Clinical Applications of Biomarkers in Prion Disease

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What is Rapidly Progressive Dementia?

Obvious Definition

A collection of symptoms caused by several different disorders that ***rapidly*** impair intellectual functioning and ***rapidly*** interfere with normal activities and relationships.

But how do we define ***rapid***?

What is Rapidly Progressive Dementia?

Research Definition

1. Dementing conditions that progress from first symptom to dementia within 1 year, or…
2. Dementing conditions that progress from first symptom to incapacitation due to dementia within 2 years, or…
3. Dementing conditions that progress from first symptom to death due to dementia within 4 years.

Day, 2022—Continuum; Satyadev et al. 2024—Ann Neurol; Kuchenbecker et al. 2024—Ann Neurol; Josephs et al. 2008—Arch Neurol

Rapidly Progressive Dementia

Prion Disease

Prion disease is one of the most common causes of RPD…

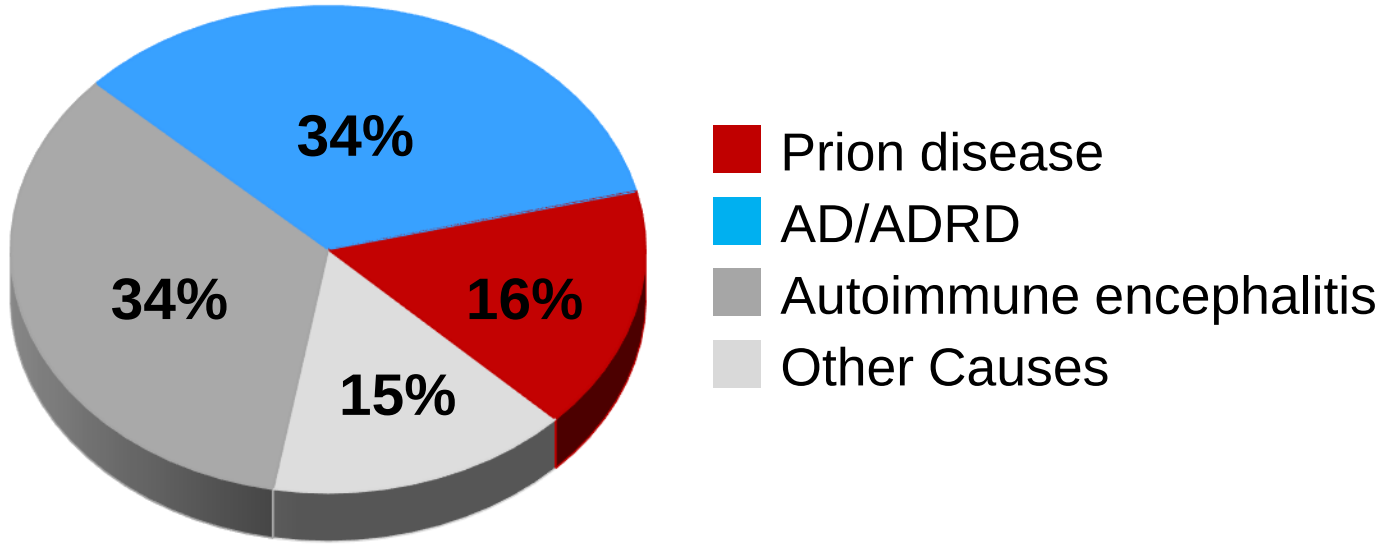
Many other diseases look like prion disease.

The RaPID Study

Rates of Progression in Dementia

Mayo Clinic and Washington University

K23AG064029



Satyadev et al. 2024—Ann Neurol; Kuchenbecker et al. 2024—Ann Neurol

Rapidly Progressive Dementia

Prion Disease

Prion disease is one of the most common causes of RPD…

Many other diseases look like prion disease.

This reality emphasizes the need to,

- Improve recognition of patients **with** prion disease.
- Improve recognition of patients **without** prion disease.
- Do it **early** in the symptomatic course.

The Promise of Biomarkers

Definition

Biomarker: A measurable indicator of a biological state or condition.

The ideal biomarker:

- Provides a reliable measure of disease activity
- Is measurable early in the disease process
- Is non-invasive, reproducible, and repeatable
- Predicts response to treatment and future outcomes (case-by-case).

Biomarkers in Prion Disease

Objectives

1. Apply available biomarkers to accurately identify patients with prion disease.
2. Use biomarkers to improve early recognition of patients without prion disease (i.e., *mimics*).
3. Adapt biomarkers to inform survival in patients with prion disease.

Biomarkers in Prion Disease

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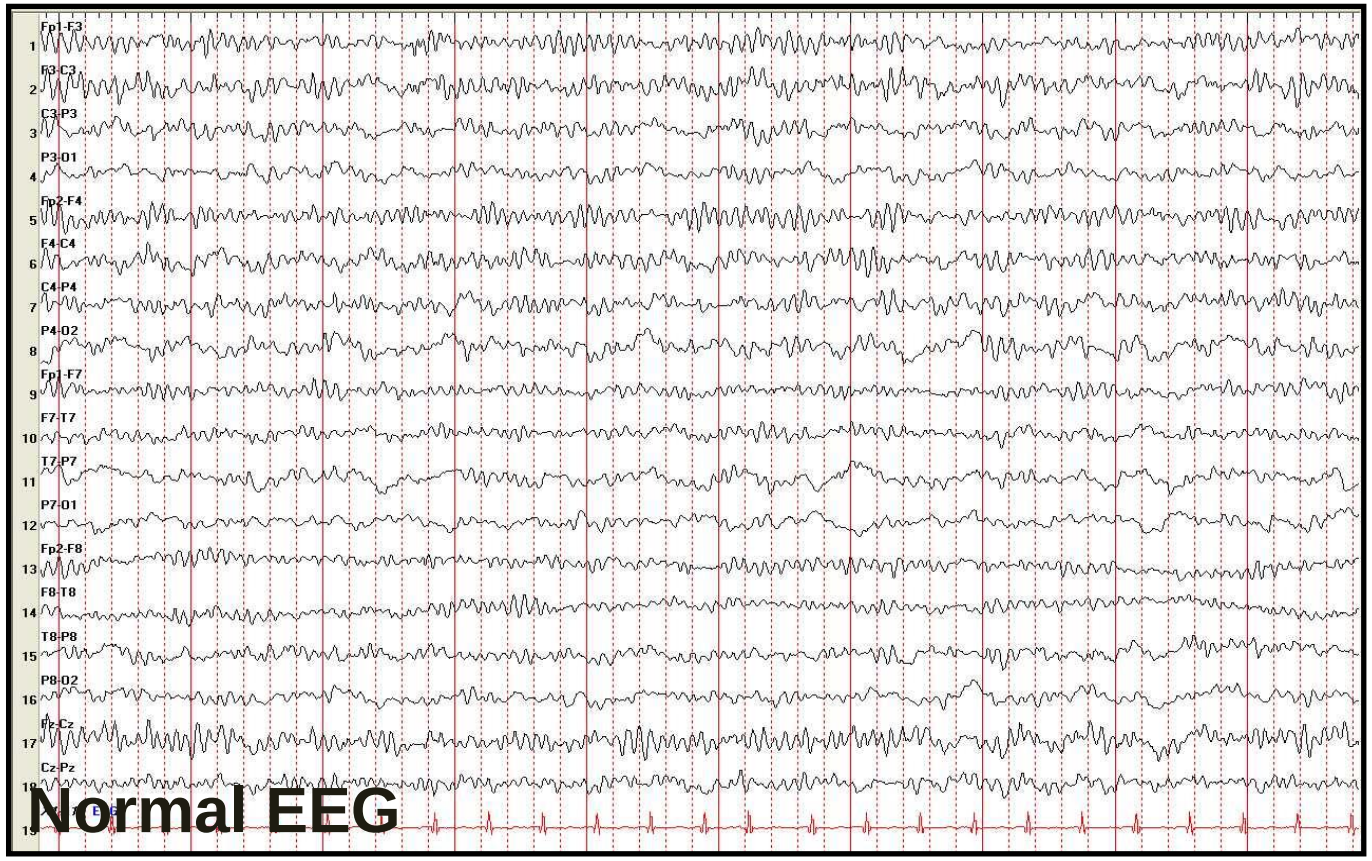
Biomarkers in Prion Disease

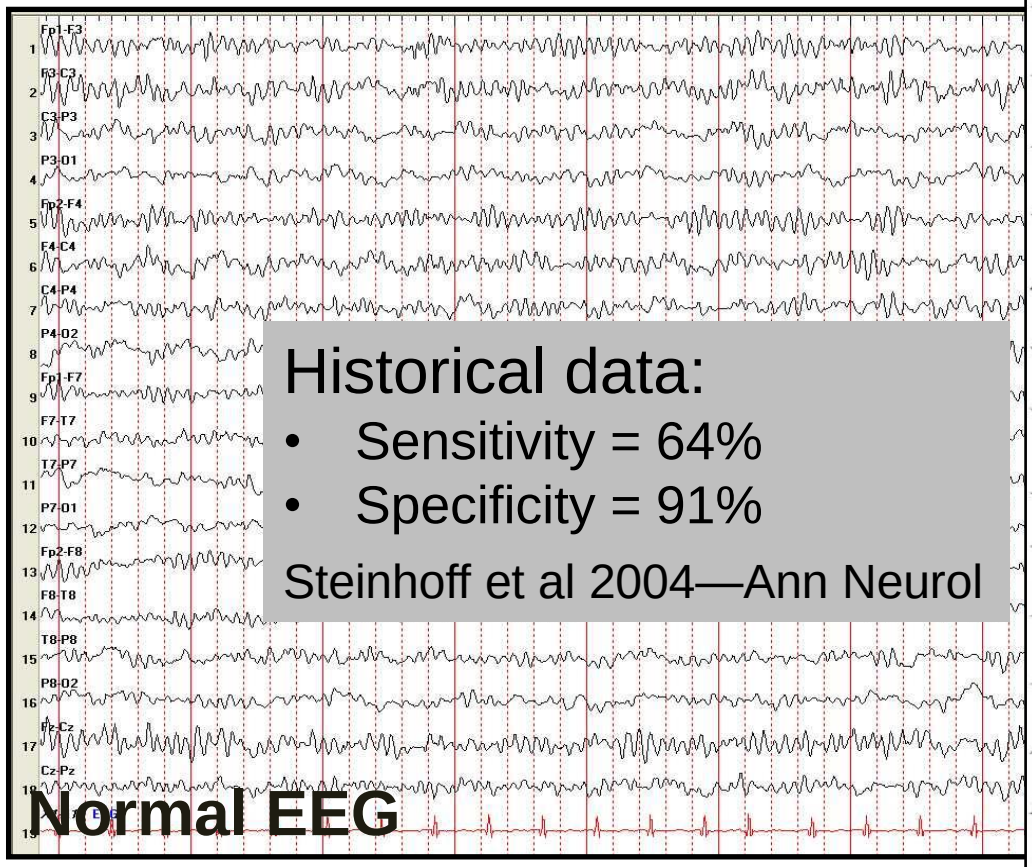
EEG



Normal EEG

Biomarkers in Prion Disease

EEG

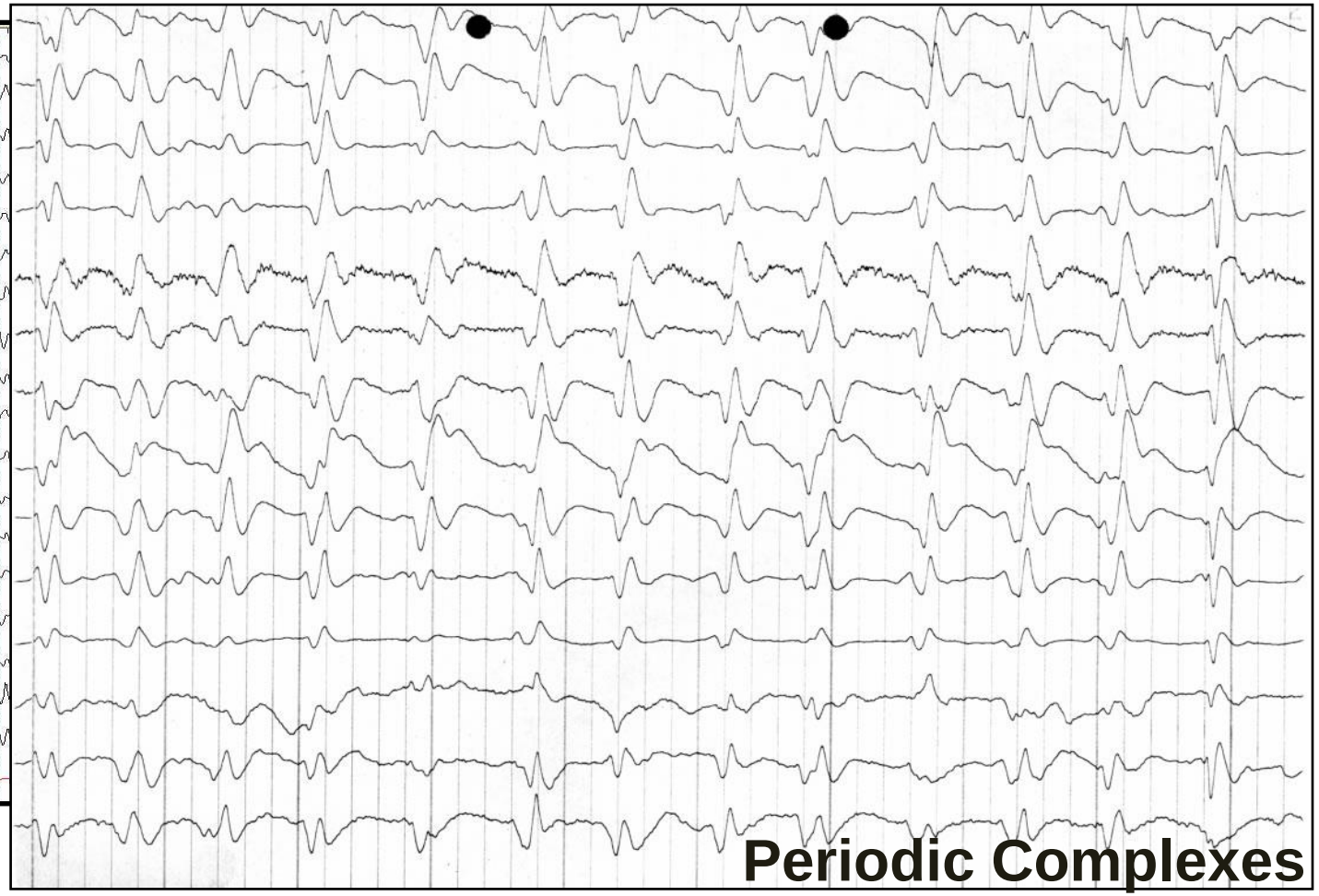


Historical data:

- Sensitivity = 64%
- Specificity = 91%

Steinhoff et al 2004—Ann Neurol

Normal EEG



Periodic Complexes

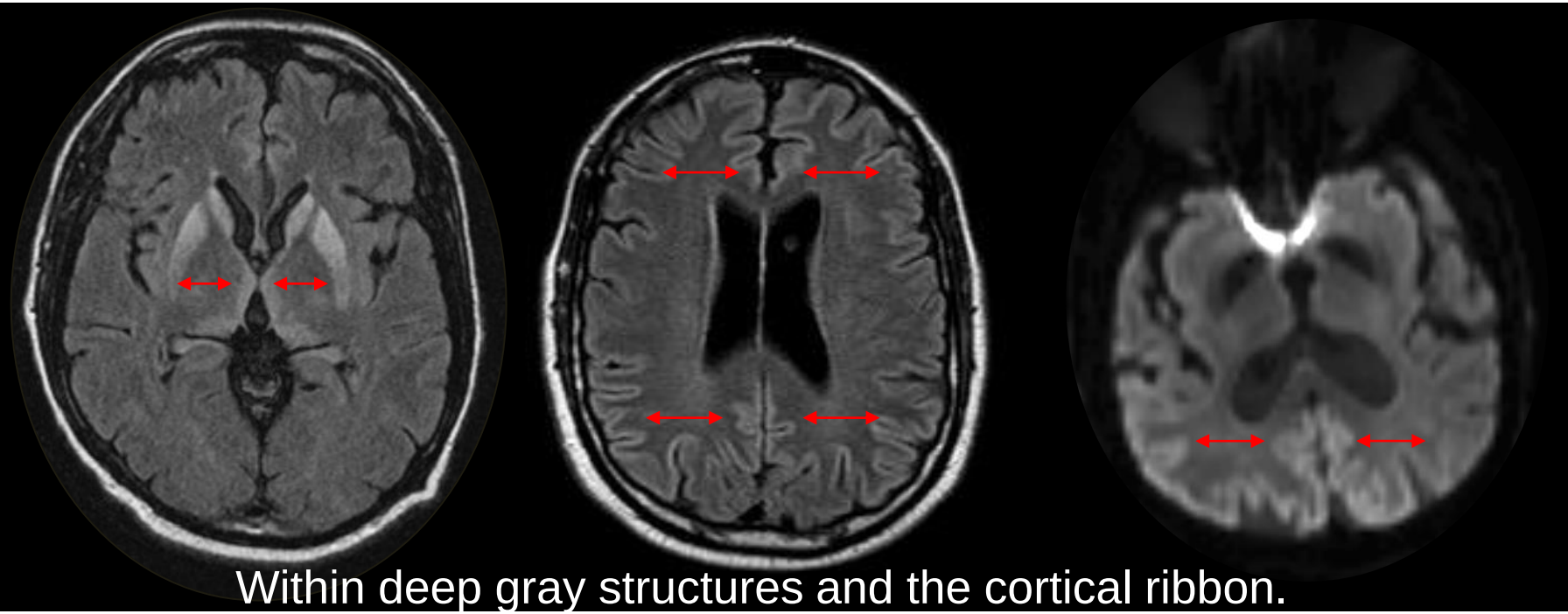
Periodic complexes have long been a part of CJD diagnostic criteria.

Biomarkers in Prion Disease

MRI

MRI: restricted diffusion & FLAIR changes

CJD Diagnosis	**MRI**
	DWI & FLAIR
Sensitivity	80-98%
Specificity	74-98%



Within deep gray structures and the cortical ribbon.

Young et al. 2005—AJNR; Vitali et al. 2011—Neurology; Hermann et al. 2021—Lancet Neurol; Caverzasi et al. 2014—Neuroimage Clin;

Biomarkers in Prion Disease

CSF

CSF: Total Tau and protein 14-3-3

CJD Diagnosis	CSF Measures	
	Total Tau†	14-3-3
Sensitivity	92	79
Specificity	65	39

- Tau and protein 14-3-3 are abundant proteins in the CNS that can be measured in CSF.
- Levels rise in association with rapid neuronal damage; thus, are sensitive but ***not*** specific for CJD. Elevations are *also* seen in patients with rpAD/ADRD.

† >1150 pg/mL, NPDPSC Assay

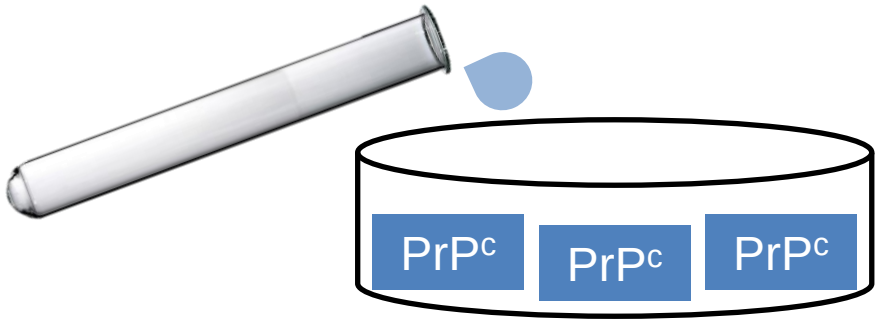
Biomarkers in Prion Disease

CSF

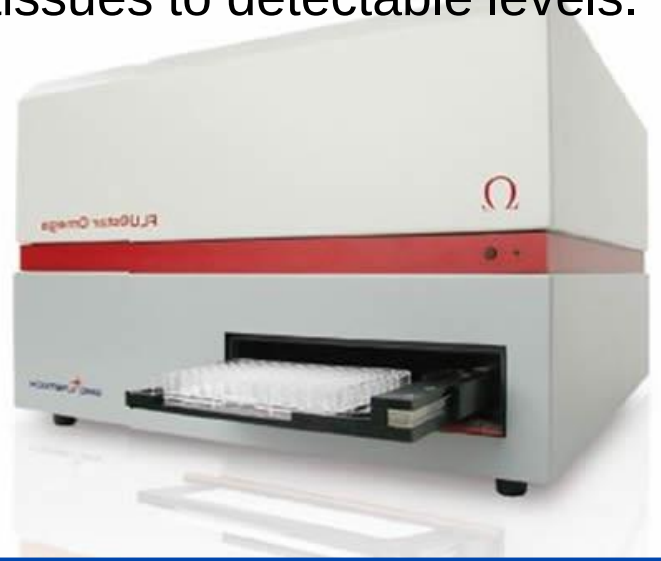
CSF: Real-Time Quaking-Induced Conversion (RT-QuIC) assay

A new, ultra-sensitive method for detecting human prion protein:

- RT-QuIC exploits the self-replicating (seeding) power of misfolded PrP^{Sc}, using recombinant prion protein as a substrate to amplify very small amounts of PrP^{Sc} from patient tissues to detectable levels.



No PrP^{Sc} = Not CJD



Foutz *et al*. 2017—Ann Neurol

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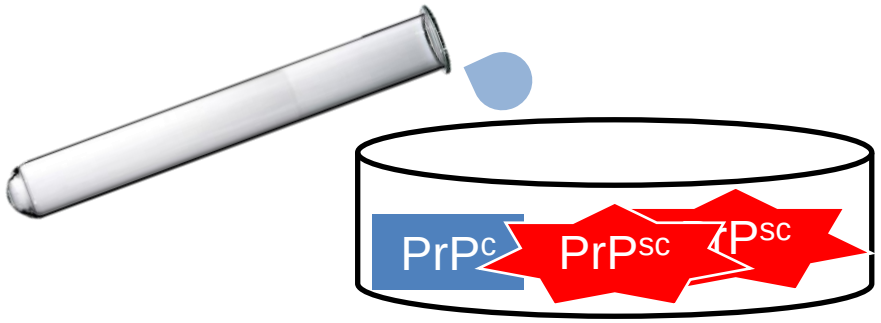

PrP^{Sc} (!) = CJD

Foutz *et al*. 2017—Ann Neurol

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- Operationalization in clinical practice has revolutionized the diagnostic approach to prion disease, enabling antemortem diagnosis with high sensitivity and specificity.

Rhoads et al. 2020—Neurology; Hermann et al. 2018—Neurology

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National Prion Pathology Surveillance Center Data:

- RT-QuIC positive in 449/497 of patients with autopsy-confirmed CJD (sensitivity, **90.3%**).
- RT-QuIC positive in 1/69 patients *without* CJD (specificity, **98.5%**).

Rhoads et al. 2020—Neurology; Hermann et al. 2018—Neurology

Biomarkers in Prion Disease

CSF

CSF: Real-Time Quaking-Induced Conversion (RT-QuIC) assay

A good test—but *not* a QUICK test.

- The test takes 48-72 hr to run.
- Typical time from LP to reporting 2-3 weeks.

Lazar et al. 2022—Neurology Clin Pract

Biomarkers in Prion Disease

CSF

CSF: Real-Time Quaking-Induced Conversion (RT-QuIC) assay

A good test—but *not* a PERFECT test.

- FALSE NEGATIVE tests are encountered in clinical practice.

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Real-time quaking-induced conversion assays for prions: Applying a sensitive but imperfect test in clinical practice

Biomarkers in Prion Disease

CSF

CSF: Real-Time Quaking-Induced Conversion (RT-QuIC) assay

A good test—but *not* a PERFECT test.

- FALSE NEGATIVE tests are encountered in clinical practice.

● More likely in younger patients ● patients with lower CSF t-tau/14-3-3 ● CSF contaminated with RBC ("*bloody tap*") ● selected genetic forms of prion disease ● patients with fatal insomnia ● patients with VV1 or MM2 sCJD subtype ●

Jones et al. 2023—Eur J Neurol; Rhoads et al. 2018—Neurology; Abu-Rumeileh et al. 2019—J Neurol

Biomarkers in Prion Disease

CSF

CSF: Real-Time Quaking-Induced Conversion (RT-QuIC) assay

A good test—but *not* a PERFECT test.

- FALSE NEGATIVE tests are encountered in clinical practice.
- Recommendations when RT-QuIC returns *unexpectedly* negative…

1. (Re)Consider the differential diagnosis (TRUE negative test results are more likely).
2. Leverage additional diagnostic tests to make the correct diagnosis.

Jones et al. 2023—Eur J Neurol

Biomarkers in Prion Disease

How well do biomarkers perform in practice?

Clinically-accessible biomarkers perform well in typical clinic cohorts.

Diagnostic Tests at Presentation	N	Sensitivity
EEG		
Periodic discharges/PSWC	17/105	16%
Brain MRI		
Consistent with CJD	88/115	**77%**
CSF analysis		
14-3-3	54/90	60%
T-tau (>1149 pg/mL)	81/92	**88%**
RT-QuIC positive	66/71	**93%**

Typical MRI findings, elevated CSF T-tau, or positive RT-QuIC were detected in 107/110 patients assessed at Mayo Clinic (**sensitivity, 97%**).

Shir et al. 2022—*JAMA Open*

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High performing tests should be ordered in all patients with suspected prion disease.

Shir et al. 2022—*JAMA Open*

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Reevaluate use of low performing tests in clinical practice.

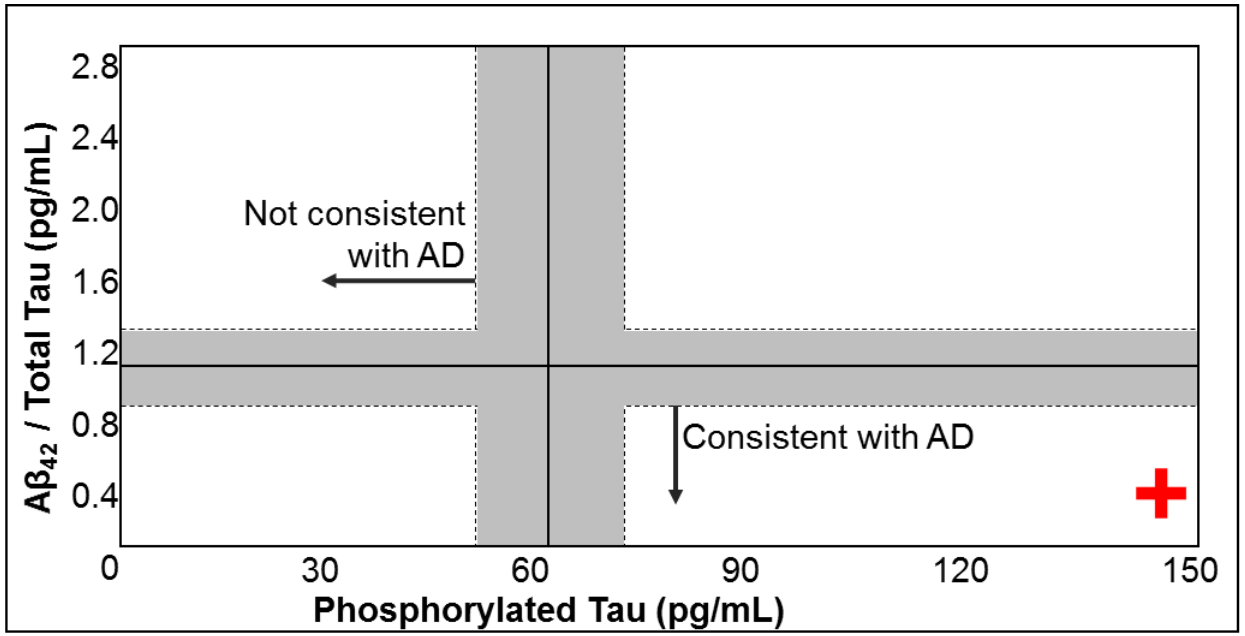
Shir et al. 2022—*JAMA Open*

Biomarkers of Neurodegenerative Disease

Other Biomarkers

CSF “AD” biomarkers may inform diagnosis of CJD.

- Commercial assays measuring Aβ, total and phosphorylated tau can accurately diagnose AD.
  - Accuracy is achieved through panels of biomarkers incorporating AD-specific and non-specific biomarkers.



Test	Technical Result
Aβ 42	525.2 pg/mL
T-Tau	1667.55 pg/mL
P-Tau	161.75 pg/mL

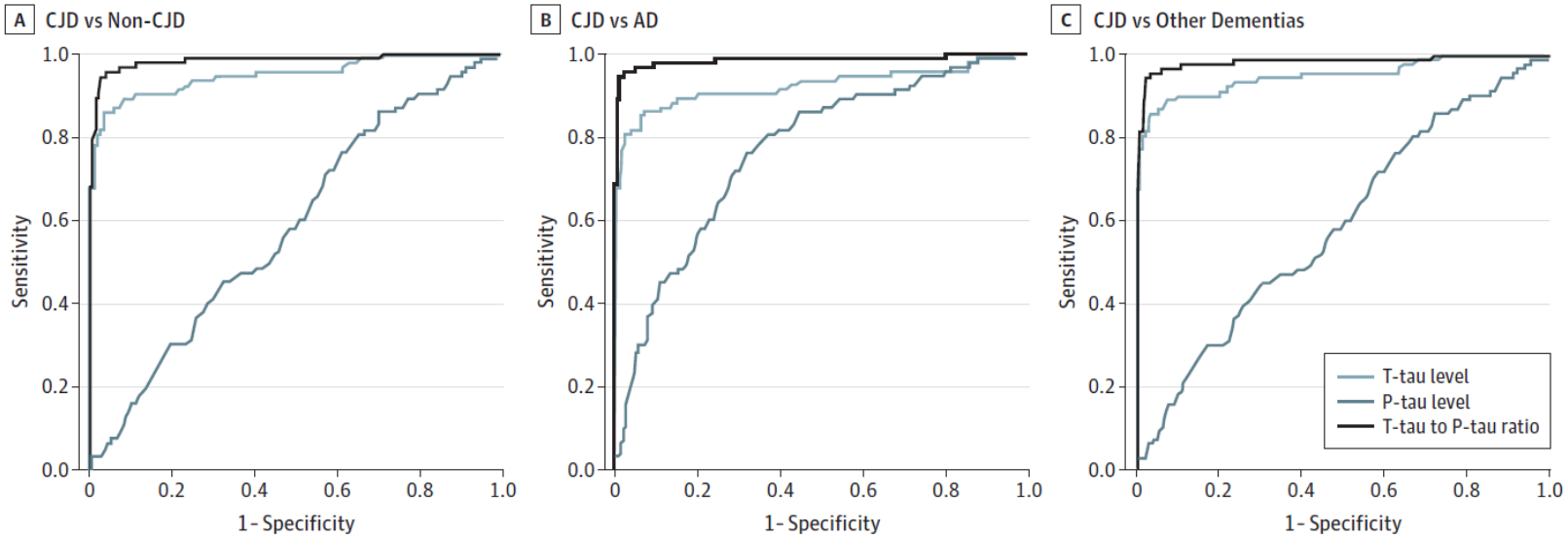
Biomarkers of Neurodegenerative Disease

Other Biomarkers

CSF “AD” biomarkers may inform diagnosis of CJD.

- Commercial assays measuring Aβ, total and phosphorylated tau can accurately diagnose AD.
- May discriminate between CJD and other neurodegenerative diseases.
  - Total tau is elevated in both diseases (usually much higher in CJD).
  - Phosphorylated tau is elevated in AD (disproportionate to total tau).

Figure 1. Discriminatory Power of Total (T)-Tau and Phosphorylated (P)-Tau Levels and the T-Tau to P-Tau Ratio



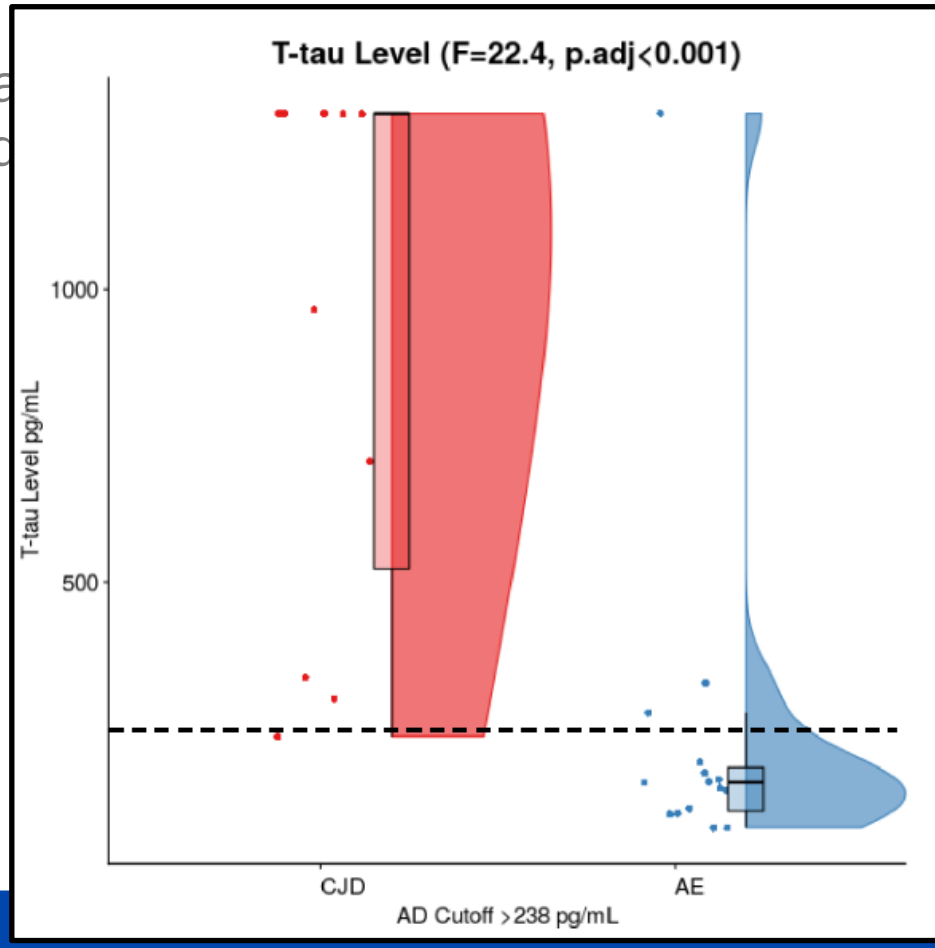
Skillback et al. 2014—JAMA Neurol

Biomarkers of Neurodegenerative Disease

Other Biomarkers

CSF “AD” biomarkers may inform diagnosis of CJD.

- Commercial assays measuring Aβ, total and phosphorylated ta
- May discriminate between CJD and other neurodegenerative d
- May discriminate between CJD and autoimmune encephalitis.
  - Total tau is higher in patients with CJD (median >1300 pg/mL) than AE (median 158 pg/mL).
    - 91% of CJD patients had elevated t-tau vs 20% of AE.



Chang et al. 2022—Eur J Neurol

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(Mis)Diagnosis of Prion Disease

Treatment Responsive RPD

Treatment-responsive causes of RPD are frequently recognized...

- At autopsy in patients with suspected CJD
  - 352/1106 (32%) brain autopsies performed at the National Prion Disease Center from 2006-2009 were **negative for prion disease**.
    - Most had *other* neurodegenerative diseases (AD/ADRD).

Chitravas et al. 2011—Ann Neurol

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    - Most had *other* neurodegenerative diseases (AD/ADRD).
    - 20% had **potentially treatable causes** of RPD (**!**)
      - Immune-mediated disorders, n=26 (37%)
      - Neoplasms, n=25 (35%)
      - Infections, n=14 (20%)
      - Metabolic / toxic encephalopathy, n=6 (8%)

Chitravas et al. 2011—Ann Neurol

(Mis)Diagnosis of Prion Disease

Treatment Responsive RPD

Treatment-responsive causes of RPD are frequently recognized...

- At autopsy in patients with suspected CJD
  - 352/1106 (32%) brain autopsies performed at the National Prion Disease Center from 2006-2009 were **negative for prion disease**.
  - Autoimmune encephalitis (AE) was confirmed at autopsy in **22/384 (5.7%)** patients with suspected CJD assessed via the Dutch Prion Disease Surveillance Center.

Chitravas et al. 2011—Ann Neurol; Maat et al. 2015—Neurology: N2

(Mis)Diagnosis of Prion Disease

Treatment Responsive RPD

Treatment-responsive causes of RPD are frequently recognized...

- At autopsy.
- During life in patients with suspected CJD
  - RaPID Study Cohort: 11/175 (6.3%) patients enrolled in our prospective study of RPD met clinical criteria for probable CJD but did not have CJD.

CJD Mimics	n
Autoimmune encephalitis - Ab-mediated (NMDAR, LGI1, GlyR, AMPA) - Intracytoplasmic (Hu/ANNA-1)	**6**
AV fistula	**1**
CAA-ri/ABRA	**1**
FTLD-MND	**1**
Neurosarcoidosis	**1**
Systemic SLE with polypharmacy	**1**

(Mis)Diagnosis of Prion Disease

Identifying CJD Mimics

Improving *early-detection* of CJD mimics in practice

- Clinical features and readily-accessible tests were compared between mimics (n=11) and patients with definite or probable CJD (with positive RT-QuIC; n=93).

(Mis)Diagnosis of Prion Disease

Identifying CJD Mimics

Improving *early-detection* of CJD mimics in practice

- Clinical features and readily-accessible tests were compared between mimics (n=11) and patients with definite or probable CJD (with positive RT-QuIC; n=93).
- Age-at-symptom onset, % females, and presenting symptoms were similar.

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- Clinical features and readily-accessible tests were compared between mimics (n=11) and patients with definite or probable CJD (with positive RT-QuIC; n=93).
- Age-at-symptom onset, % females, and presenting symptoms were similar.
- Motor signs (e.g., FBDS, myoclonus, dyskinesias, parkinsonism) were detected in all mimics (11/11), but only 49/93 (53%) CJD cases.

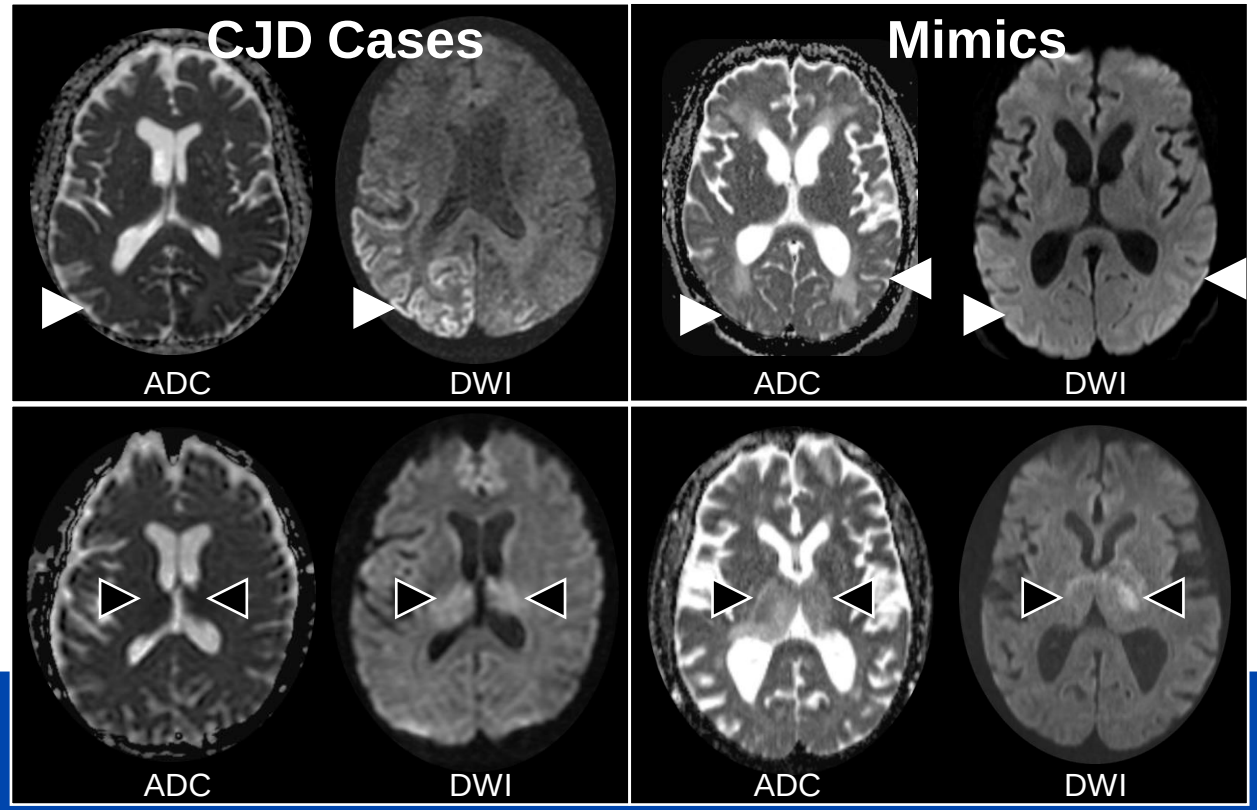
Lazar et al. 2022—Neurology®: CP

(Mis)Diagnosis of Prion Disease

Identifying CJD Mimics

Improving *early-detection* of CJD mimics in practice

Accessible Tests	CJD Cases	Mimics	p value
MR brain compatible with CJD	66 (71%)	6 (55%)	0.31



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Rapidly Resulting	**MR brain compatible with CJD**	66 (71%)	6 (55%)	0.31
	EEG			
	- Normal	16 (19%)	2 (18%)	>0.99
	- Non-specific slowing	66 (77%)	8 (73%)	0.72
	- Epileptiform discharges	11 (13%)	2 (18%)	0.64
	- Periodic discharges / PLEDS	16 (19%)	1 (9%)	0.68
	CSF			
	- WBC >5 cells /hpf	**4 (4%)**	**5 (45%)**	**<0.001**
	- Protein >45 mg/dL	**39 (42%)**	**10 (90%)**	**0.003**
	- Glucose <40 mg/dL	0	1 (9%)	0.11

Lazar et al. 2022—Neurology®: CP

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	- Glucose <40 mg/dL	0	1 (9%)	0.11
Late Resulting	**Disease-Associated Autoantibodies**			
	- **Serum**	**0/71**	**5/9 (56%)**	**<0.001**
	- **CSF**	**0/79**	**5/10 (50%)**	**<0.001**
	CJD Biomarkers			
	- 14-3-3	64/89 (72%)	4/10 (40%)	0.07
	- **Total tau >1150 pg/mL**	**74/82 (90%)**	**2/10 (20%)**	**<0.001**
	- **RT-QuIC positive**	**77/80 (96%)**	**0/9**	**<0.001**

(Mis)Diagnosis of Prion Disease

Identifying CJD Mimics

Improving *early-detection* of CJD mimics in practice

Alternate (non-CJD) diagnoses should be considered in patients with **early motor dysfunction** and **abnormal routine CSF studies**, providing an opportunity for early treatment.

- Autoimmune encephalitis, sarcoidosis, and select neurodegenerative diseases may mimic CJD at presentation.

(Mis)Diagnosis of Prion Disease

Identifying CJD Mimics

Improving *early-detection* of CJD mimics in practice

Alternate (non-CJD) diagnoses should be considered in patients with **early motor dysfunction** and **abnormal routine CSF studies**, providing an opportunity for early treatment.

Detection of **disease-associated autoantibodies** in a patient with suspected CJD should prompt further investigation.

- Although may still be prion disease (false positive tests are recognized).

(Mis)Diagnosis of Prion Disease

Identifying CJD Mimics

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Alternate (non-CJD) diagnoses should be considered in patients with **early motor dysfunction** and **abnormal routine CSF studies**, providing an opportunity for early treatment.

Detection of **disease-associated autoantibodies** in a patient with suspected CJD should prompt further investigation.

"Negative" findings on sensitive tests (RT-QuIC, MRI, t-tau) in a patient with suspected CJD should prompt further investigation.

- Although may still be prion disease.

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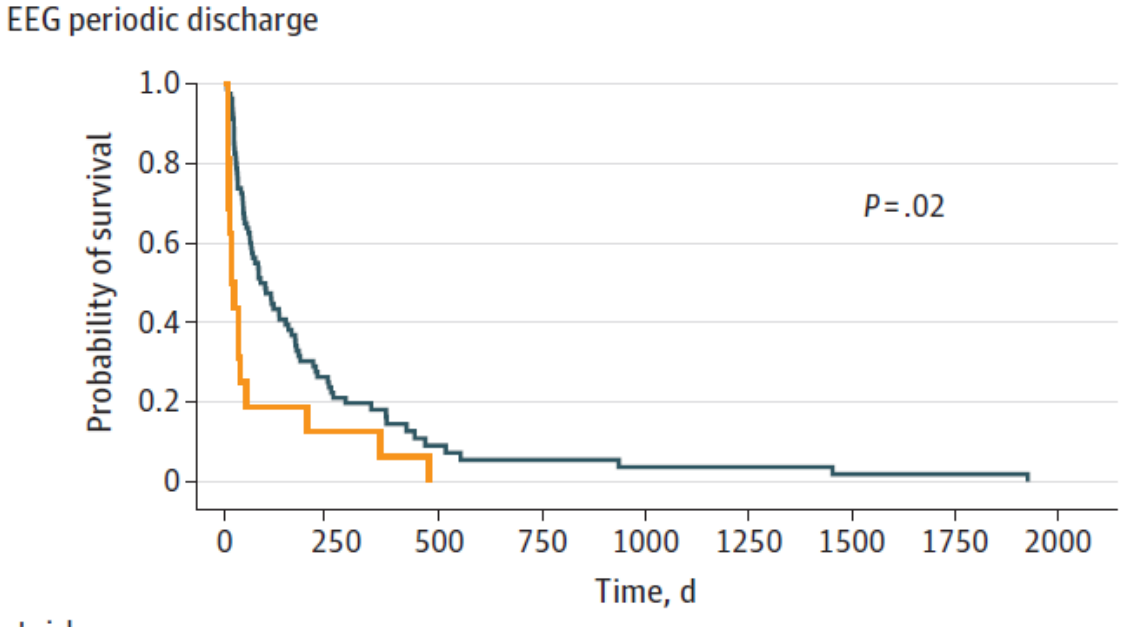
Informing Outcomes

Predicting survival in patients with prion disease.

Select biomarkers may inform rates of progression / survival.



- Periodic discharges at first evaluation associated with shorter mean survival.
  - Present: 104.5 [95%CI, 25.7-183.2] days
  - Absent: 211.4 [95%CI, 152.7-309.8] days

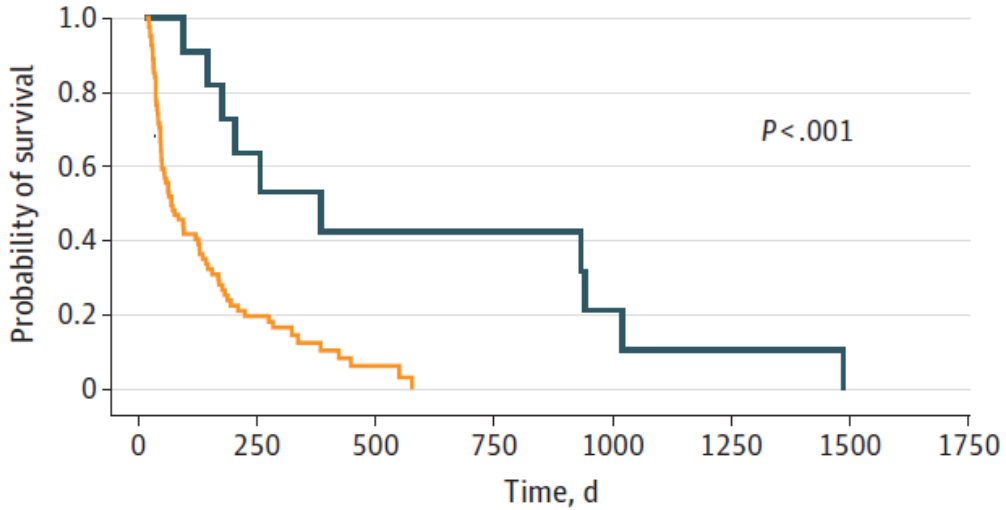
Shir et al. 2022—JAMA Open

Informing Outcomes

Predicting survival in patients with prion disease.

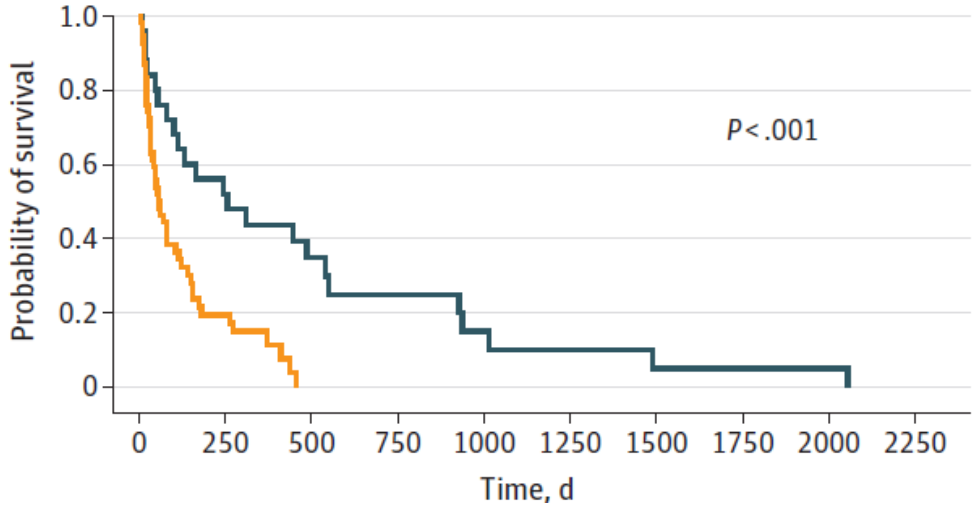
Select biomarkers may inform rates of progression / survival.

CSF T-tau levels



- T-tau >1149 pg/mL = 133 [95%CI, 97.3-168.6] days
- T-tau < 1149 pg/mL = 579.6 [95%CI, 274.9-884.2] days

CSF protein 14-3-3 levels



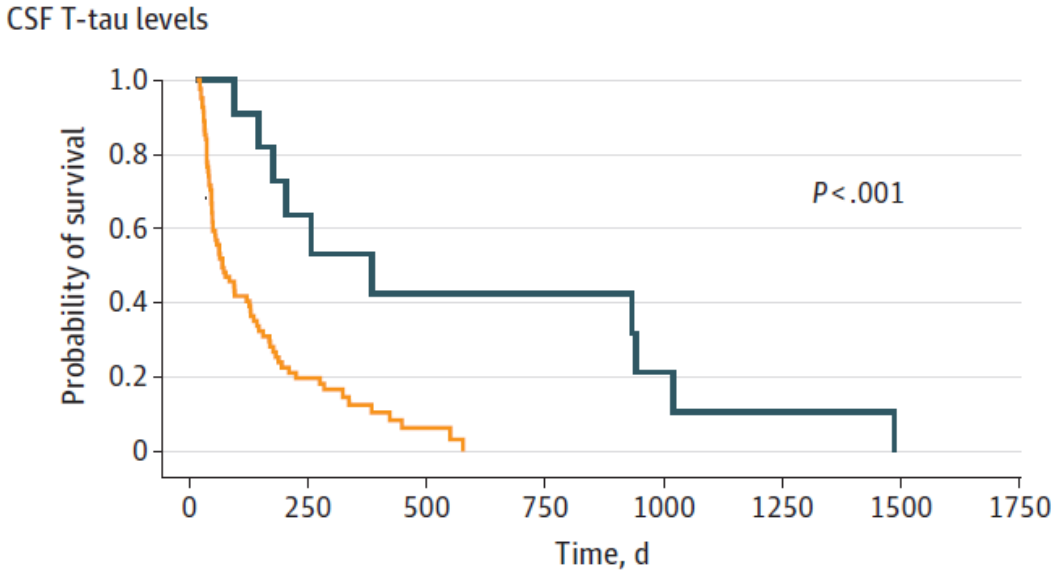
- Elevated = 124.5 [95%CI, 85.8-163.2] days
- Not elevated = 478.9 [95%CI, 253.8-704.0] days

Shir et al. 2022—JAMA Open

Informing Outcomes

Predicting survival in patients with prion disease.

Select biomarkers may inform rates of progression / survival.



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- T-tau < 1149 pg/mL = 579.6 [95%CI, 274.9-884.2] days

- Elevated CSF t-tau
  - Associated with faster declines in patients with symptomatic AD.
  - Reduced survival in patients with DLB.

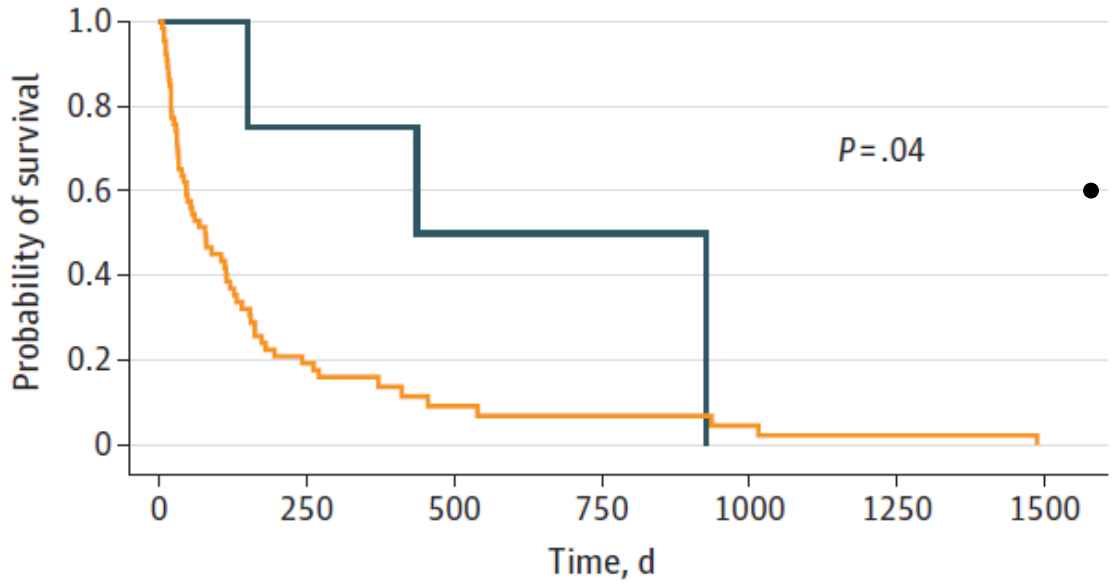
Snider et al. 2009—Arch Neurol; Bostrom et al 2009—Dement Geriatr Cogn Disord

Informing Outcomes

Predicting survival in patients with prion disease.

Select biomarkers may inform rates of progression / survival.

RT-QuIC



- Negative or indeterminate RT-QuIC associated with longer mean survival.
  - Negative: 610.5 [95%CI, 211.7-1009.3] days
  - Positive: 186.9 [95%CI, 135.5-298.9] days

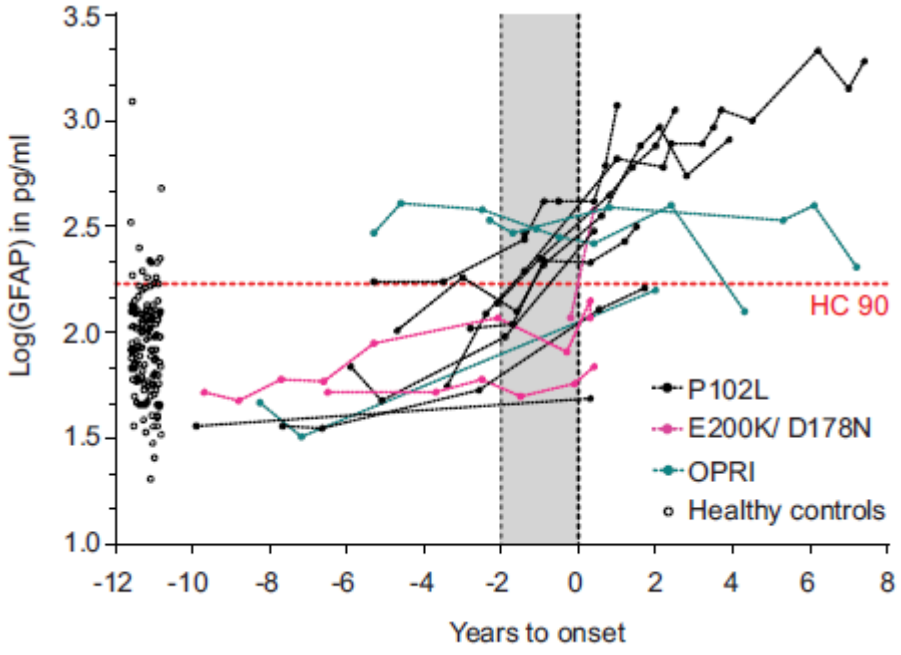
Shir et al. 2022—JAMA Open

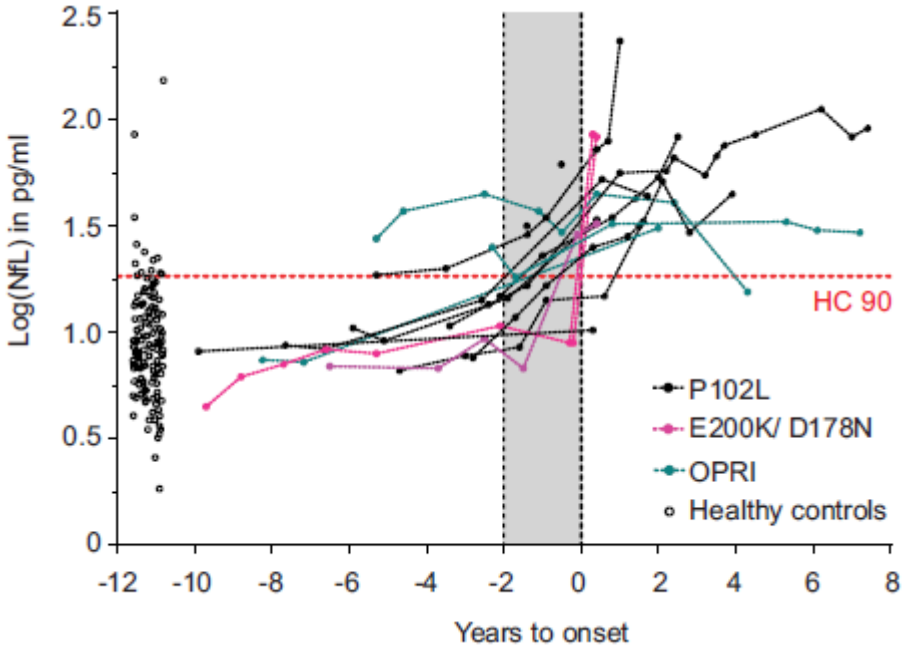
Informing Outcomes

Predicting survival in patients with prion disease.

Select biomarkers may inform rates of progression / survival.

- Plasma NfL and GFAP begin to rise within 2 years of symptom onset in patients with familial prion disease.



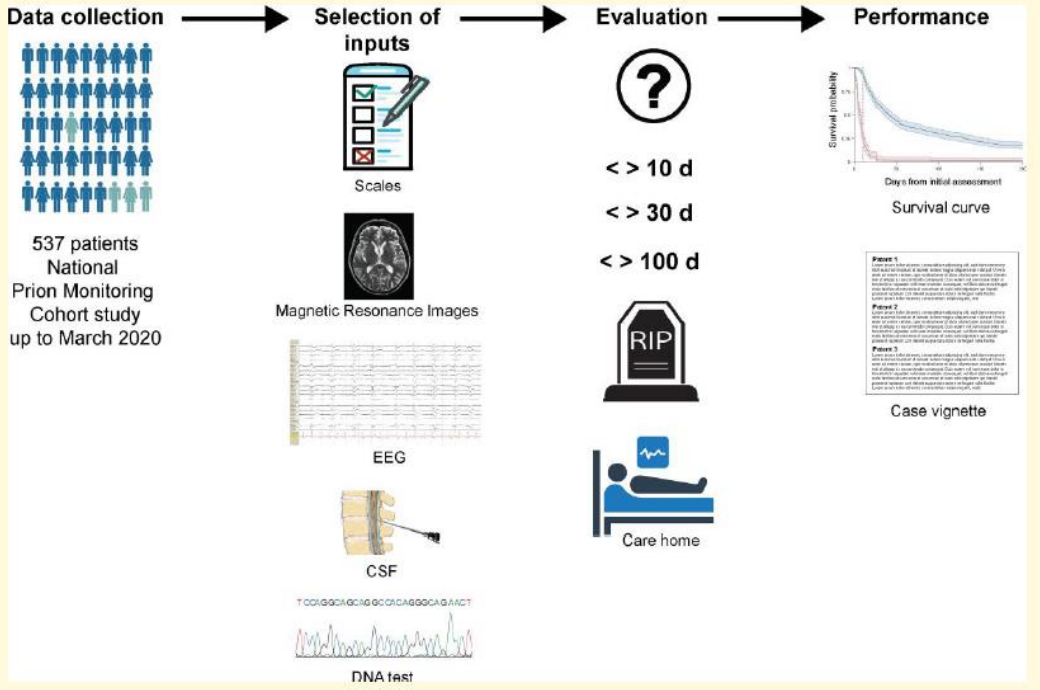


Mok et al. 2023—Brain

Informing Outcomes

Predicting survival in patients with prion disease.

Integrated models may offer further insight into the factors that influence survival.



Llorens et al. 2020—Alz&Dement; Nihat et al. 2022—Brain Communications

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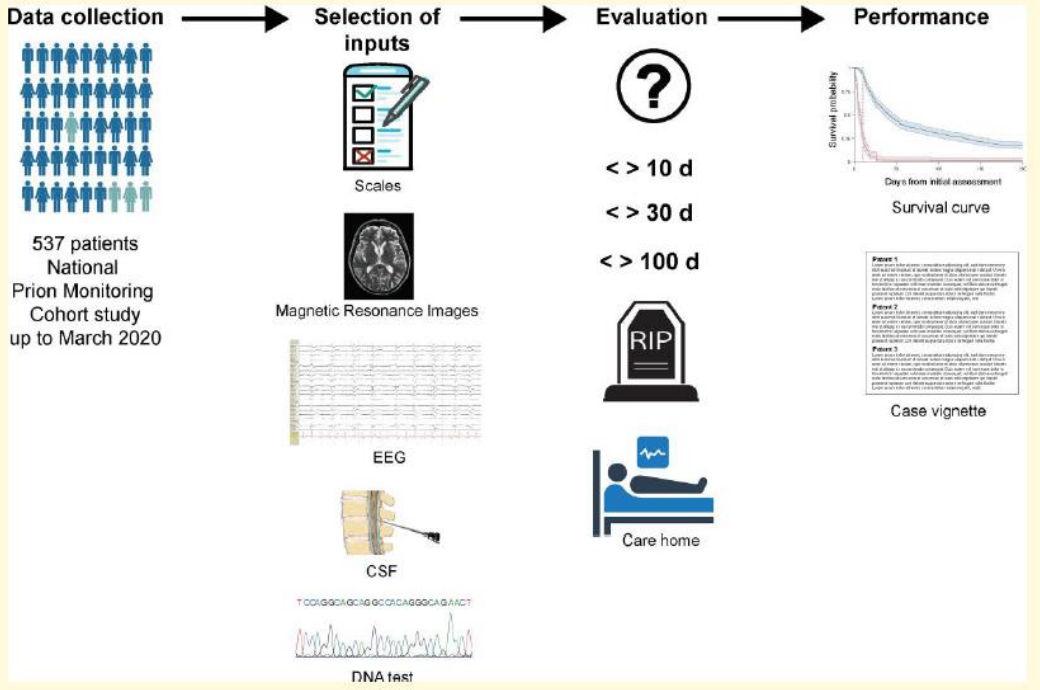

Model containing **age**, **sex**, **codon 129 genotype**, and **CSF t-tau** performed best at predicting 6-month survival.

- AUC 0.686 [95%CI: 0.665-0.707]

Llorens et al. 2020—Alz&Dement; Nihat et al. 2022—Brain Communications

Informing Outcomes

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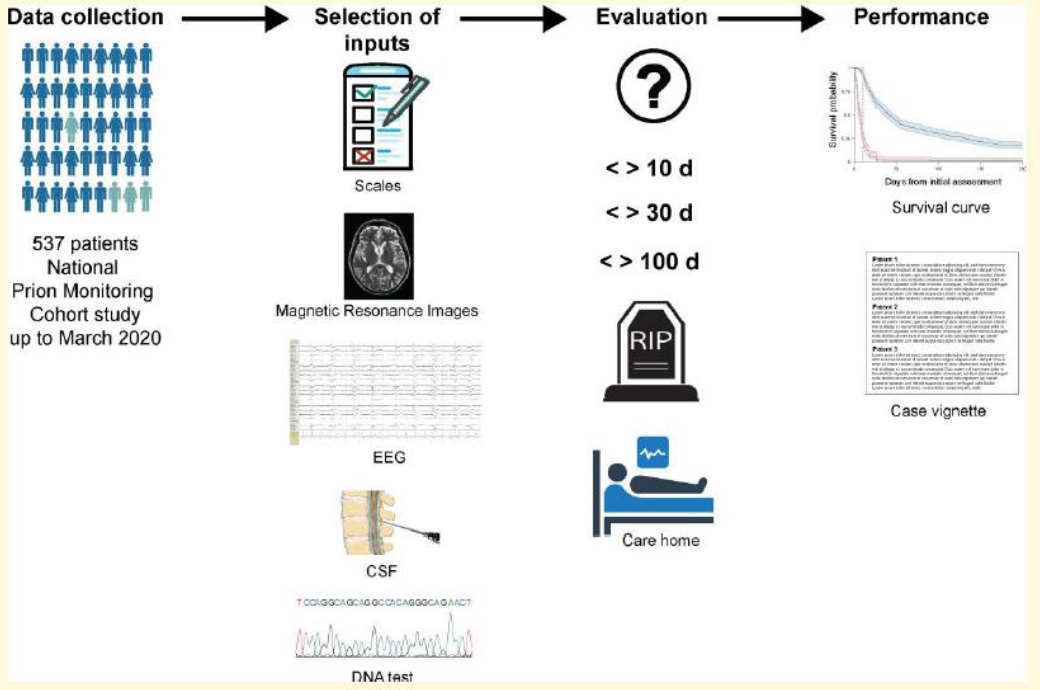


Models containing **sex**, **days since symptom onset**, **codon 129 genotype**, **MRI abnormalities**, **functional scales** and **clinical measures** effectively predicted survival.

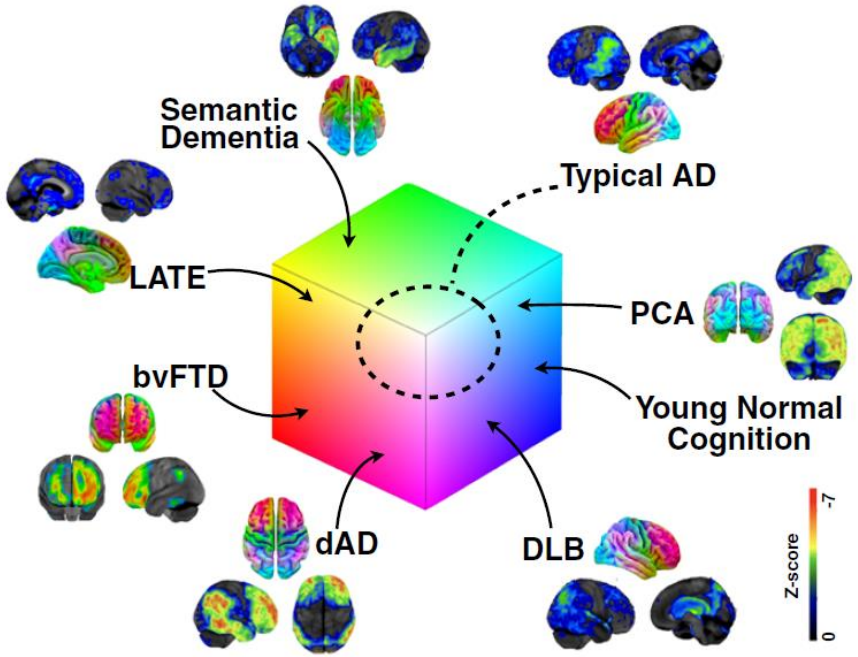
- AUC >0.90

Llorens et al. 2020—Alz&Dement; **Nihat et al. 2022—Brain Communications**

Informing Outcomes

Predicting survival in patients with prion disease.

Patterns of network degeneration may serve as intermediate phenotypes between molecular pathophysiology and clinical manifestations in AD/ADRD.



Data-driven metabolic clusters generated from FDG-PET images (n=40 patients).

Jones et al. 2022—Nature Comm.; Vogel et al. 2023—Nature Rev Neurosci

Informing Outcomes

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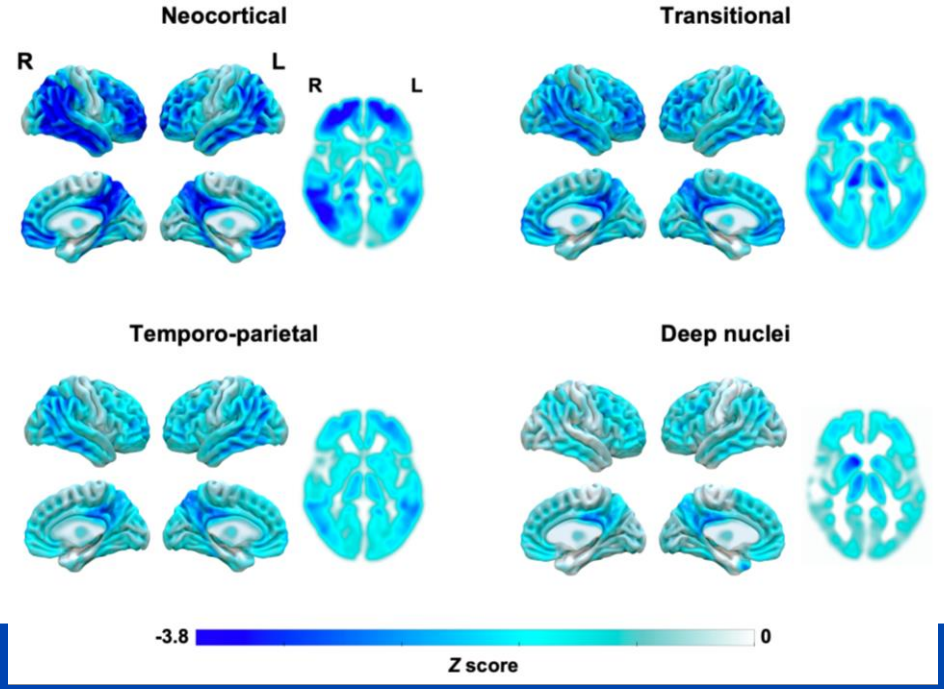

Data-driven metabolic clusters generated from FDG-PET images (n=40 patients).

- Generated **four distinct patterns of metabolic activity**, reflecting patterns of whole-brain hypometabolism relative to age- and sex-matched cognitively normal controls.

Informing Outcomes

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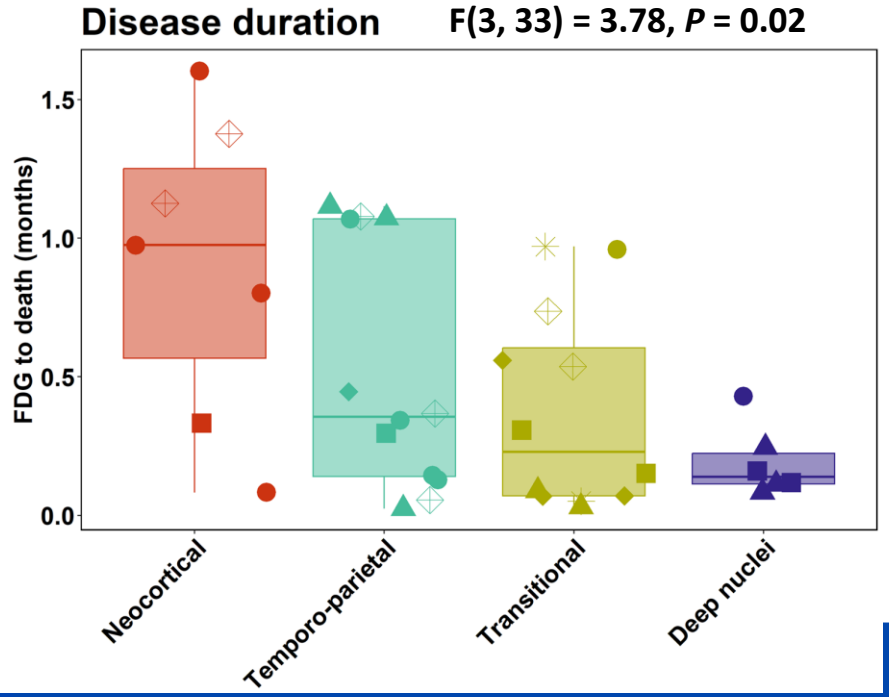
Patterns of network degeneration may serve as intermediate phenotypes between molecular pathophysiology and clinical manifestations in AD/ADRD.



Data-driven patterns of metabolism associated with survival.

- Patients with disproportionate involvement of deep nuclei (vs neocortical structures) experienced shorter disease duration.

Informing Outcomes

Predicting survival in patients with prion disease.

Patterns of network degeneration may serve as intermediate phenotypes between molecular pathophysiology and clinical manifestations in AD/ADRD.

FDG-PET may identify **common pathways** (i.e., neural networks) that influence survival in patients with neurodegenerative disease.

- Potential to inform clinical care/counseling
- Monitor progress/response in clinical trials of putative disease-modifying therapies

Data-driven patterns of metabolism associated with survival.

- Patients with disproportionate involvement of deep nuclei (vs neocortical structures) experienced shorter disease duration.

Summary

Clinical Applications of Biomarkers in Prion Disease

Advances in disease-specific biomarkers have revolutionized the clinical evaluation of patients with suspected prion disease.

- Supporting accurate diagnoses of prion disease.

Summary

Clinical Applications of Biomarkers in Prion Disease

Advances in disease-specific biomarkers have revolutionized the clinical evaluation of patients with suspected prion disease.

Other diseases may be mistaken for prion disease (CJD mimics). Selected clinical features and diagnostic tests can recognize mimics early in the symptomatic course.

- Supporting early intervention of patients with potentially treatment-responsive diseases.

Summary

Clinical Applications of Biomarkers in Prion Disease

Advances in disease-specific biomarkers have revolutionized the clinical evaluation of patients with suspected prion disease.

Other diseases may be mistaken for prion disease (CJD mimics). Selected clinical features and diagnostic tests can recognize mimics early in the symptomatic course.

Selected biomarkers associate with survival in patients with prion disease.

- May inform clinical care/counseling and disease-specific mechanisms that influence progression.
- May serve as surrogate outcomes in clinical trials of putative disease-modifying therapies.
- Results validated in patients with prion disease may be translated to patients with other neurodegenerative diseases (AD/ADRD).

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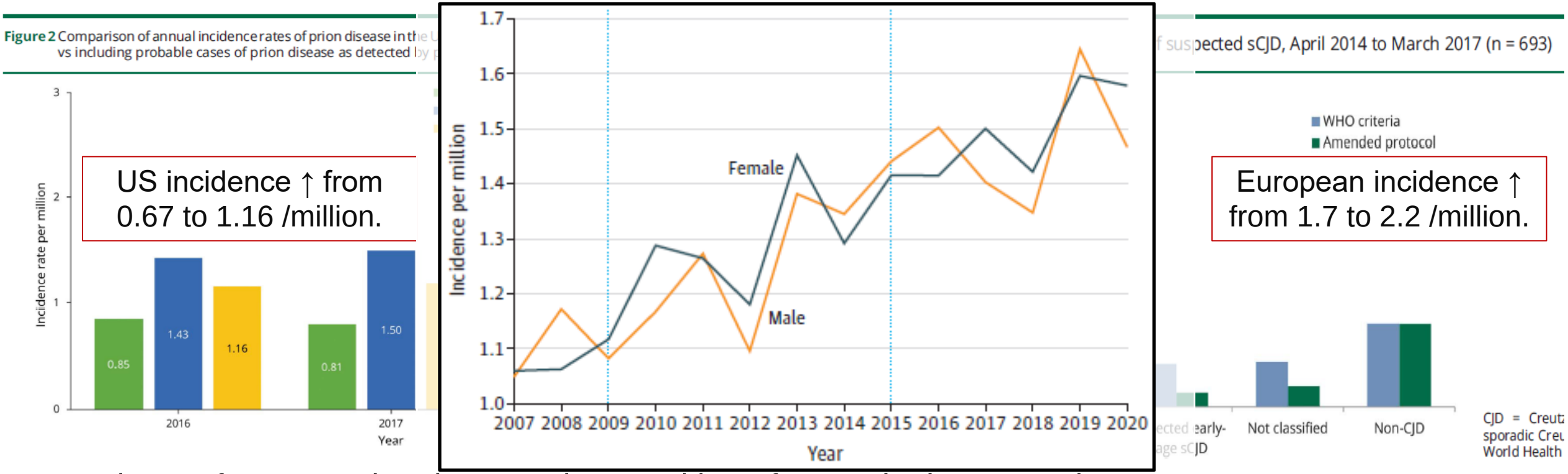
Biomarkers in Prion Disease

CSF

CSF: Real-Time Quaking-Induced Conversion (RT-QuIC) assay



- Advent of RT-QuIC has improved recognition of cases in the US and Europe.

Rhoads et al. 2020—Neurology; Hermann *et al*. 2018—Neurology; Crane et al. 2024—JAMA Neurology

Disclosures

Gregory S Day

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Speakers Bureau

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Stock holdings

ANI Pharmaceuticals