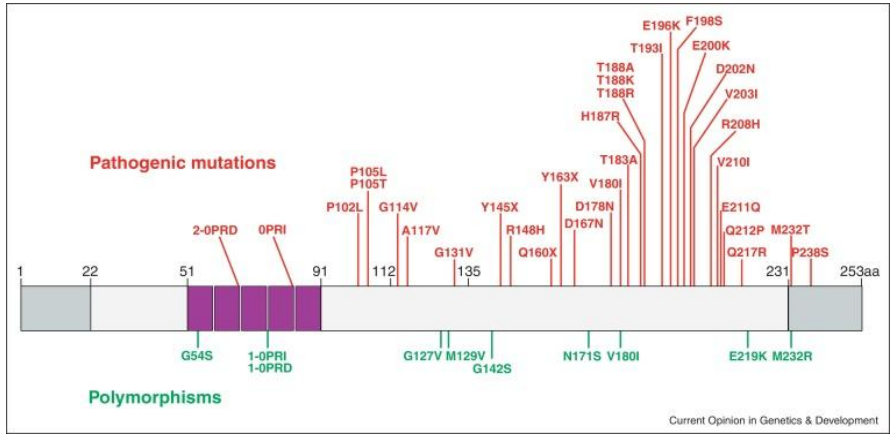
H & E Staining



Immunohistochemistry

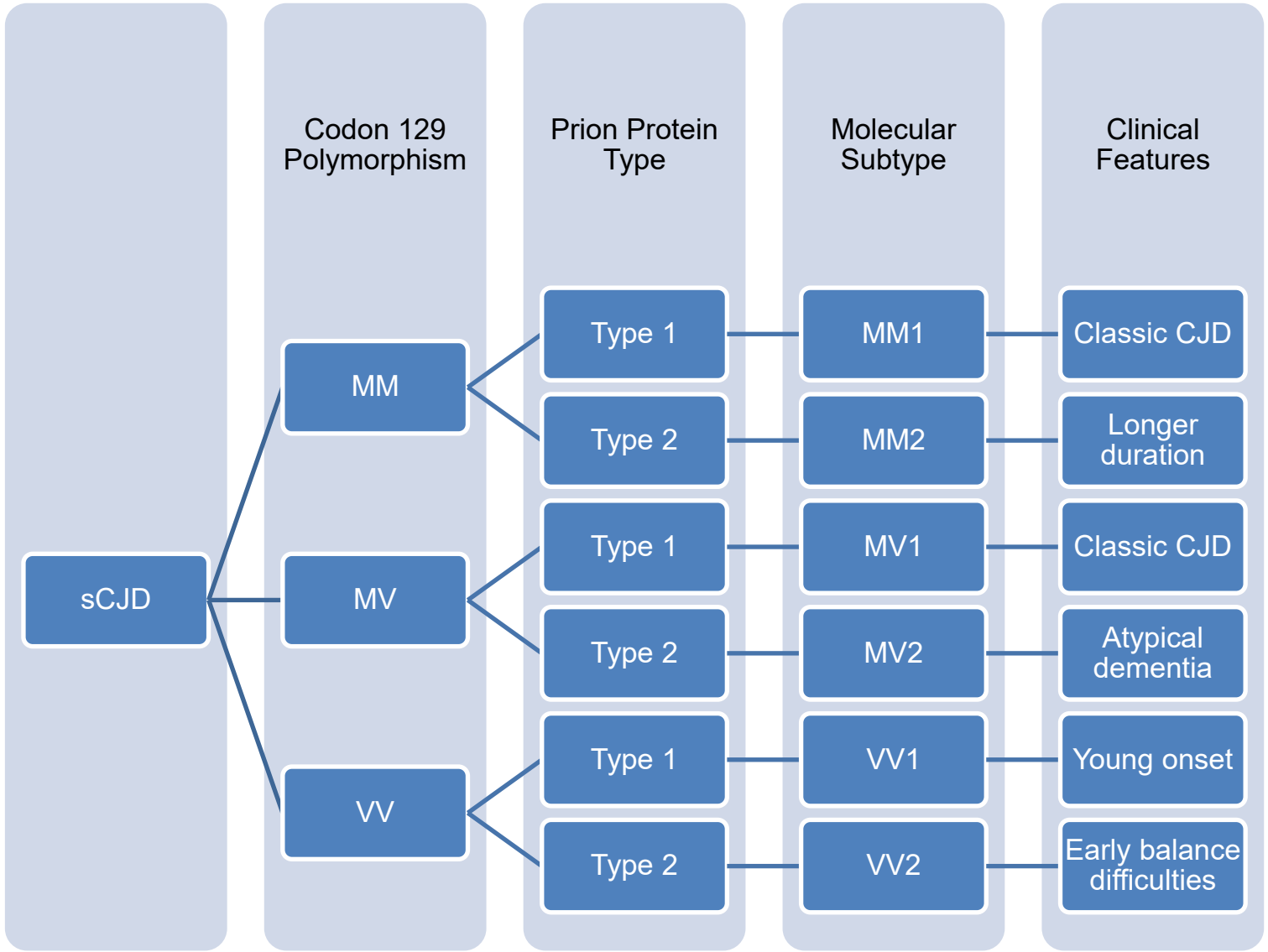


Western Blot



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

Clinical Therapeutics

- Why there is reason to be Moore hopeful about the field of prion disease (7/11, 9a)
- Research grant recipients (7/11)
  - Nina Oberbeck (11:10a)
- Drug Development Panel (7/12, 11:20a)

Thank You!