

# Ethical Issues in Dementia Research and Care: Emerging Considerations

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# Disclosures

## 2009 to present

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- 2009-2011 employed at Bristol-Myers Squibb in CT, USA (on leave from UBC)
  - Full time employee, stocks, stock options
- From 2012 consulting, lectures, travel expenses
  - Eli Lilly, Kyowa Kirin, Nutricia, GE Healthcare, Biogen, ISIS
  - NIH, Alz Societies in Canada, New York Academy of Science, One Mind for Research, Fidelity Biosciences, Institute of Clinical and Economic Review MGH
- Clinical trials/research sponsored by
  - Roche, Genentech, Baxter, NIH, CIHR

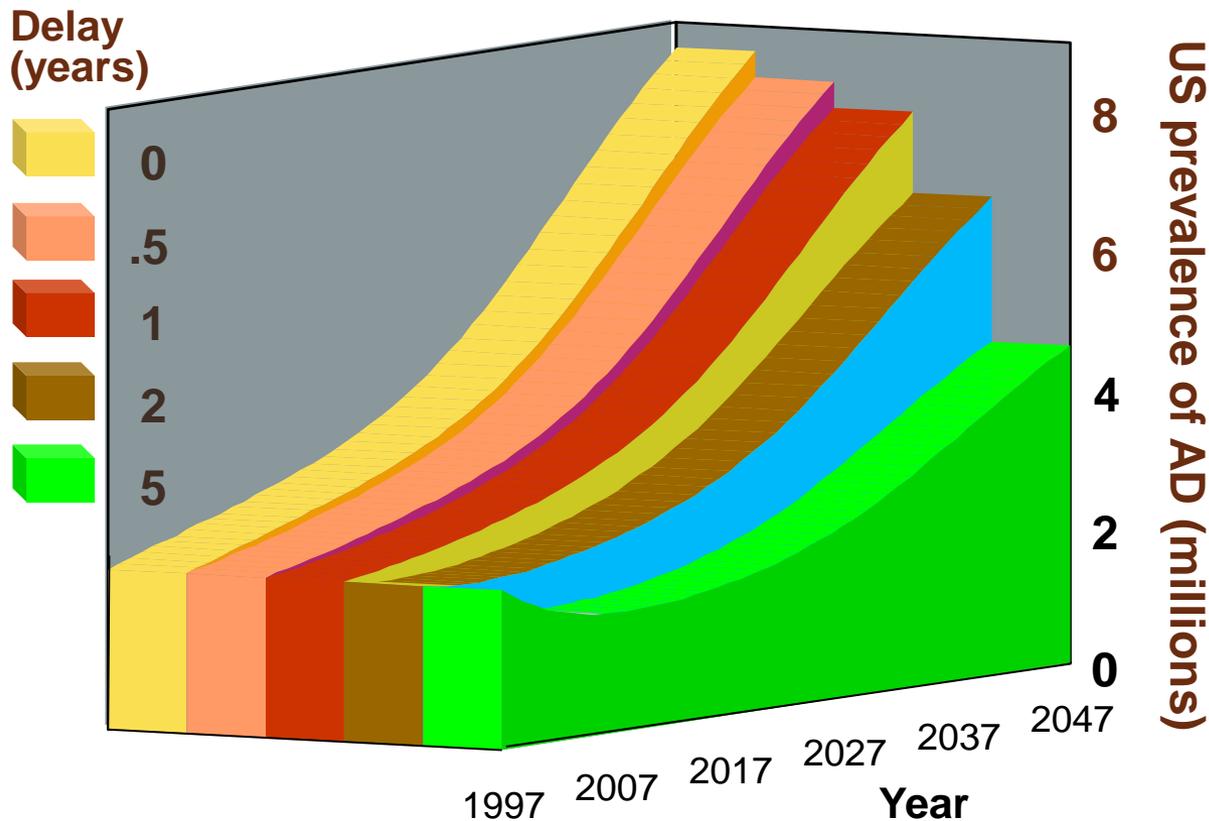
# A Selection of Ethical Issues in Alzheimer's Disease Research and Care

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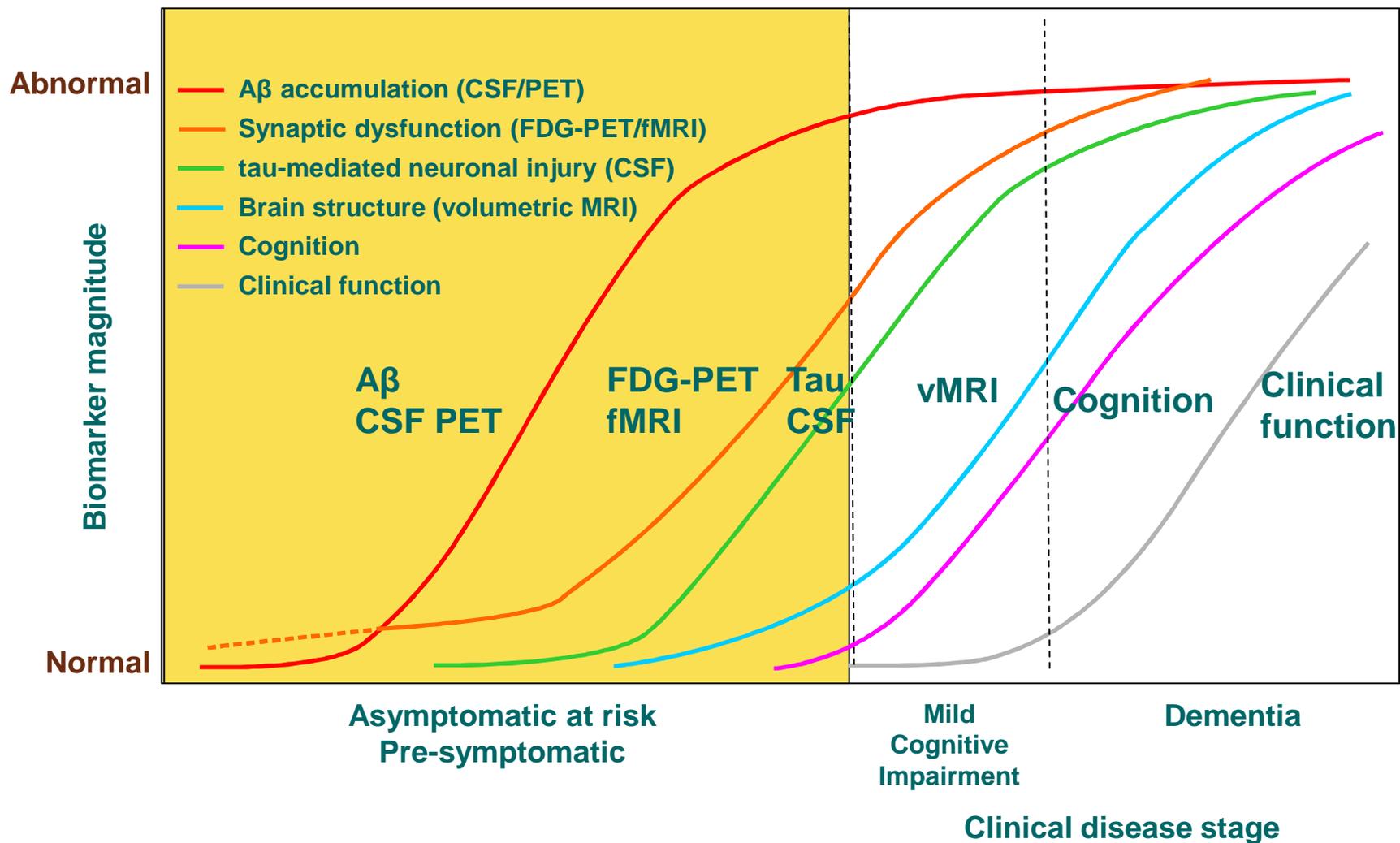
- **The disease: Identifying its pathology before symptoms begin**
- **Disease prevention: in those “asymptomatic at risk” or “pre-symptomatic”**
- **Consent and capacity to consent within a longer term disease process**
- **Genes and genetic risk: research, care, commercialization, and privacy**
- **End of life: respect for living wills, feeding, advanced directives**

# Stating the Research Goal

“ Delaying the onset of AD by 5 years would be associated with a reduction in AD prevalence of 50% ”



# The Window to Prevention of Alzheimer's Disease: The Long Preclinical Phase



# Ethical Considerations

- **Scientific validity**

- Therapeutic targets:
- Lack of surrogate outcome measures

- **Risks and Benefits**

- Primary prevention will not reduce symptoms at the outset
- Years for clinically meaningful effects
- Risks of longer term exposure to treatment
- Mitigating therapeutic misconception
- Continuing the consent process

- **Diagnostic Disclosure in preclinical disease**

- Establishing a community viewpoint
- Assessment of harm to participants
- Provisions for handling of incidental findings
- Understanding the predictive risks

# A Framework for Ethics Analysis of Alzheimer Disease Prevention Trials

A No Identifiable Genetic Risk			
Asymptomatic		Symptomatic	
BioM - 1	BioM + 2	BioM - 3	BioM + 4

B Intermediate Genetic Risk (e.g., Family history, ApoE e4+)			
Asymptomatic		Symptomatic	
BioM - 5	BioM + 6	BioM - 7	BioM + 8

C High Genetic Risk (e.g., Autosomal-Dominant AD)			
Asymptomatic		Symptomatic	
BioM - 9	BioM + 10	BioM - 11	BioM + 12



Risk for Dementia



Therapeutic Risk-Benefit Ratio

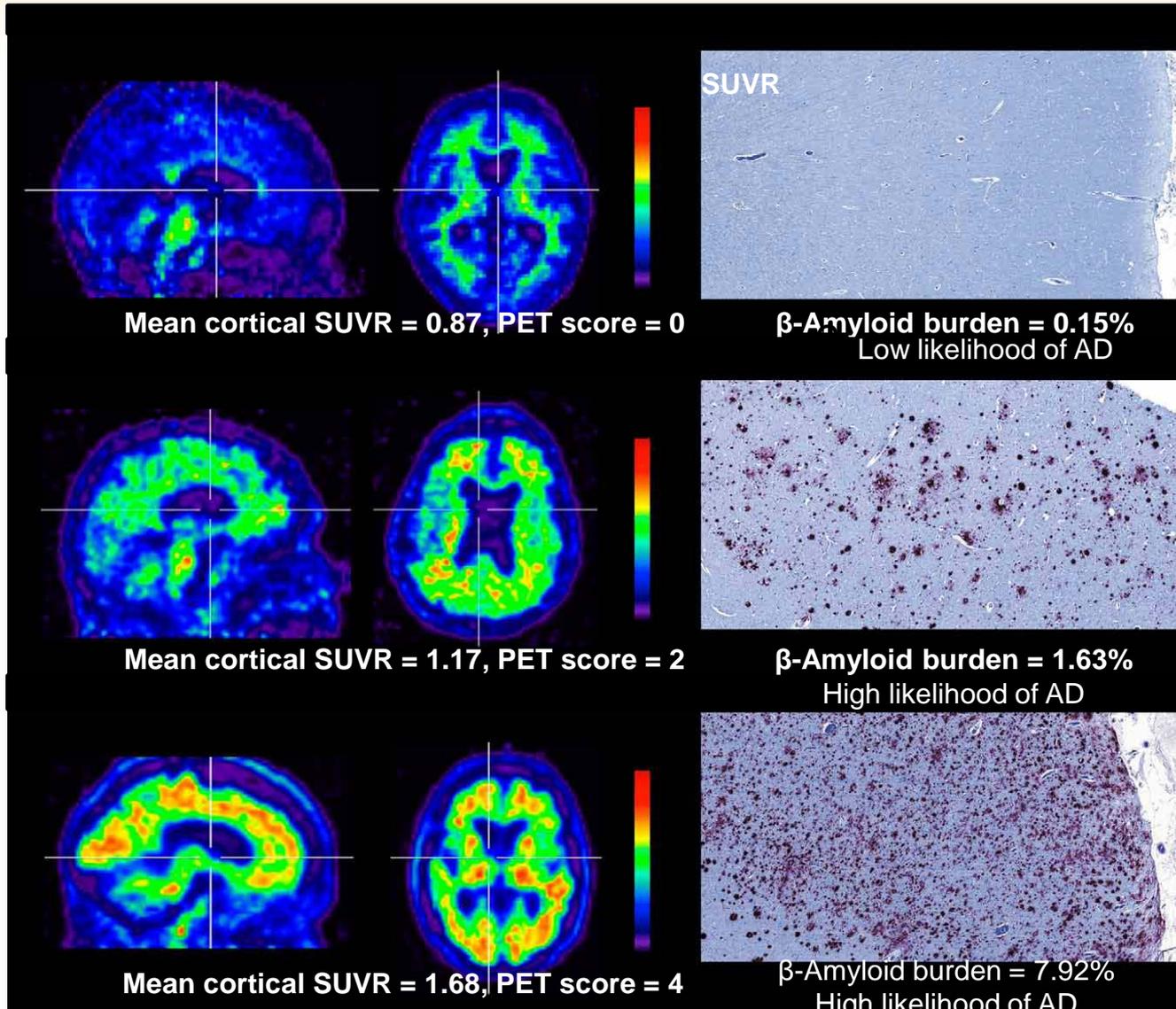
# Summary: Complexity of Considerations

- **Public good attached to prevention of AD**
- **Threat to our well being as a society without effective treatment**
- **Risks of long term preventive treatment without**
  - **Apparent symptomatic benefit**
  - **Established and validated targets of established disease**
  - **Surrogate outcome measures**
- **Diagnostic disclosure**
  - **Disease onset: pathology vs symptoms**
  - **Risks of harm vs benefits**

# Backup Slides

# Amyloid PET Imaging in Alzheimer's Disease

## Florbetapir PET Scans



- Visualizing the disease pathology in the living brain
- Very high agreement in diagnosis between post mortem and amyloid PET scan in 96%

# Prevention of Cognitive Impairment and AD 2014

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- **Treatment of hypertension mid life: level 1**
- **Avoid estrogens and vitamin E >400 IU : level 1**
- **No clear benefits to date in RCTs from:**
  - **Gingko Biloba**
  - **NSAIDs Naprosyn and Celecoxib \***
  - **Estrogens/progesterone \***
- **Current trials**
  - **Vital-Cog: Vitamin D and omega 3 FA**
  - **AIBL Lifestyle Intervention:**
  - **Zinfandel Piaglitazone**
  - **Preadvise: Vit E and Selenium**
  - **DIAN, API, A4 with amyloid lowering treatments**

# Scorecard for Amyloid Immunotherapy for AD 2014

Name of drug	Status of Completed Trials	Comment
<b>Bapineuzumab</b>	Phase 3 studies (x2) Mild to Moderate AD	Negative trials Terminated program
<b>Solaneuzumab</b>	Phase 3 studies (x2) Mild to Moderate AD	Negative trials Currently mild AD and prevention of AD in DIAN
<b>Gammagard IVIG</b>	Phase 2-3 (x1) Mild to Moderate AD	Negative trial n/a
<b>Gantenerumab</b>	Phase 2 trial in prodromal AD	Prevention of AD in DIAN Phase 3 Prodromal AD
<b>Crenezumab</b>	Phase 1	Phase 2 API trial Prevention in PS 1 FAD
<b>BAN 2401</b>	Phase 1	Phase 2 Early AD

# Amyloidopathy in Healthy Older Adults

Range of amyloid positive PET scans in cognitively normal is 20-30%

	Ages	Criteria	PET amyloid criteria	Prevalence Amyloid +
Aizenstein H et al <sup>1</sup>	65-88	Not MCI and Not Dementia	> 1 region abn	21%
Landau S et al <sup>2</sup>			SUVR > 1.10	29%
Mielke MM et al <sup>3</sup>	70-92		Comparing SUVR 1.4 with 1.5 as cutoff	44% > 1.4 31% > 1.5
Sperling R et al <sup>4</sup>	50-92		Qualitative	14% > age 80, 25%
			Quantitative	23%

1. Aizenstein H et al; Arch Neurol 2008, Landau S et al Annals Neurol 2012  
Mielke MM et al Neurology 2012, Sperling R et al Neurobiol Aging 2013

# Neuropathological Studies of Cognitively Normal: CERAD Ratings of Neuritic Plaques

	<b>Religious Order Study <sup>1</sup></b> <b>N=98</b>	<b>Rush Memory and Aging Project <sup>1</sup></b> <b>N=36</b>	<b>Mayo Alzheimer Patient Registry <sup>2*</sup></b> <b>(n=39)</b>
Not present	41%	47%	59%
Possible (sparse)	13%	8%	33%
Probable (Moderate)	37%	39%	5%
Definite (Frequent)	9%	6%	0%

<sup>2</sup> differentiated core vs neuritic plaque