

Prion Disease Basics - Clinical

Brian Appleby



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Overview

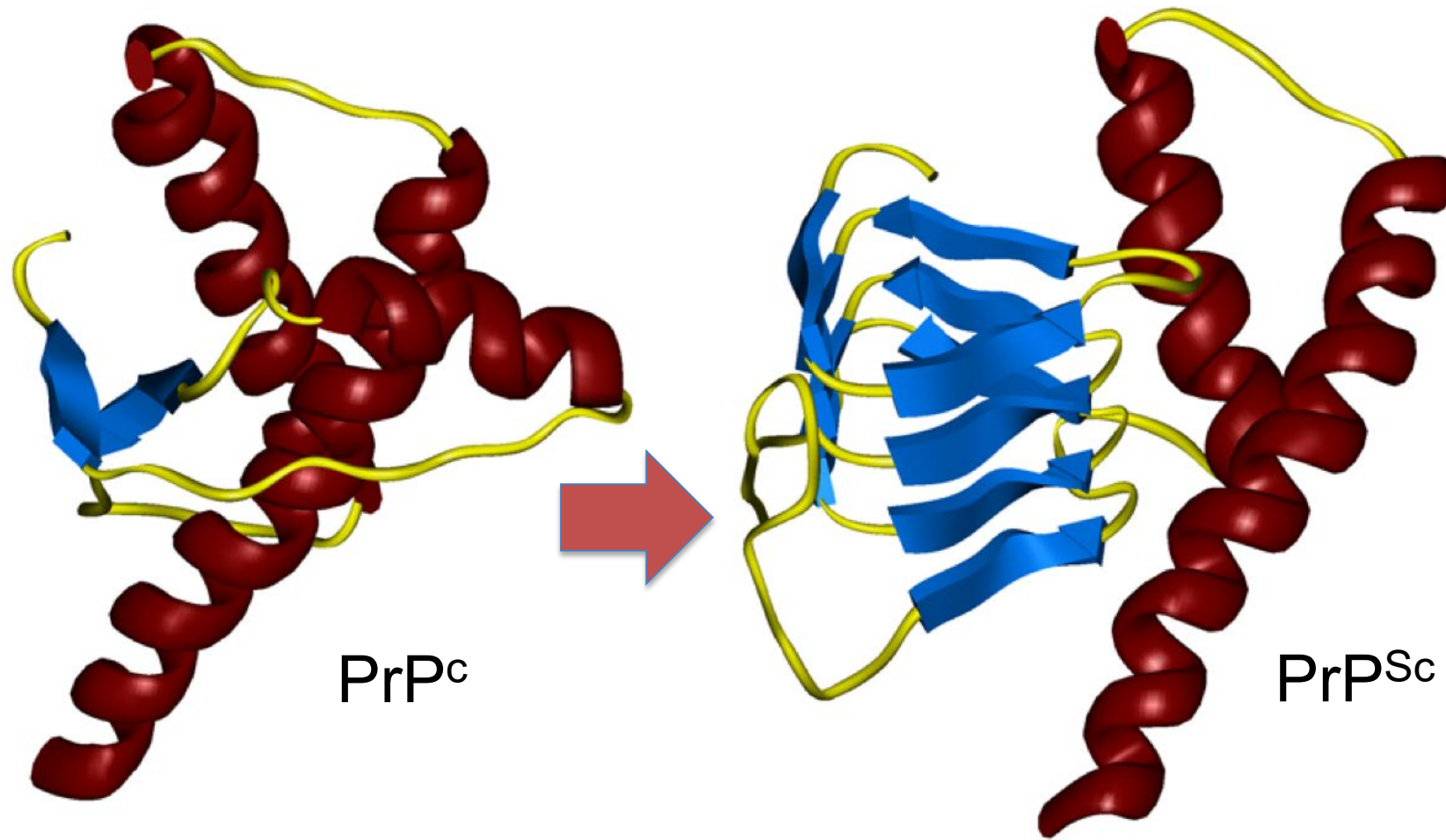
- What is a prion?
- Review demographic features of prion disease
- Review the diagnostic process for prion disease
- Why is there so much clinical variability?



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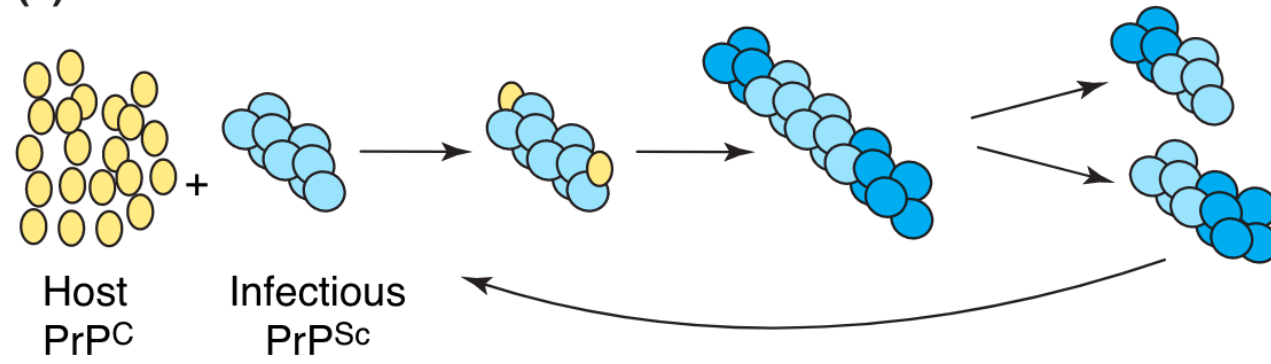
What is a prion?



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(a)



Causes of Prion Disease

Sporadic Prion Diseases

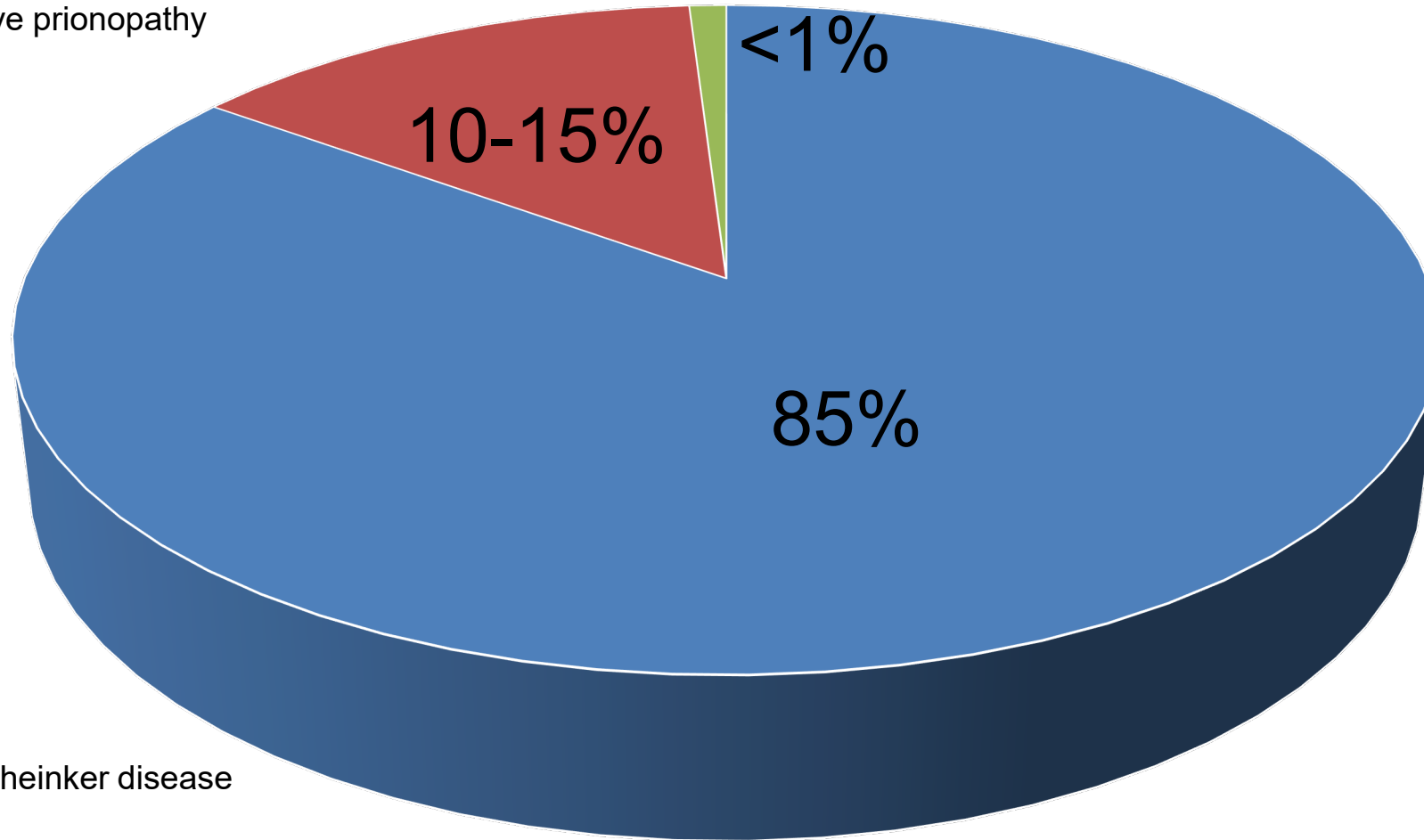
Sporadic CJD
Variably protease sensitive prionopathy
Sporadic fatal insomnia

Acquired Prion Diseases

Kuru
Iatrogenic CJD
Variant CJD

Genetic Prion Diseases

Genetic CJD
Gerstmann-Straussler Scheinker disease
Fatal familial insomnia



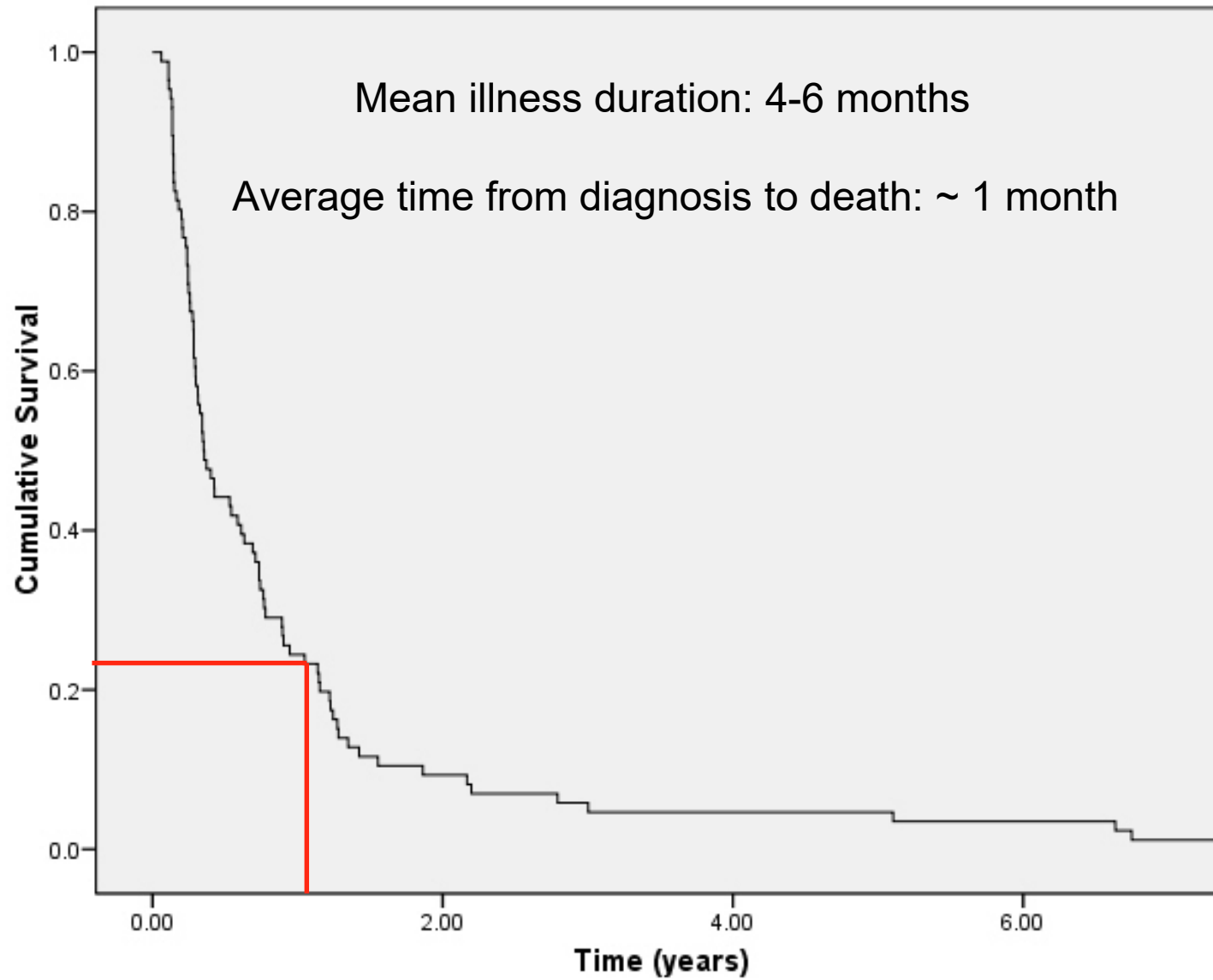
■ Sporadic ■ Genetic ■ Acquired



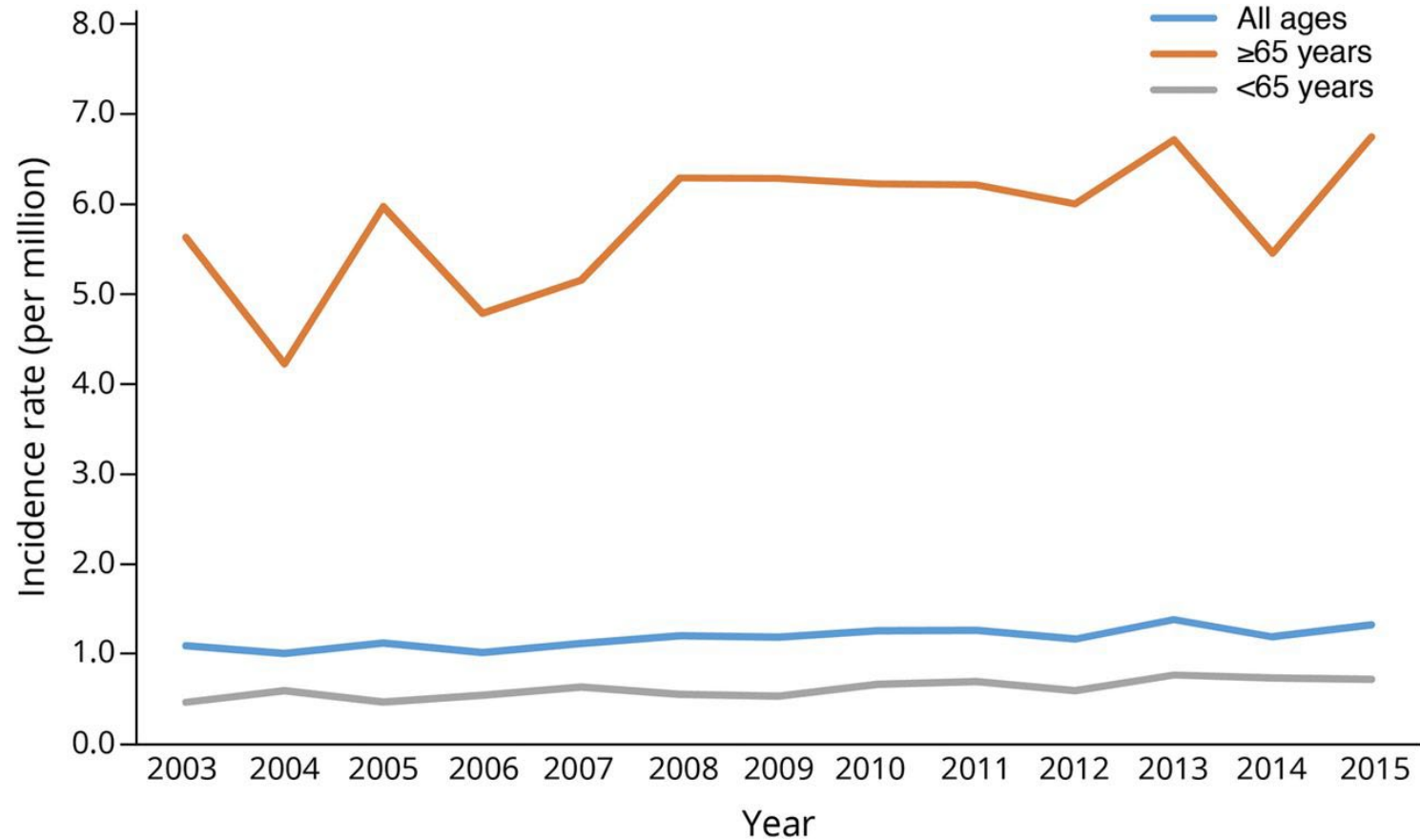
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Survival Time in Sporadic Creutzfeldt-Jakob Disease (n=90)



Epidemiology



1/ 6,239 US deaths per year



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Maddox RA, *Neurology* 2019



ORIOLE PARK
at
CAMDEN YARDS

$45,000/6,200 = \sim 7$ people

Clusters

- Primarily investigated by CDC and local health depts with NPDPSA 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 my 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



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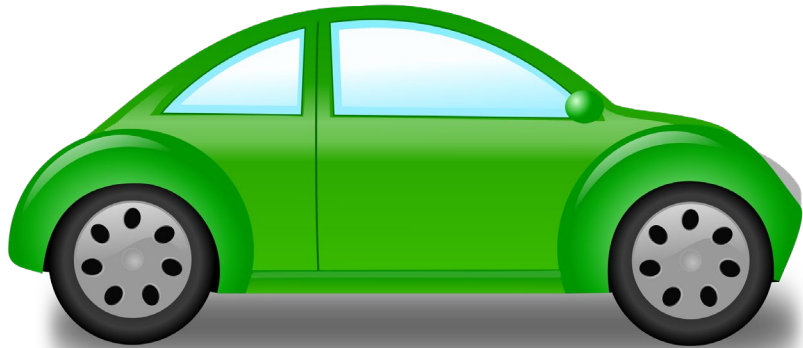
How is prion disease diagnosed and why
does it take so long?



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The diagnostic process is not unique to medicine



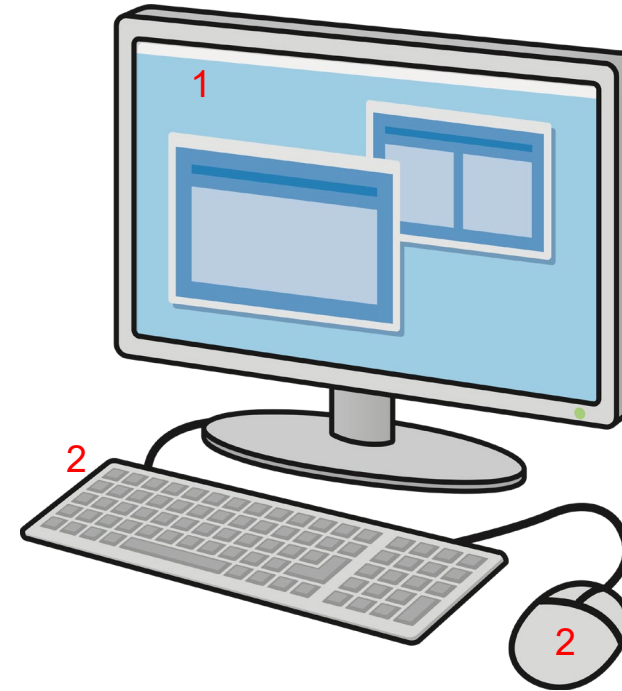
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Medical diagnoses typically start with recognizing syndromes

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



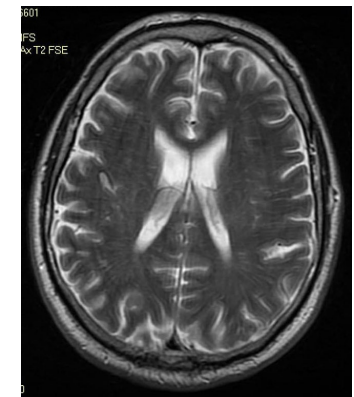
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Prion Disease (CJD), Initial Evaluation



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



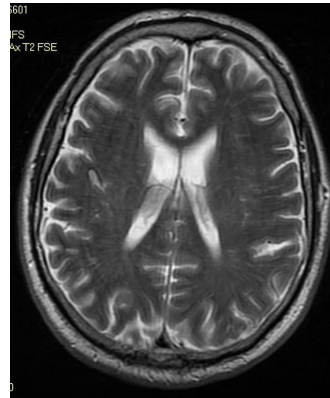
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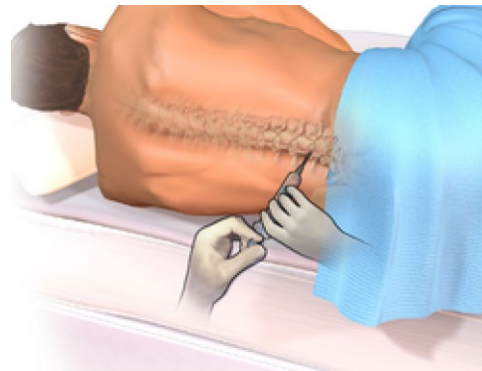
Prion Disease (CJD), Second Visit



List of Possible Causes
Blood vessel disease
Infections
Inflammation



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



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Diagnostic Criteria for CJD

Definitive diagnosis requires autopsy

Probable clinical diagnosis:

At least two clinical signs with dementia:

1. Myoclonus (jerky movements)
2. Incoordination/imbalance or visual symptoms
3. Weakness or Parkinson's like symptoms
4. Akinetic mutism

-AND-

At least one of the following:

1. Specific pattern on electroencephalogram (EEG)
2. 14-3-3 in CSF and disease duration < 2 years
3. Brightness in basal ganglia or at least two cortical regions (temporal, parietal, or occipital) on brain MRI

-OR-

+ RT-QuIC on tissue (usually CSF) in setting of any neuropsychiatric syndrome

Typical Symptoms of Human Prion Disease

Cognitive
impairment

Gait
impairment

Abnormal
movements

Visual
disturbances

Muscle
weakness

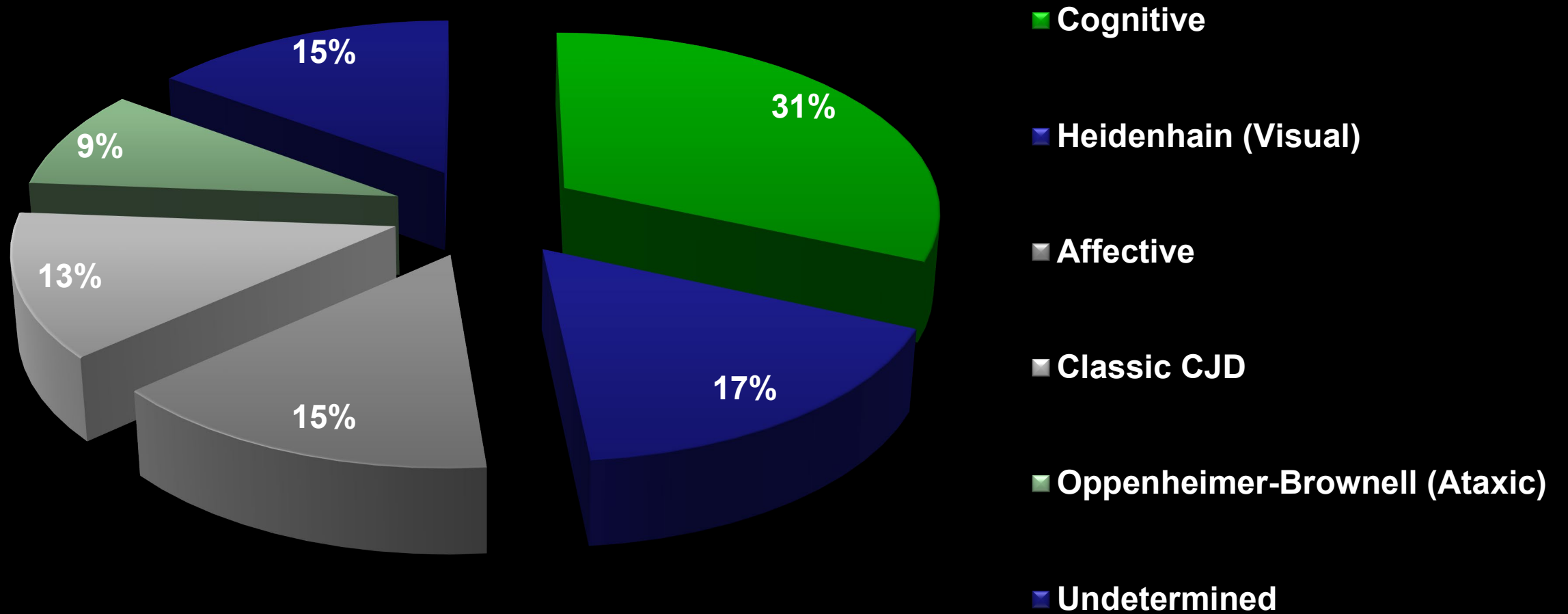
Psychiatric
symptoms



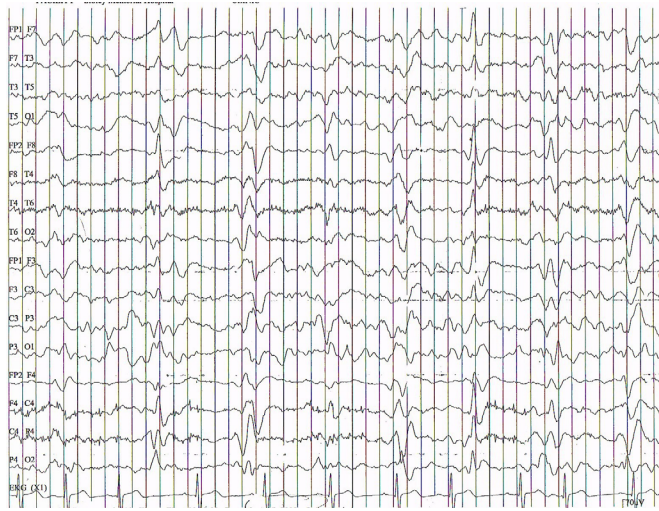
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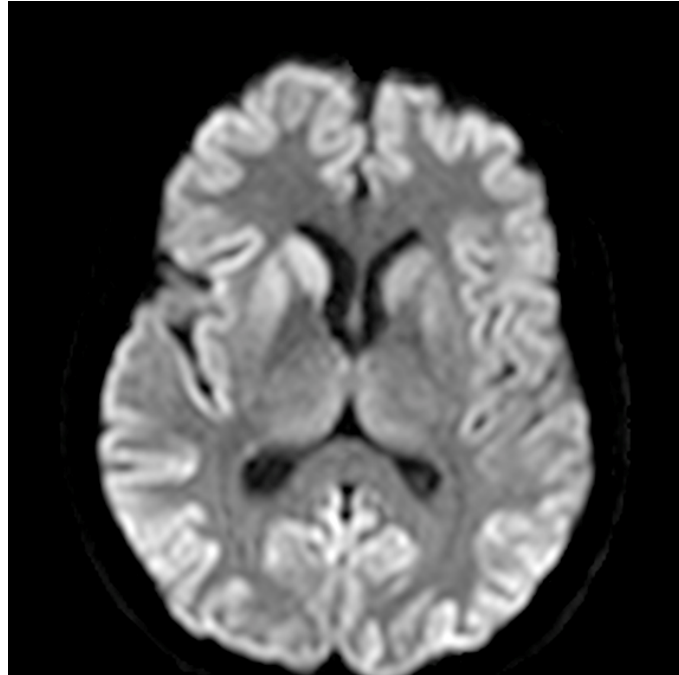
Sporadic CJD Initial Clinical Symptoms



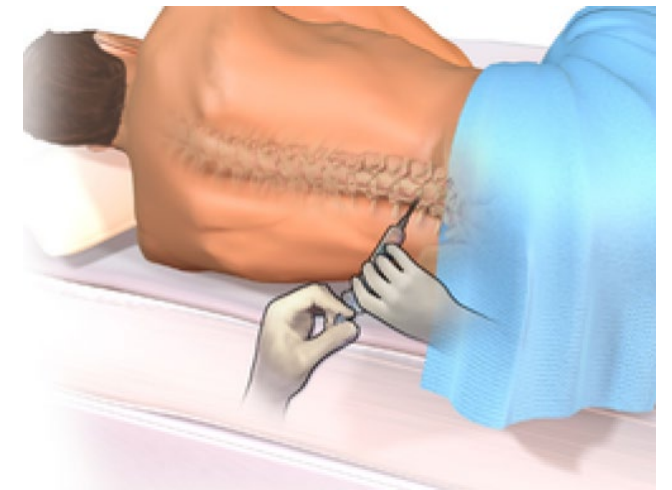
Prion Disease Tests



- 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



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Diagnostic Test Characteristics

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

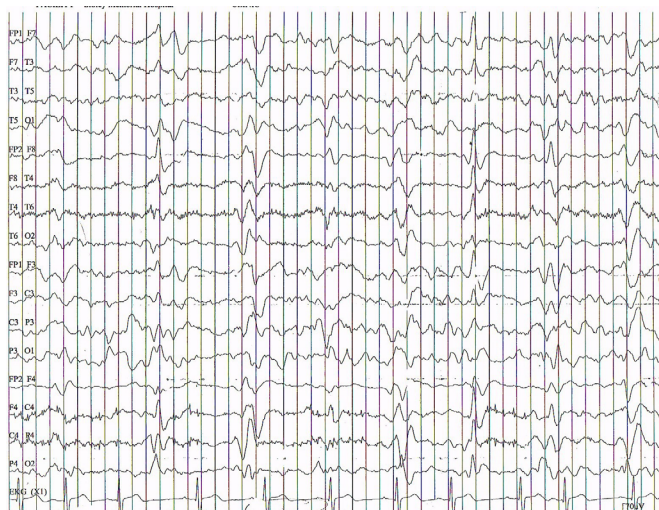
Specificity: How well does the test **ONLY** find the disease that we are looking for? (Narrow)



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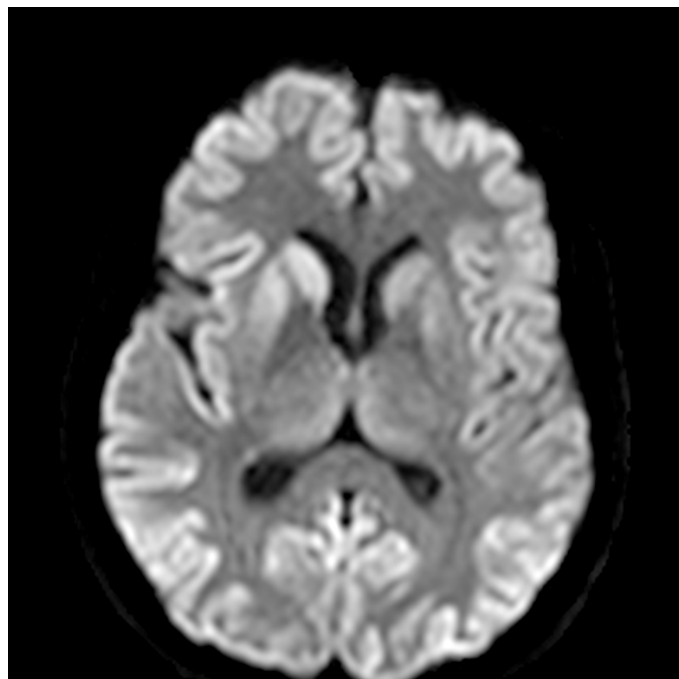
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CJD Diagnostic Test Characteristics



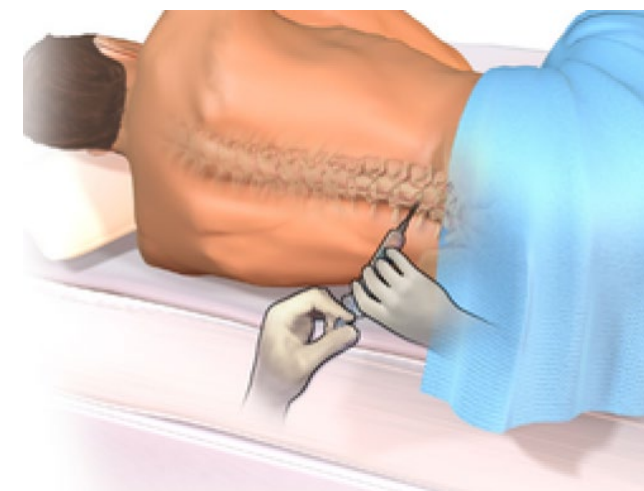
Not very sensitive
Fairly specific

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



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Cerebrospinal Fluid Tests

Markers of brain cell injury:

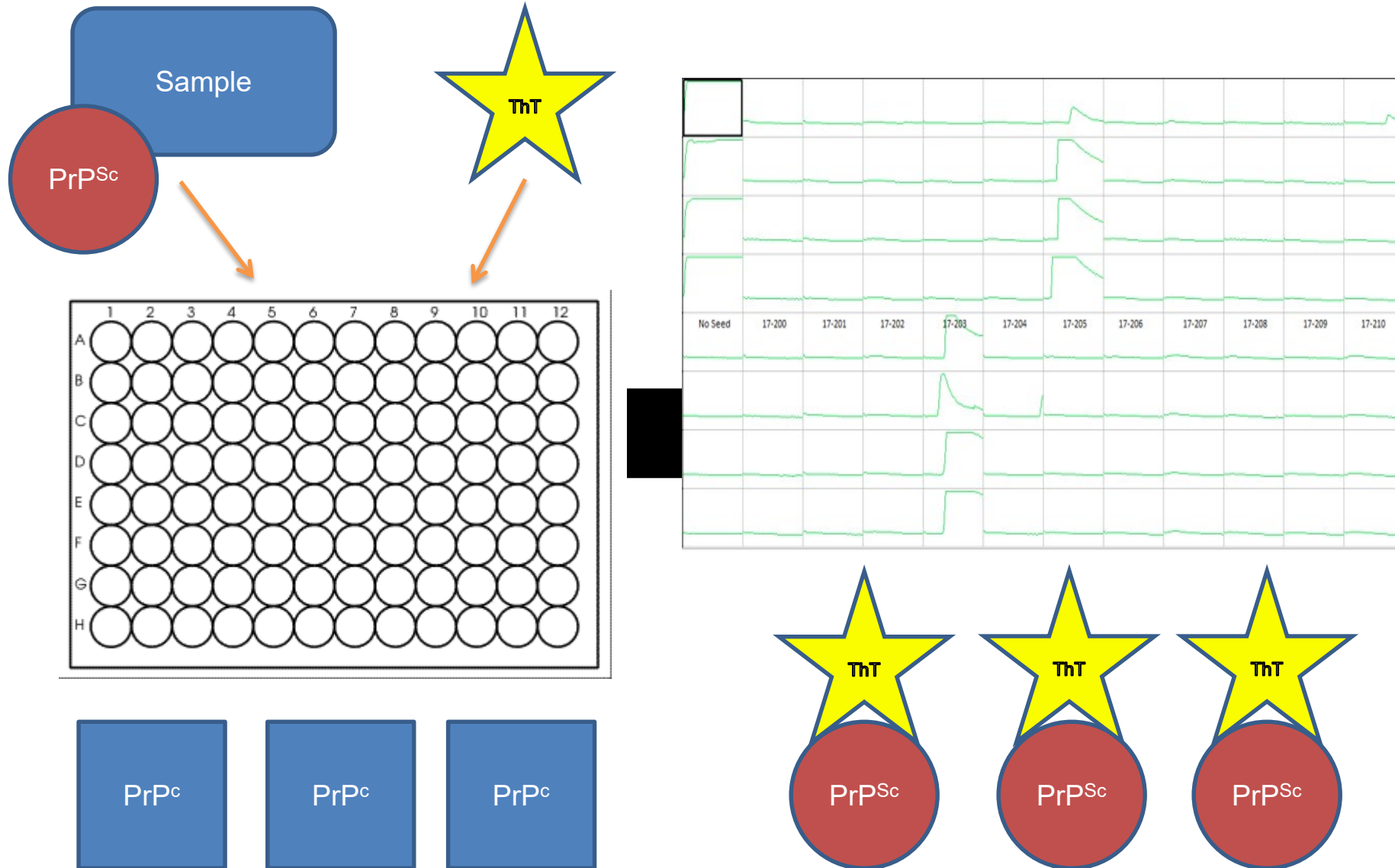
- 14-3-3
- Total tau

Disease specific test:

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



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



Main Limitations for Diagnosing Prion Disease

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



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What about Artificial Intelligence?

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. Stroke or Transient Ischemic Attack (TIA)
2. Alzheimer's Disease
3. Primary Progressive Aphasia (PPA)
4. Frontotemporal Dementia (FTD)
5. Parkinson's Disease
6. Amyotrophic Lateral Sclerosis (ALS)
7. Brain Tumor
8. Normal Pressure Hydrocephalus (NPH)
9. Subdural Hematoma
10. Medication side effects
11. Hypothyroidism
12. Vitamin Deficiency (B12, Folate)
13. Multiple Sclerosis (MS)
14. Wilson's Disease

The above work-up that was suggested was within normal limits. Two months later she developed issues with executive functioning, vision changes, balance difficulties that affected her walking, and tremors. Revisit the list of possible diagnoses and list them in order of likelihood with this new information.

1. Neurodegenerative Disease (specifically Corticobasal Degeneration or Progressive Supranuclear Palsy)
2. Lewy Body Dementia
3. Multiple System Atrophy (MSA)
4. Parkinson's Disease with Dementia
5. Vascular Dementia
6. Creutzfeldt-Jakob Disease (CJD)
7. Brain Tumor
8. Normal Pressure Hydrocephalus (NPH)
9. Paraneoplastic Syndromes
10. Chronic Subdural Hematoma
11. Chronic Traumatic Encephalopathy (CTE)
12. Wilson's Disease (less likely given age)
13. Multiple Sclerosis (MS) (less likely given age)

ChatGPT4o



all of the above diagnostic tests were normal, except the 14-3-3 and total tau proteins in the spinal fluid was elevated. Revisit the possible diagnoses in order of likelihood.

Given that the 14-3-3 protein and total tau protein levels are elevated in the cerebrospinal fluid (CSF), the most likely diagnosis should now focus on conditions that are typically associated with these findings. Here is the revised list of possible diagnoses, ordered by likelihood:

1. **Creutzfeldt-Jakob Disease (CJD)**
2. **Paraneoplastic Syndromes (particularly those affecting the nervous system)**
3. **Rapidly Progressive Alzheimer's Disease**
4. **Neurodegenerative Diseases with Atypical Presentation (e.g., atypical forms of frontotemporal dementia)**
5. **Other Rapidly Progressive Dementias (including other prion diseases)**

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

ChatGPT4o



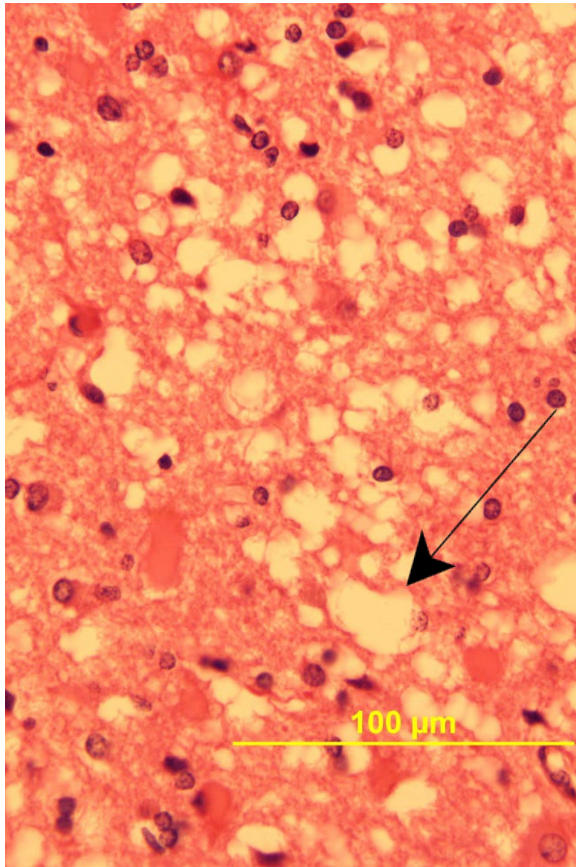
Why is there so much clinical variability in prion disease?



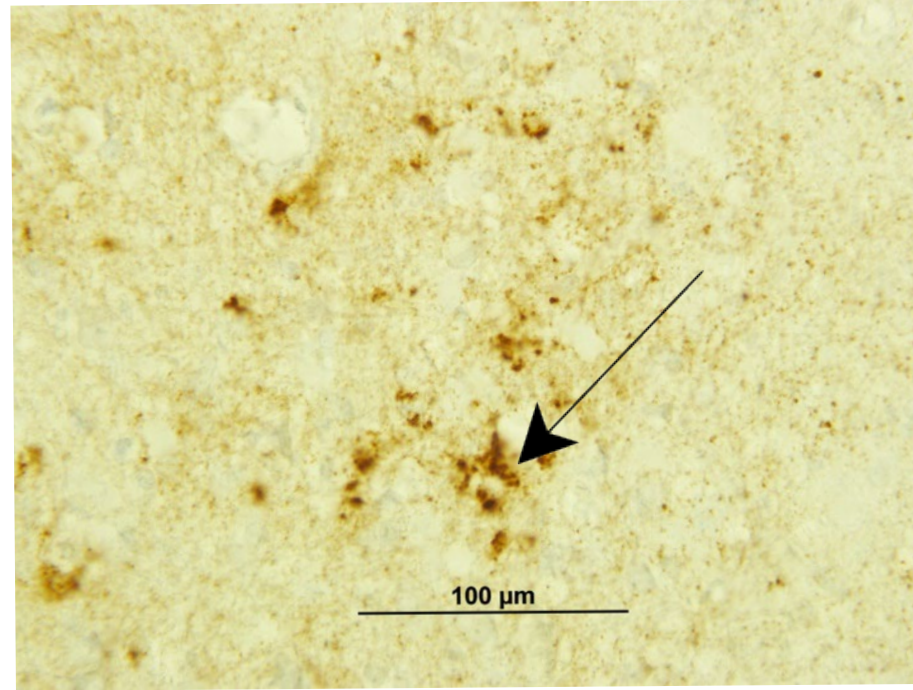
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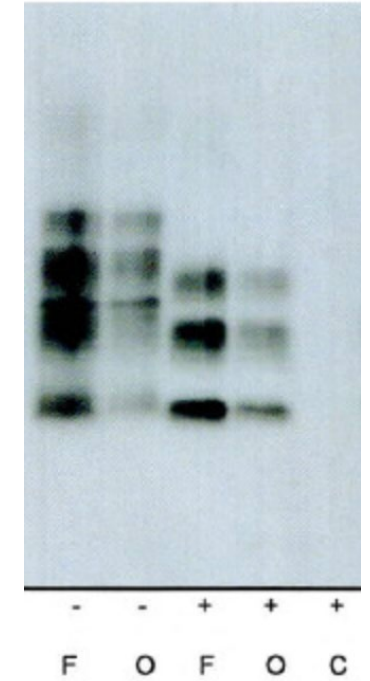
Information Obtained at Autopsy



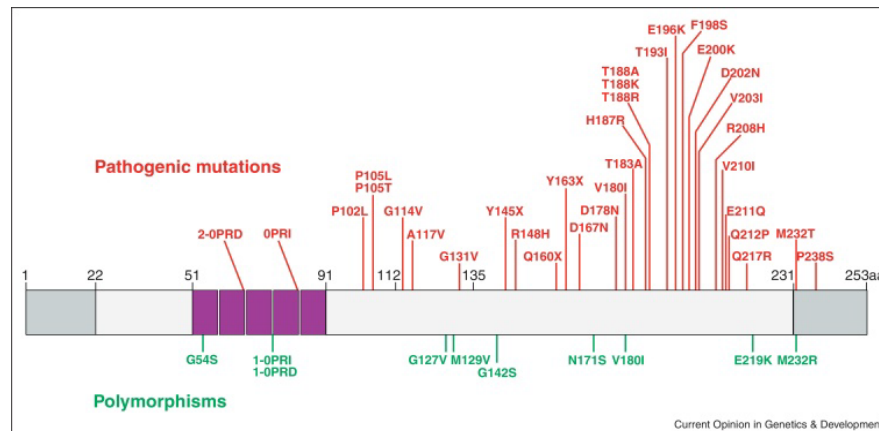
H & E Staining



Immunohistochemistry



Western Blot



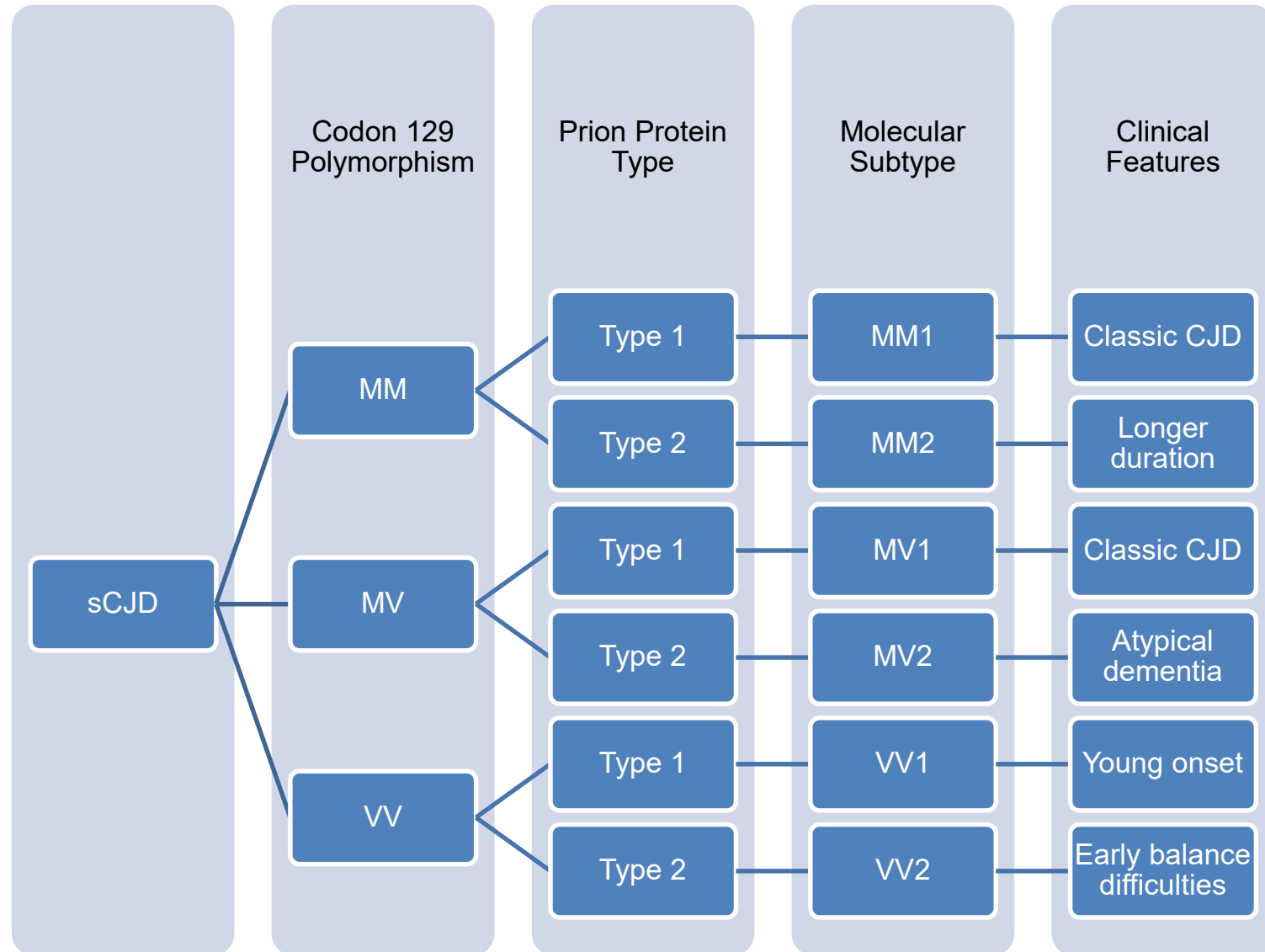
Prion protein gene
genetic testing



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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



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Thank you!
Questions/Comments?



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