

National Prion Disease Pathology Surveillance Center  
Departments of Pathology and Neurology



SCHOOL OF MEDICINE

# **Mandate and New Programs National Prion Disease Pathology Surveillance Center**

Presented by Jiri G. Safar  
July 16, 2017

# ORGANIZATIONAL STRUCTURE

## NATIONAL PRION DISEASE PATHOLOGY SURVEILLANCE CENTER

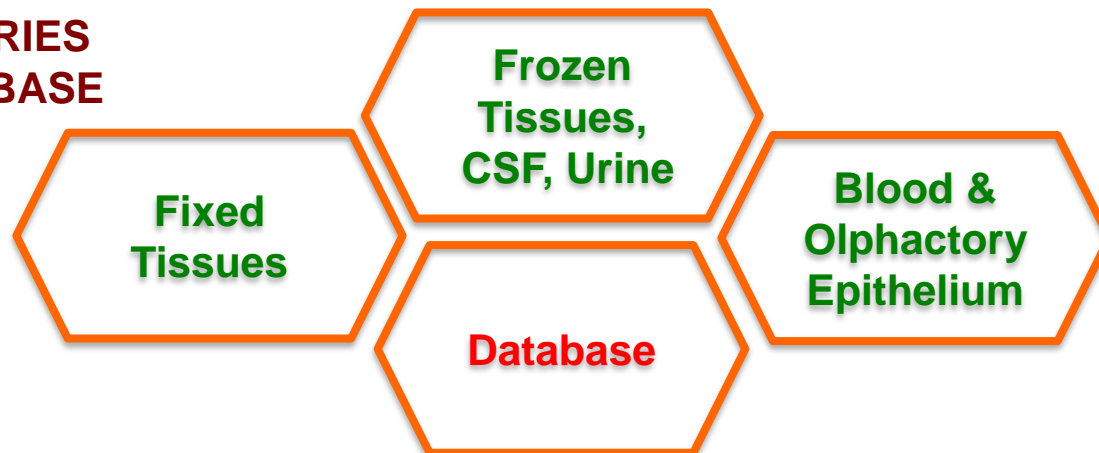
<b>Director:</b>	<b>Jiri Safar, Scientific Leadership, Program Oversight</b>
<b>Co-Directors:</b>	<b>Mark Cohen, Diagnostic and Research Neuropathology</b> <b>Brian Appleby, Clinical Reviews and Advocacy</b>
<b>Clinical Lab Director:</b>	<b>Dan Rhoads, Laboratory Diagnostics and Compliance</b>
<b>Associate Director:</b>	<b>Wenquan Zou, Prion Strain Typing</b>
<b>Other Program Faculty:</b>	<b>Lan Zhou, Genetic Diagnostics; Marta Couce, Neuropathology</b>

### Advisory Board:

**Chair - Cliff Harding, Chair of Pathology**  
**Anthony Furlan, Chair of Neurology**  
**Mark Chance, Vice Dean for Research**  
**Jonathan Haines, Chair of Epidemiology & Biostatistics**

**James Ironside, Director and Professor, CJD Center, University of Edinburgh, UK**  
**Debbie Yobs, President, CJD Foundation**  
**Bernardino Ghetti, Distinguished Professor, Indiana University**

### REPOSITORIES AND DATABASE



# Center Mandate

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- **Perform autopsies of all atypical dementias in US suspected of prion disease to establish definite diagnosis and accumulate autopsy-verified epidemiological data for CDC**
- **Determine the origin of prion disease — sporadic, familial, iatrogenic, or zoonotic — using molecular differentiation of prion strains in the brain tissue and sequencing of *PRNP* gene**
- **In collaboration with CDC, identify epidemiological foci and monitor changes in the incidence and prevalence of human prion disease**
- **Monitor the spectrum of human prions in the US**
- **Develop and validate new rapid methods for detection and differentiation for human prions**
- **Serve as a Reference Laboratory for human prion disease in US**
- **Maintain repository fully characterized human prion tissues and body fluids for future research**

# Origin and Classification of Human Prion Diseases

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## Manifestation (Frequency)

## Diseases

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### 1. Sporadic (90%)

Creutzfeldt-Jakob disease (CJD), familial insomnia (sFI), Variably Protease-Sensitive Prionopathy (VPSPr)  
age-adjusted incidence is 4-6 cases/million in age 65-79 worldwide

### 2. Inherited (10%)

Genetic forms of CJD, Gerstmann-Sträussler-Scheinker disease, and fatal familial insomnia (FFI)

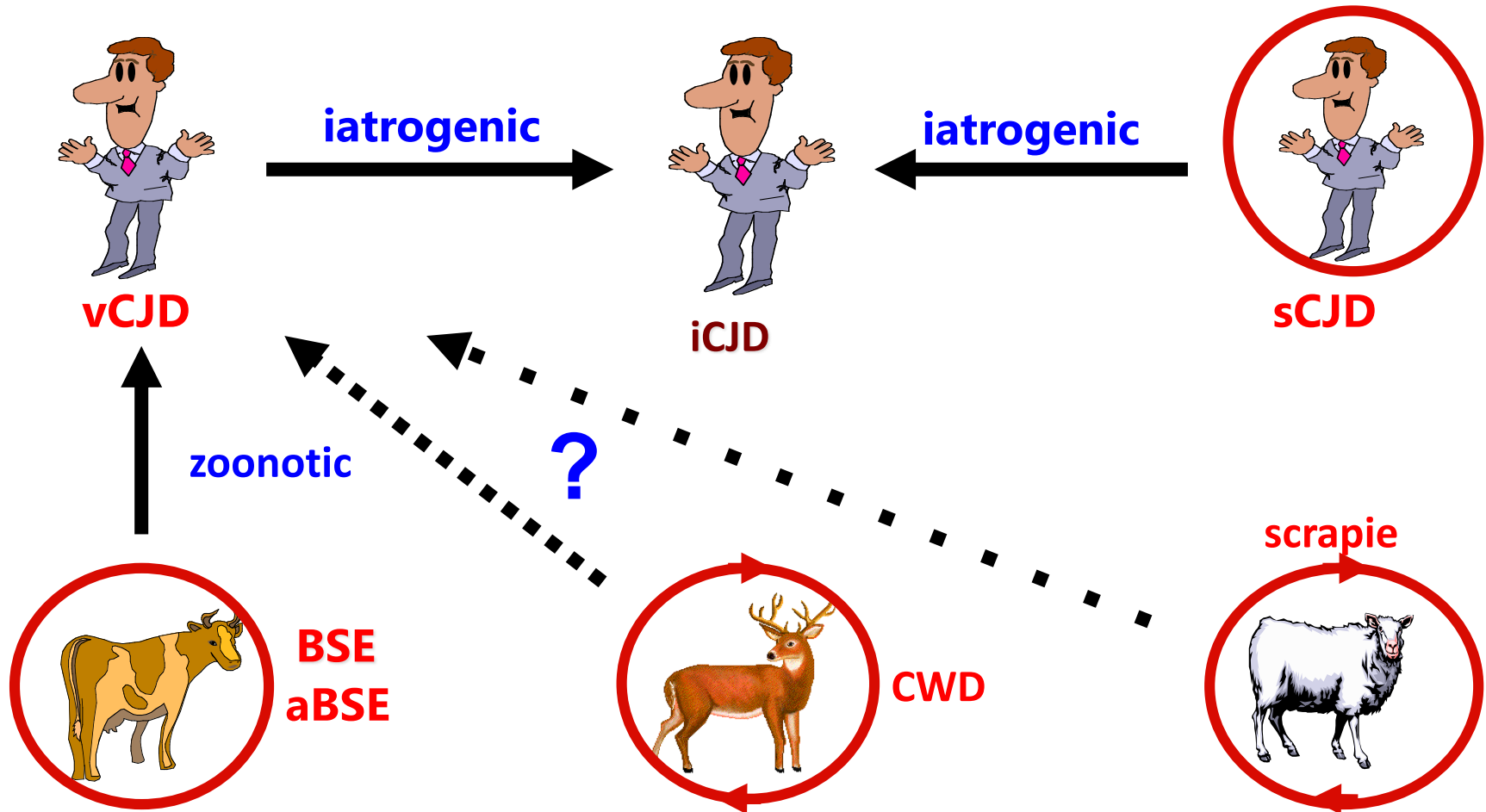
### 3. Infectious (<1%)

Kuru among New Guinea natives transmitted by cannibalism  
Iatrogenic CJD caused by growth hormone derived from human pituitaries, dura mater and cornea transplants  
Variant CJD caused by BSE prions from contaminated beef

# Variations in Prion Protein Gene Identified by NPDPSC and Linked to Genetic Forms of Human Prion Diseases

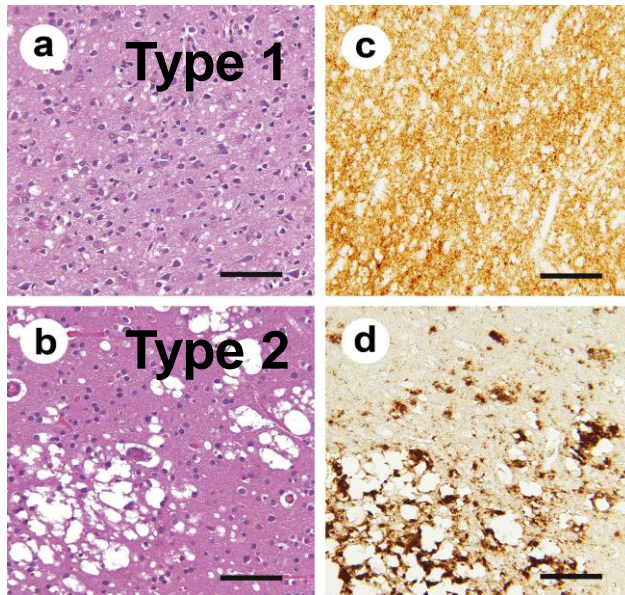
<b>Mutation</b>	<b>Total</b>	<b>Mutation</b>	<b>Total</b>
E200K-129M	220 (12)	H187R-129V	2
Insertions	64	P105S-129V	2
D178N-129M	50 (4)	A224V-129V	1
V210I-129M	45 (1)	E196A-129M	1
P102L-129M	38 (2)	G114V-129M	1
E200K-129V	36 (2)	G94S-129V	1
D178N-129V	24	H187A-129M	1
A117V-129V	19 (1)	N171S-129V	1
T188R-129V	17 (2)	P102L-129V	1
H187R-129M	10	Q160X-129M	1
F198S-129V	10	Q186X-129V	1
V180I-129M	7 (1)	Q217R-129V	1
G54S-129M	5	R148H-129V	1
R208H-129M	5 (1)	S245P-129M	1 (1)
T183A-129M	4	T183A-129V	1
R148H-129M	4	T188A-129V	1 (1)
V203I-129V	4	T188K-129V	1
E200G-129V	3	V180I-129V	1
V203I-129M	3	Q160X	1
A133V-129M	2		

# Continuing Prion Surveillance is Essential for Detection and Prevention of Zoonotic and Iatrogenic Human Prion Diseases



# Prion Center Criteria for Diagnosis and Determination of Origin of Human Prion Diseases

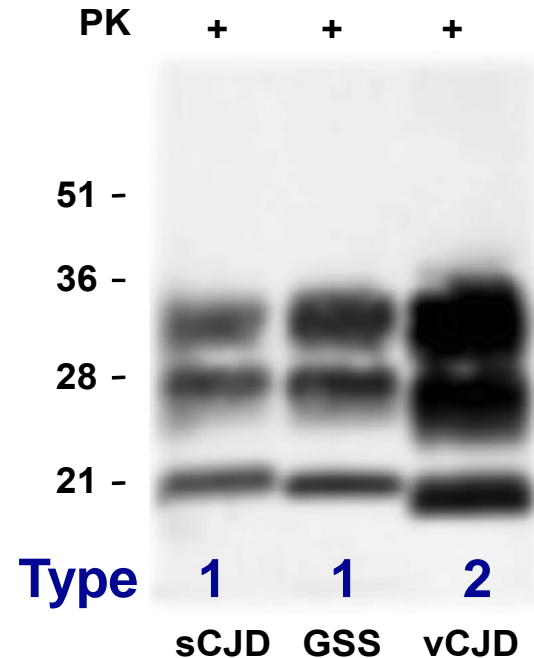
Expert  
Neuropathology



HE

Immunohisto  
chemistry

+ Prion Strain  
Differentiation



Western blots

+ Genetics

sCJD	
Codon 129	rPrPSc Type
MM	1 ↑
	2 ↓
MV	1 ↓
	2
VV	1
	2

PRNP gene  
Sequencing

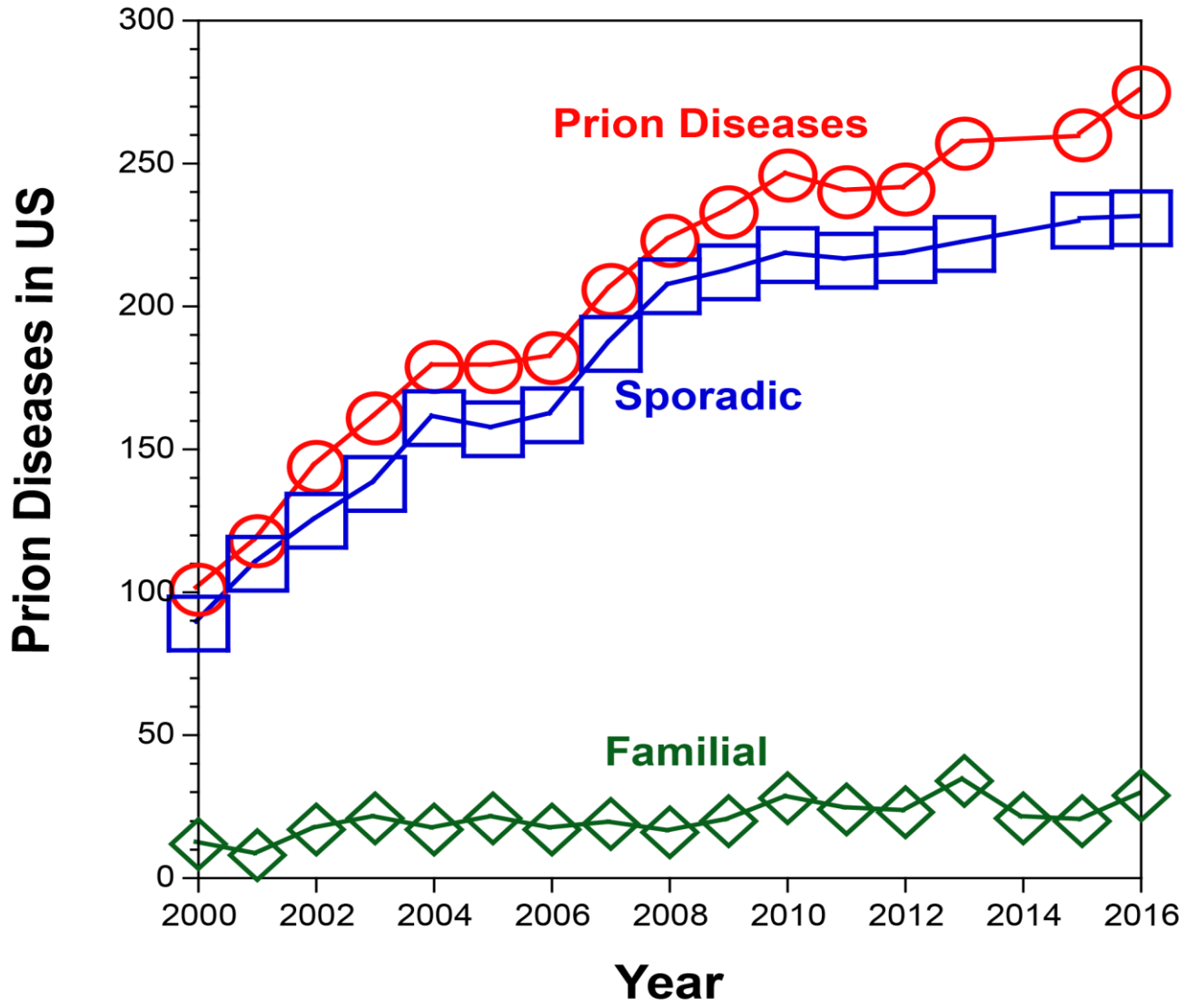
# NATIONAL PRION DISEASE PATHOLOGY SURVEILLANCE CENTER in 2016 numbers

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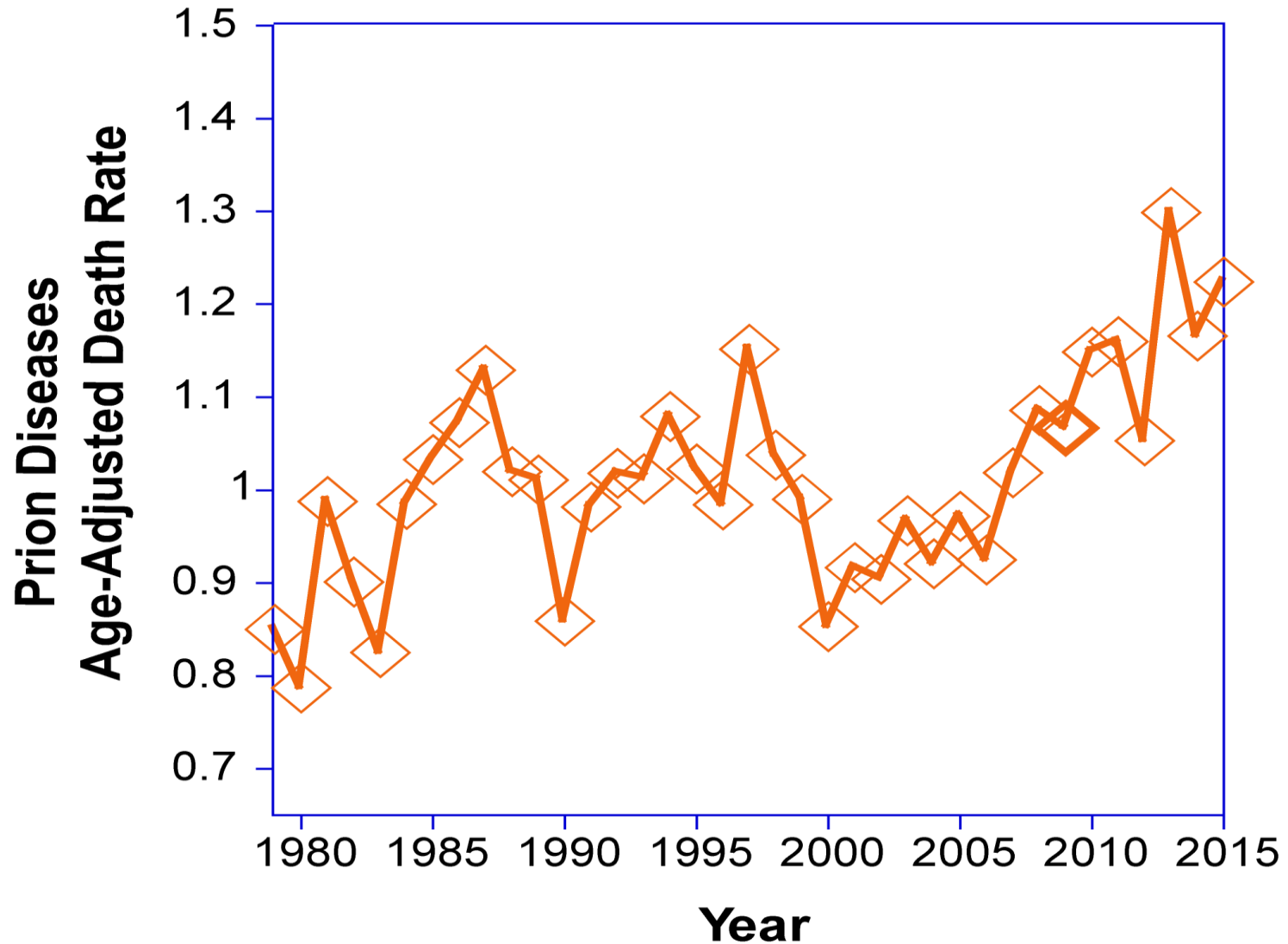
- **5,305** Diagnostic spinal fluid tests
- **332** Genetic tests for prion diseases
- **394** Cases investigated from autopsy referrals to determine the disease origin
- **275** Autopsy-verified prion positive cases
  - **246** Sporadic
  - **29** Genetic
- **11** National and international joint research projects
- **16** Scientific papers which originated at NPDPSC



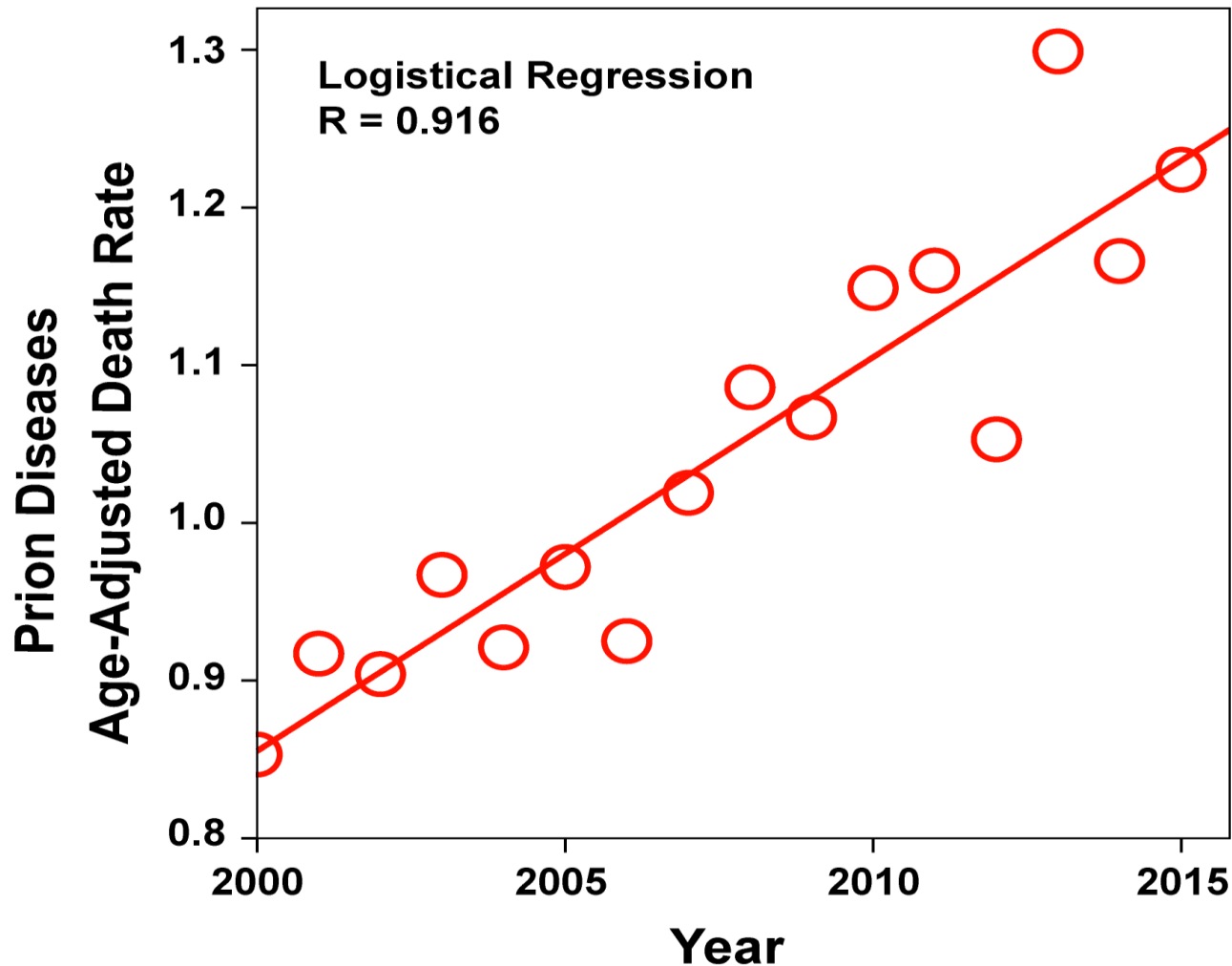
# Occurrence of Autopsy Verified Prion Diseases in the U.S.



# Raising Age-Adjusted Death Rate from Prion Diseases in the U.S.



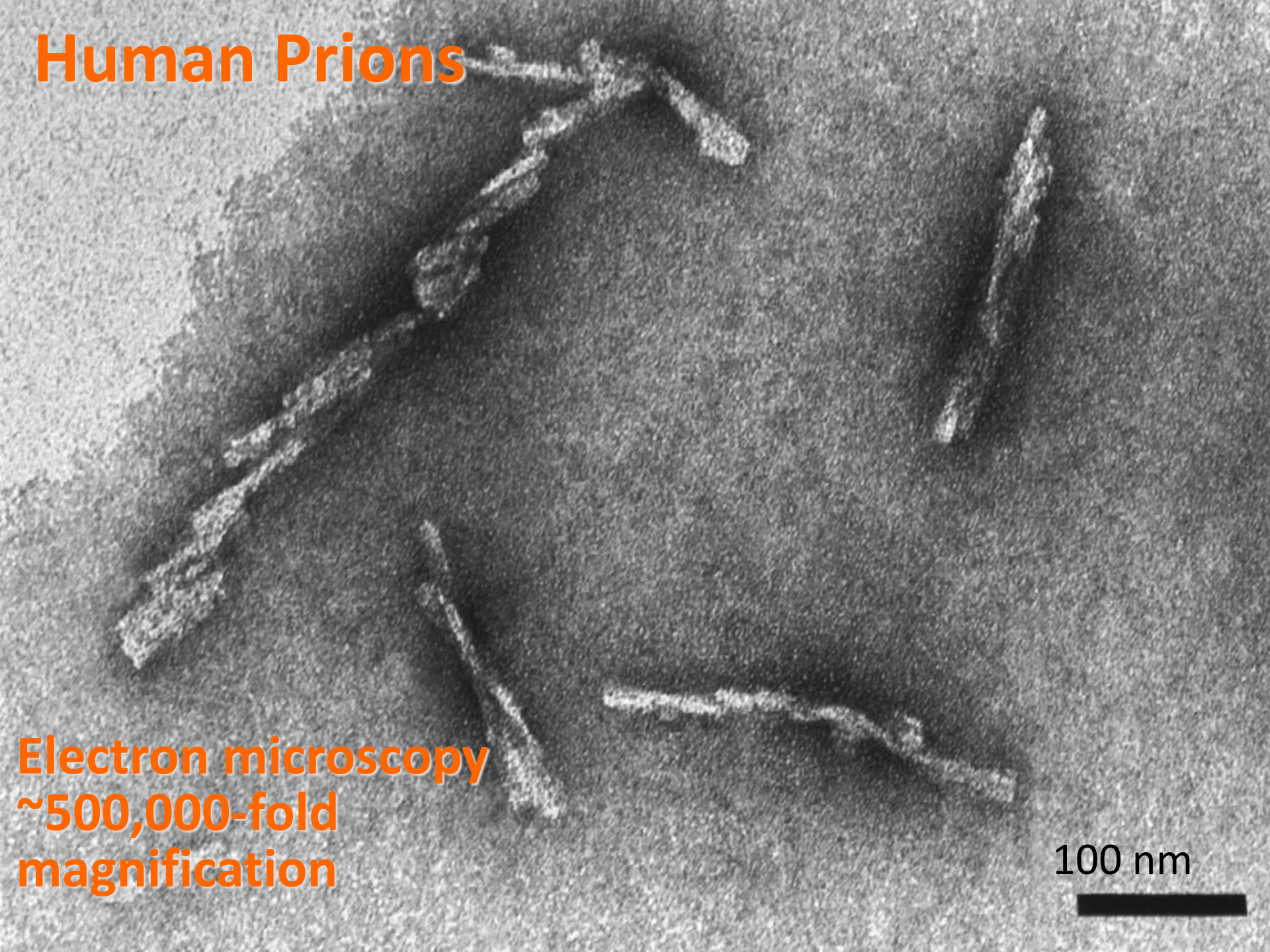
# Why is Prion Diseases Mortality In U.S. Raising?



# Human Prions

Electron microscopy  
~500,000-fold  
magnification

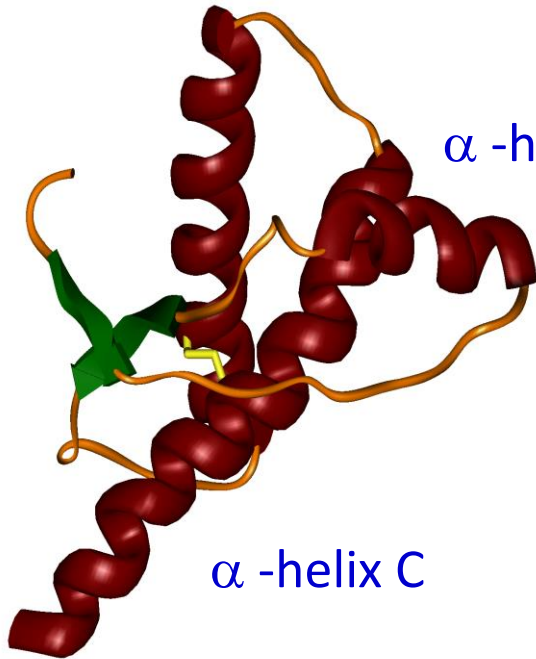
100 nm



# Distinct Conformations of Prion Protein

## Normal Cellular Prion Protein (PrP<sup>C</sup>)

$\alpha$ -helix B

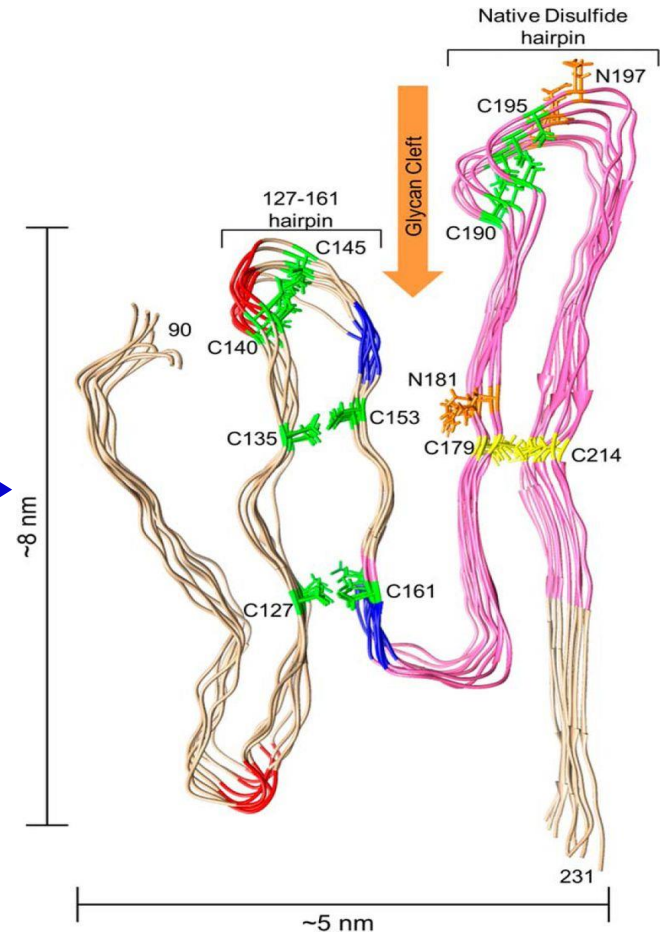


$\alpha$ -helix A

$\alpha$ -helix C

Cofactor

## Pathogenic PrP<sup>Sc</sup>



Safar et al, 1993  
James et al., 1997  
Billeter et al., 1997

Groveman, JBC 2014

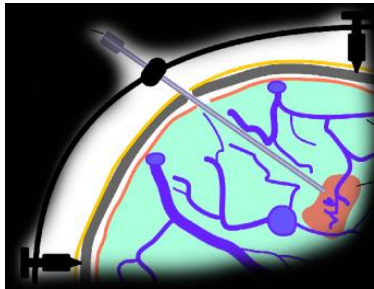
# **Urgent Need for Early Reliable Human Prion Detection and Differentiation in Living Patients**

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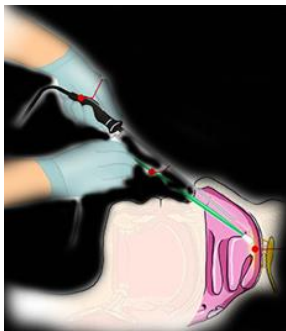
- Human prion diseases are difficult to diagnose in initial stages because they are perhaps the most heterogeneous brain disorders imitating many other diseases**
- Currently, the only way to determine the disease origin is by testing the brain after autopsy**
- There is a growing need for new ultrasensitive tests allowing detection in the earliest stages of diseases**
- Early detection and differentiation of prions is critical first step in the future therapeutic interventions**
- Although MRI may facilitate the diagnosis, the origin of changes is unknown**

# Current and Future Strategies for Early Diagnostic Testing for Human Prions in Living Patients

## Brain Biopsy



## Olfactory mucosa



## Skin ?



## CSF



# Superior Diagnostic Performance of Second Generation CSF RT QuIC at NPDPSC

## Retrospective cohort

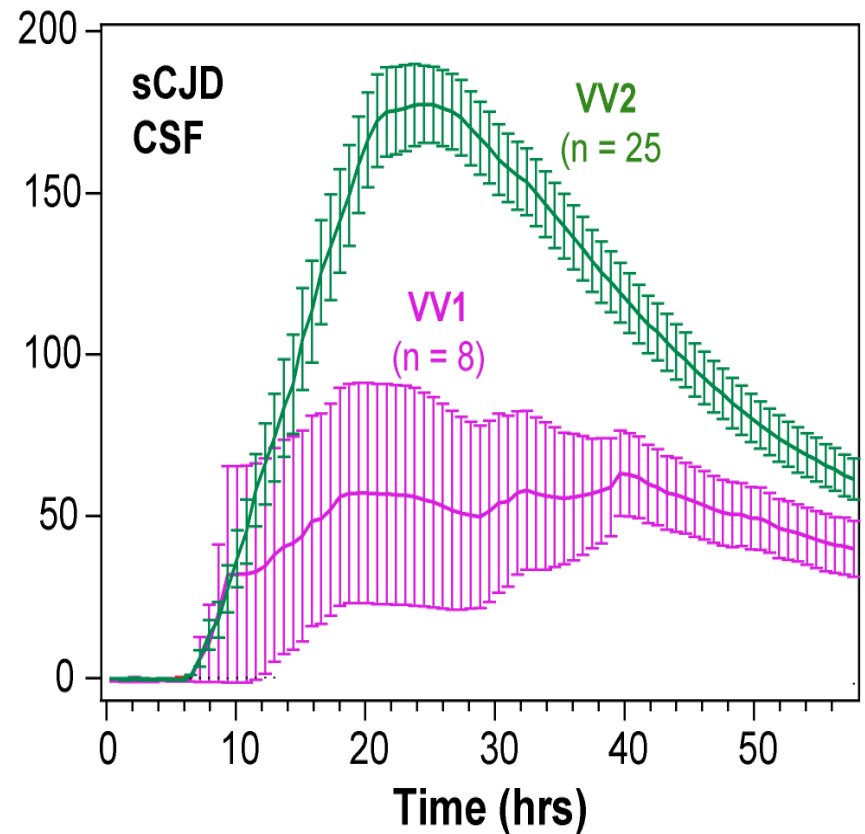
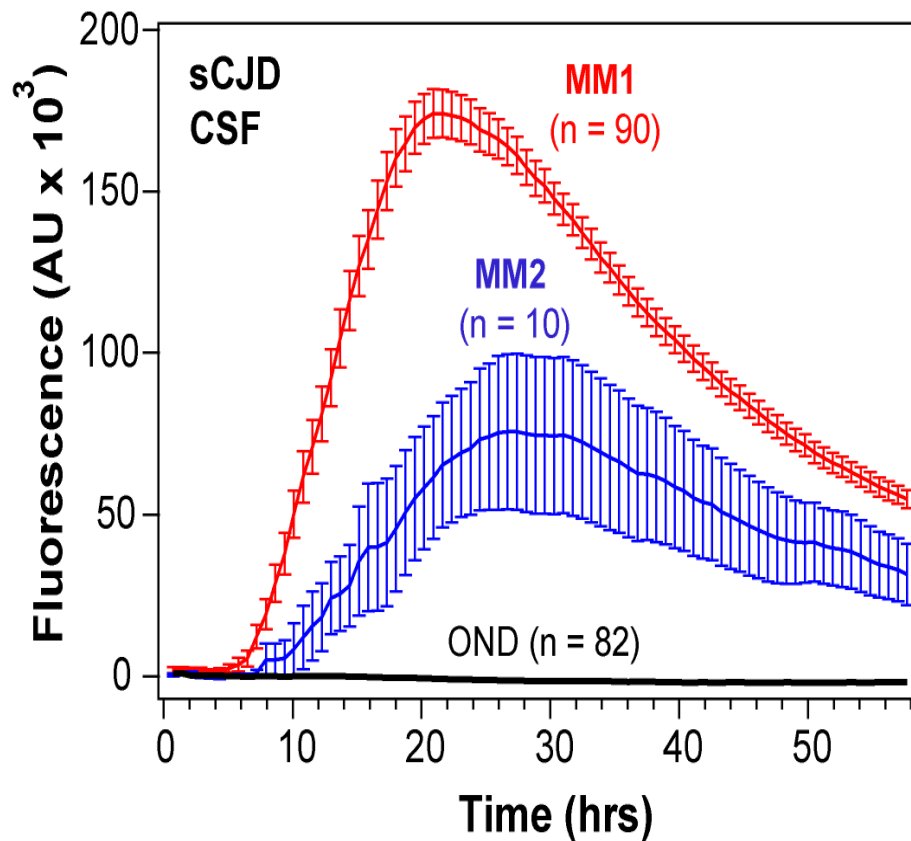
Neuropathology (n)	Prion Positive (n)	Sporadic CJD (n)	Genetic CJD (n)
193	126	111	15
<b>RT QuIC</b>			
<b>Dx Specificity (%)</b>	<b>98.5</b>	<b>98.5</b>	<b>98.5</b>
<b>Dx Sensitivity (%)</b>	<b>92.1</b>	<b>91.9</b>	<b>93.3</b>

## Prospective cohort

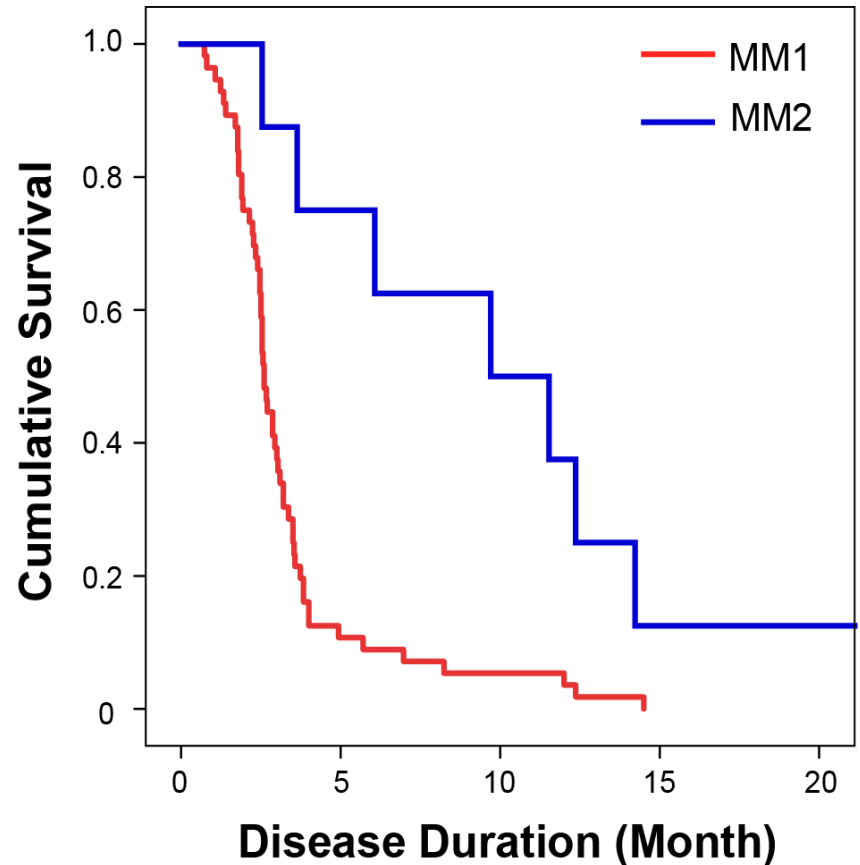
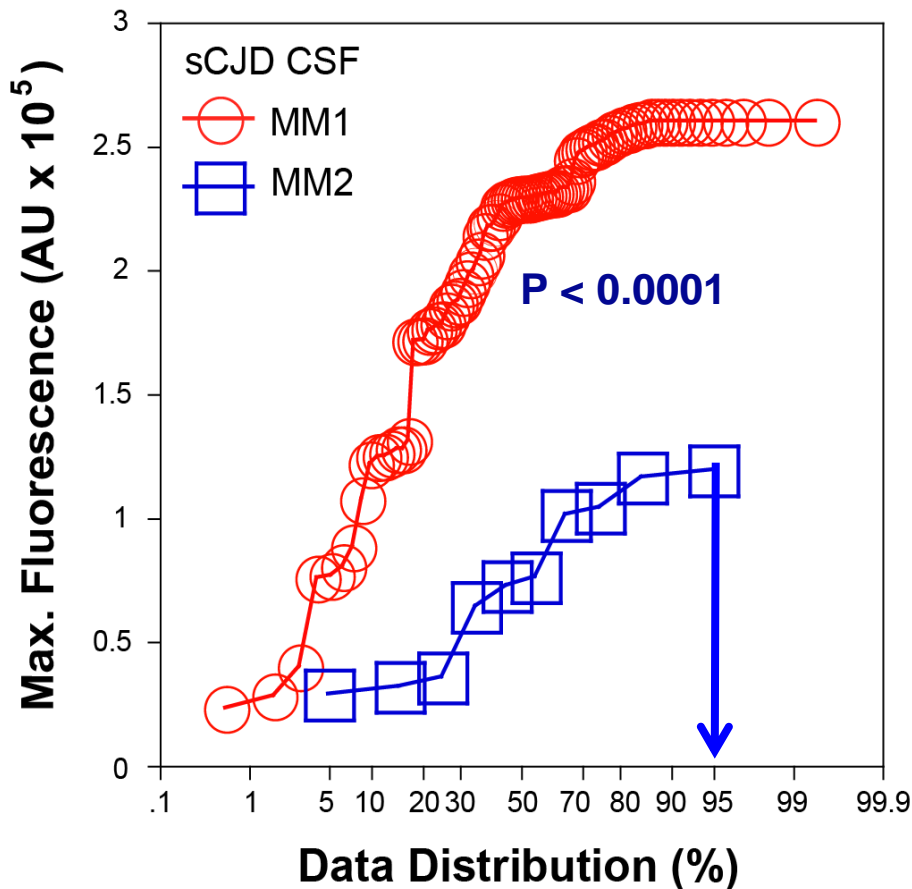
Neuropathology (n)	Prion Positive (n)	Sporadic CJD (n)	Genetic CJD (n)
79	65	63	2
<b>RT QuIC</b>			
<b>Dx Specificity (%)</b>	<b>100</b>	<b>100</b>	<b>100</b>
<b>Dx Sensitivity (%)</b>	<b>94</b>	<b>94.7</b>	<b>100</b>



# Ultrasensitive Detection and Differentiation of Distinct sCJD Prions in CSF of Living Patients with Second Generation RT QuIC



# Diagnostic and Prognostic Value of Ultrasensitive Second Generation CSF RT QuIC

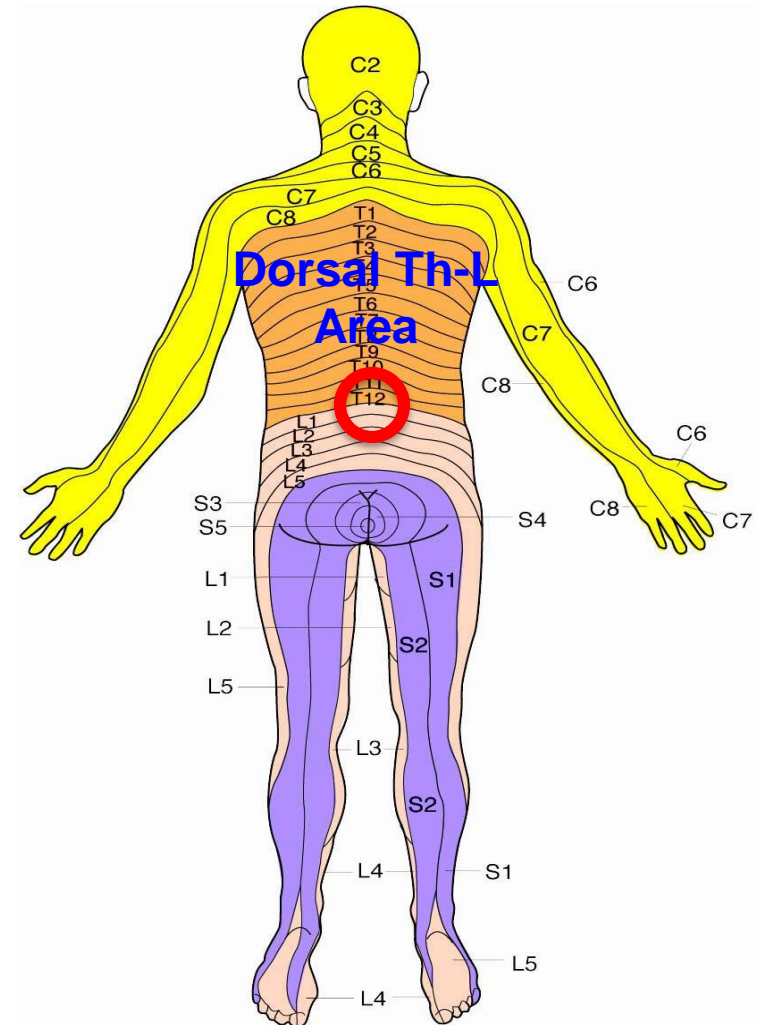
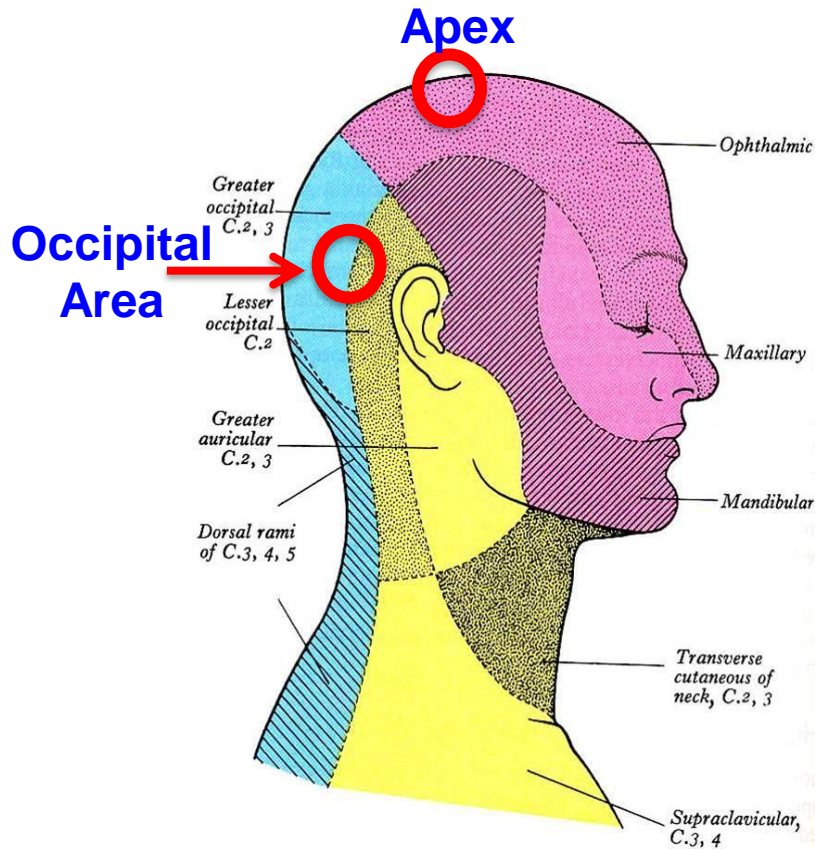


# Diagnostic and Prognostic Performance of Second Generation CSF RT QuIC

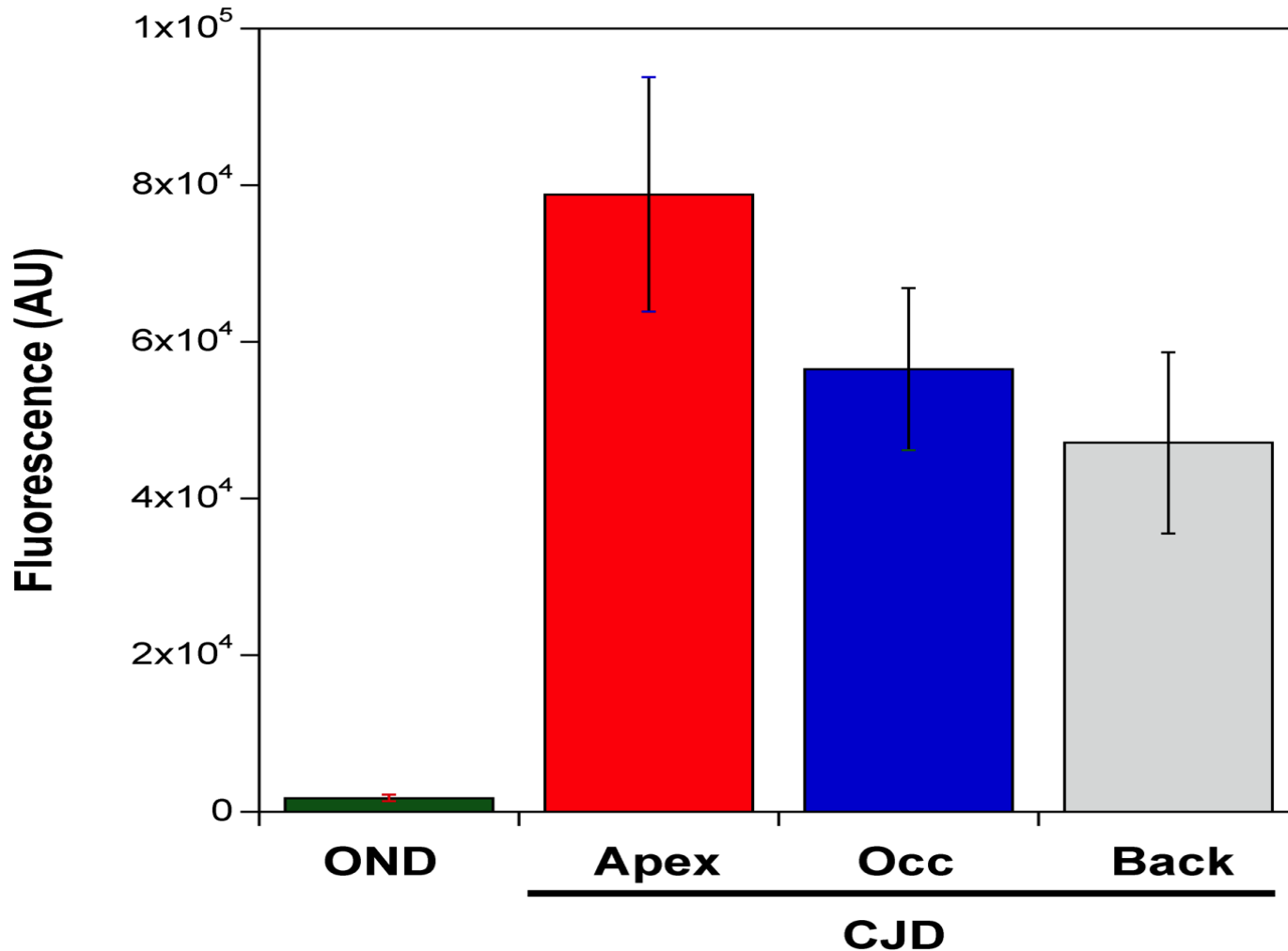
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- In autopsy-validated retrospective cohort, the diagnostic specificity of CSF RT QuIC was 98.5% and sensitivity 92-93%.
- In the continuing autopsy-validated prospective study, the diagnostic specificity thus far is 100% and sensitivity 94-95%, likely reflecting a higher proportion of cases with more aggressive disease.
- The CSF RT QuIC and genotyping performed together allow to correctly differentiate the sCJD MM1 from sCJD MM2 with 94% accuracy, and sCJD VV1 from sCJD VV2 type with 93% reliability.

# Skin Collection Protocols and Areas Tested for Prions with Second Generation RT QuIC



# Relative Levels of Human Skin Prions in Different Anatomical Areas

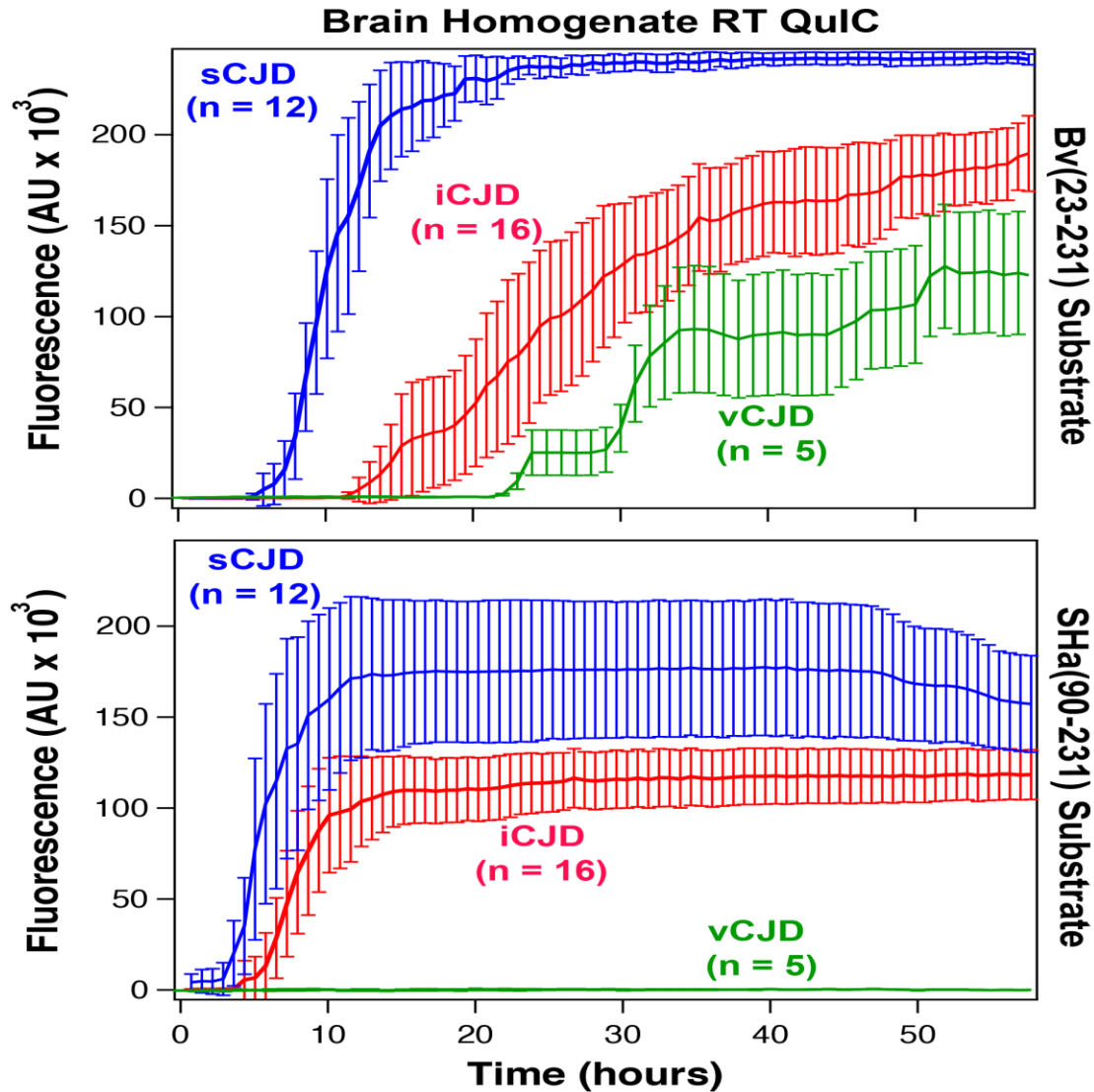


# Next Directions for Prion Diagnostics

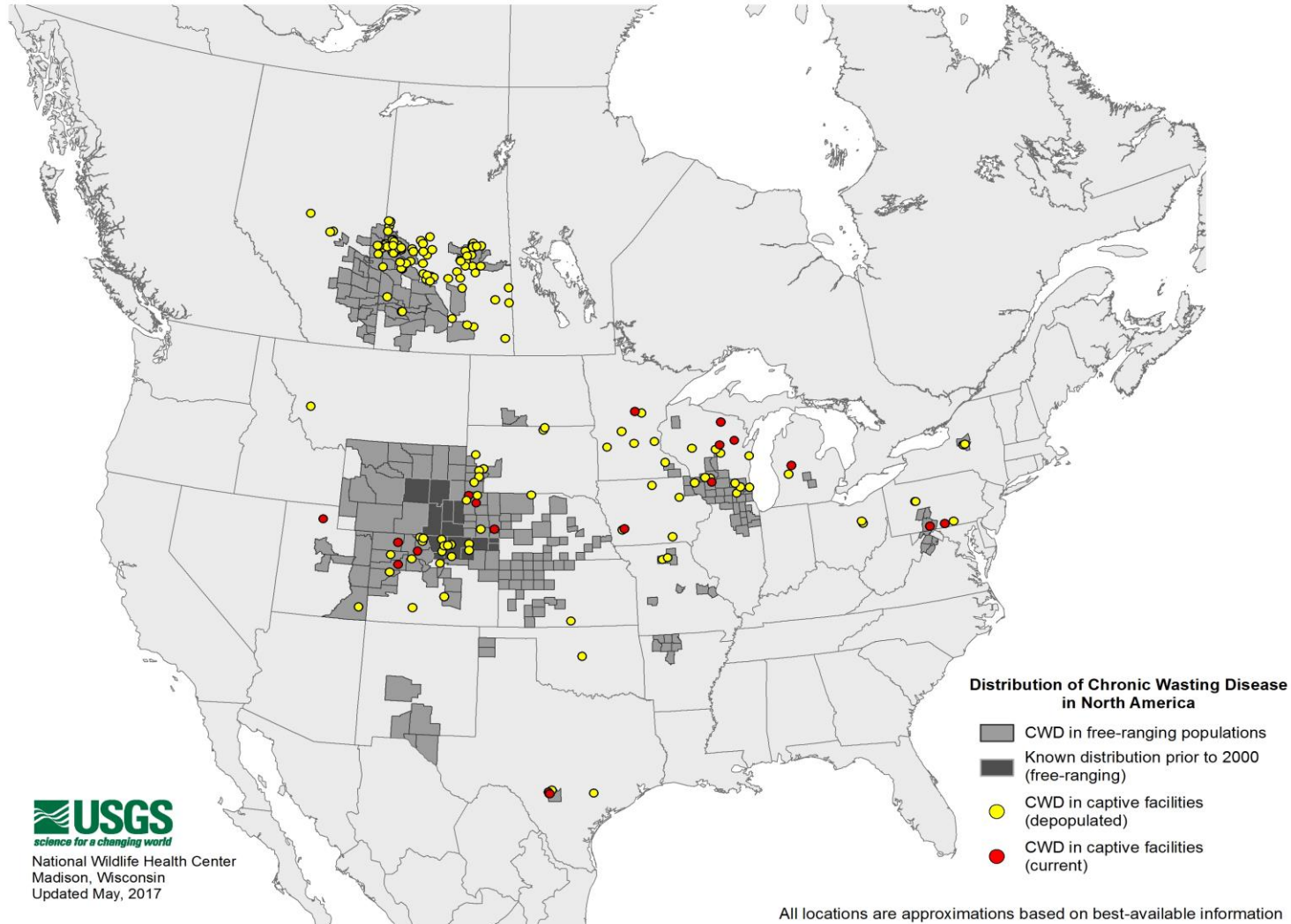
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- **Ongoing study will validate the CSF RT QuIC for diagnosis of atypical and slowly progressive prion diseases, and for presymptomatic prion carriers.**
- **Alternative PrP substrates in CSF RT QuIC should facilitate early detection and differentiation of important human prion strains including vCJD, iCJD, gCJD, VPSP<sub>r</sub>, and atypical human prions, critical for future therapeutic interventions.**
- **Ongoing prospective skin and olfactory mucosa study will determine diagnostic sensitivity and specificity of RT QuIC and extend the diagnostic applications to easily accessible tissues and body fluids.**

# New Strategies to Determine Origin of Prion Diseases with Brain Tissue RT QuIC



# Spread of Chronic Wasting Disease (CWD) of Deer and Elk in the U.S.





# Implications of CWD Epidemic in Wild Ranging Deer and Elk for Human Prion Surveillance

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- Latest laboratory experimental evidence indicate that tissues from CWD-infected deer and elk have the potential to infect humans.
- CWD prions are highly transmissible through contact, saliva, urine, and contaminated environment, including soil.
- The potentially acquired CWD in humans may exhibit phenotypes closely mimicking those of classic sporadic CJDs.
- Efficient transmission of CWD to transgenic mice will be a good model for identification of acquired CWD in humans.
- There is likely a barrier for deer- and elk-to-human transmission but it is prion strain dependent and CWD prions are highly unstable and mutable

# Next Imperative Goals and Questions for the NPDPSC and CDC

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- **Urgent need for development of test that would detect potential CWD in man and differentiate it from classical CJD**
- **Is CWD transmissible to humans in CNS or peripheral tissues?**
- **Is CWD transmission to humans dependent on the CWD prion strain?**
- **If CWD is zoonotic, what are the hallmarks of CWD infection in humans?**
- **Has CWD infection in humans already occurred?**

# National Prion Disease Pathology Surveillance Center

## Departments of Pathology and Neurology



SCHOOL OF MEDICINE

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Dianne Kofskey**



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