18th Annual Mild Cognitive Impairment Symposium and Workshop

RATES AND RISK FACTORS FOR MCI PROGRESSION

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DISCLOSURE

Mary Ganguli served on Biogen *“Patient Journey Working Group”*

in 2016 and 2017.

MCI: you've come a long way

"Petersen Criteria 1999" Amnestic MCI

Winblad Criteria 2004

MCI AAMI ARCD ACMI CIND AACD

Alphabet Soup

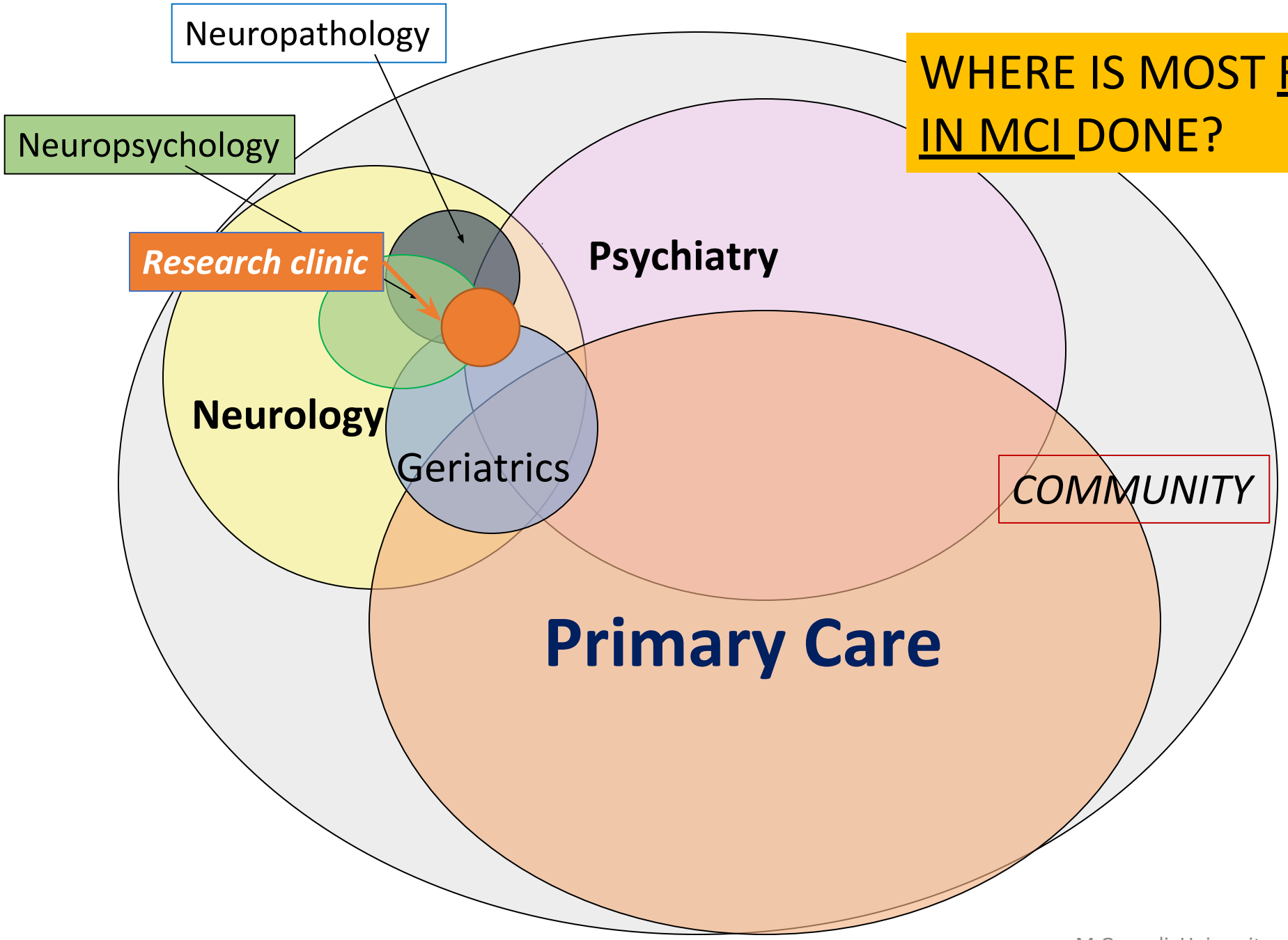
Petersen 2005

Etiologic Classification

Descriptive Classification		Degen-erative	Vascular	Psychiatric	Medical
Amnestic MCI	Single Domain	AD		Depression	
	Multi Domain	AD	VaD	Depression	
Non-amnestic MCI	Single Domain	FTD			
	Multi Domain	**DLB**	**VaD**		

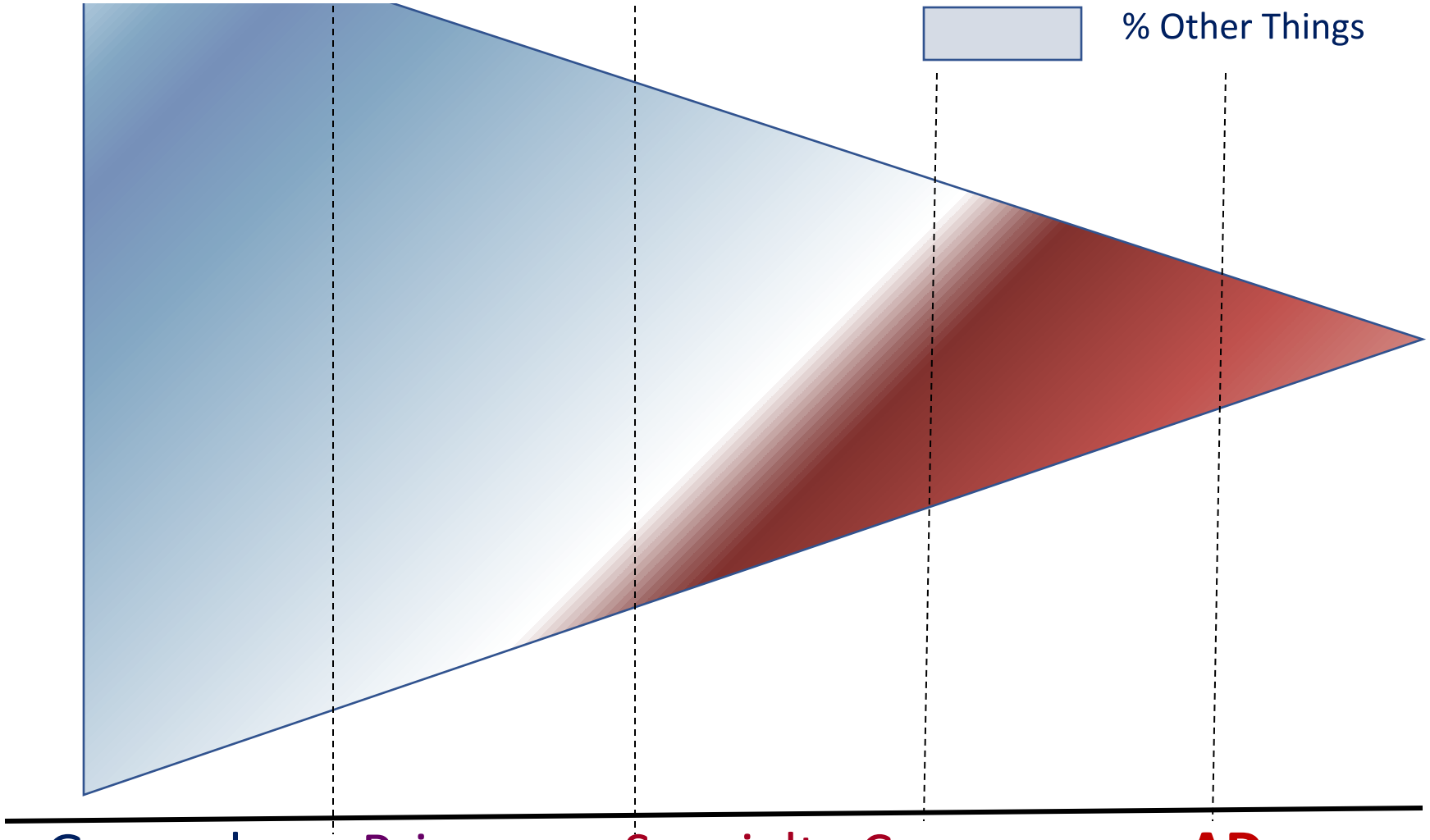
Dawn of reality

- MCI is a heterogeneous entity
- with multiple potential causes.



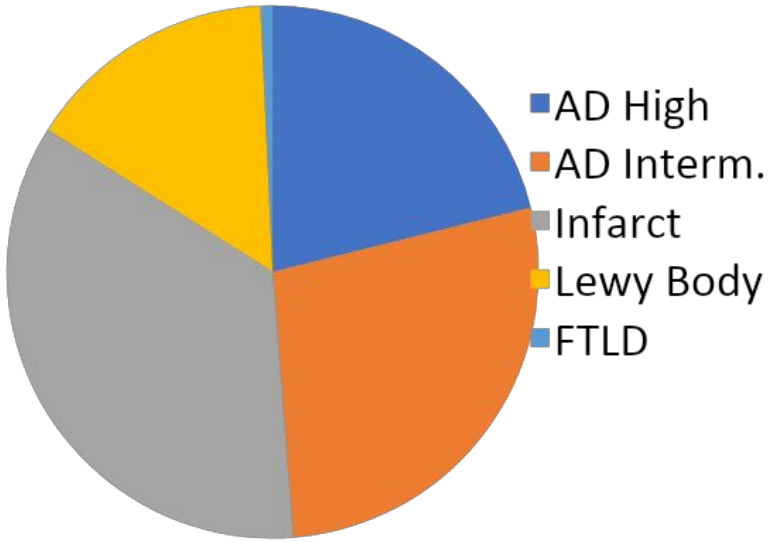
WHERE IS MOST RESEARCH IN MCI DONE?

Etiology of mild impairment

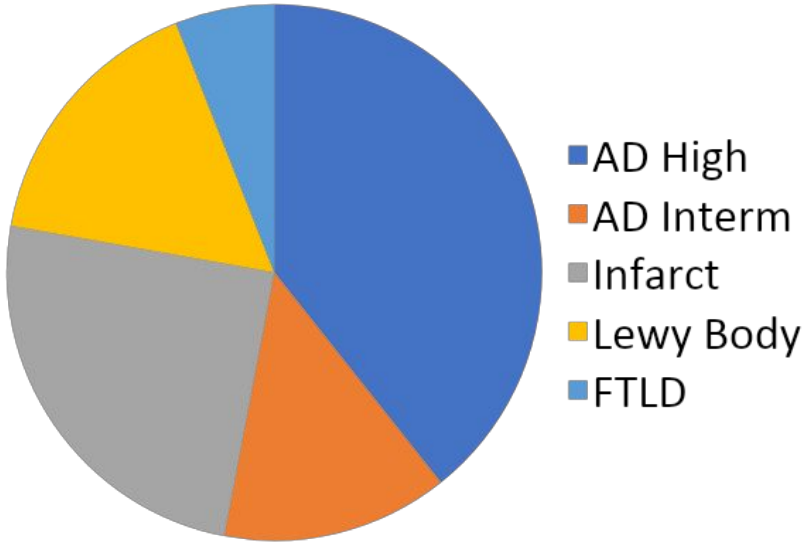


Neuropathological Diagnoses in all individuals with clinical dementia

Community Samples



Clinic Sample



Schneider JA et al., J. Alz. Disease 2009

Course and Outcome of Amnestic MCI: *Clinical Research Series*

Mayo Clinic series: 12% of amnestic MCI progress to AD dementia annually.
(Petersen et al.,1999)

Washington University series: 100% with CDR =0.5 progress to AD dementia over 9.5 years.
(Morris et al., 2001)

Harvard series: volunteer panel: 18.7% with CDR= 0.5 progress to AD dementia over 3 years.
(Daly et al., 2000)

Course and Outcome of Amnestic MCI*:
Community Cohorts

Progression to dementia/AD:

11.1% over 3 years: Eugeria study *(2001)*

8.3% over 2 years: PAQUID study *(2002)*

10-17% over 2 years: MoVIES study. *(2004)*

Reversion to normal:

40% over 2 years: PAQUID study

33-56% over 2 years: MoVIES study

Stable MCI (no change):

11-21% at 2 years: MoVIES study

Meta-analysis:

The majority of individuals meeting MCI criteria in population studies **will not** progress to dementia over ten years.

(Mitchell et al., IGJP 2008)

** Various interpretations*

Progression of MCI is not uniform.

The likelihood of progression from MCI to dementia

- will depend on the underlying etiology,
- and therefore on the setting as well.

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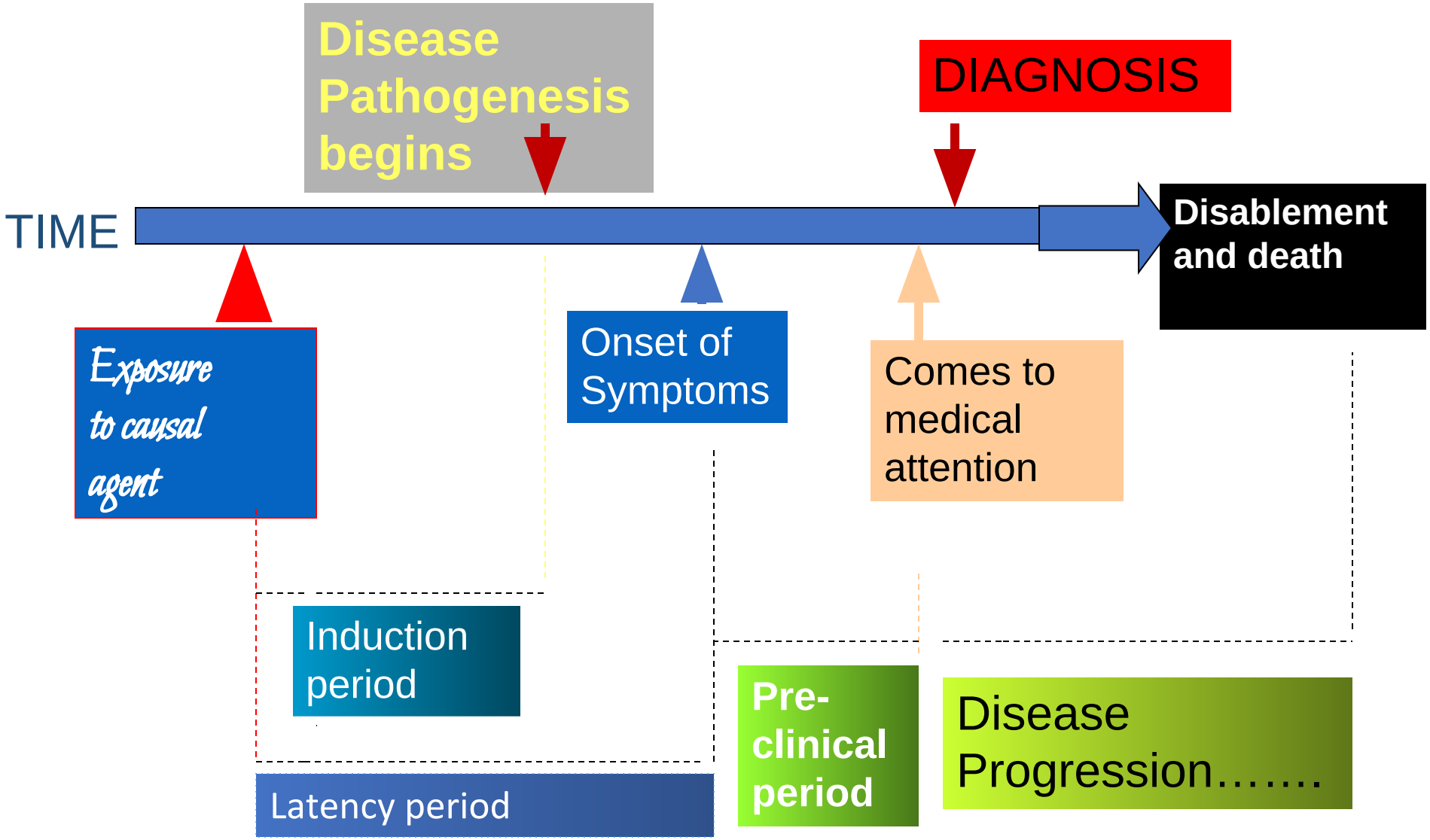
- In memory disorders clinics, the vast majority of patients progress from MCI to dementia within a few years.

Progression of MCI is not uniform.

The likelihood of progression from MCI to dementia

- will depend on the underlying etiology,
- and therefore on the setting as well.
- In memory disorders clinics, studies the vast majority of patients progress from MCI to dementia within a few years.
- In population studies, the vast majority remain at the MCI level, i.e. stably impaired;
- while a minority of MCI cases progress to dementia
- and another minority reverts to normal.



Adapted From: Nelson, Tanner, Van Den Eeden, and McGuire, 2004

Monongahela-Youghiogheny Healthy Aging Team (MYHAT)

- Cohort study funded in Sept 2005 by NIA.
- Objectives:
  - Identify older adults who are cognitively normal or only mildly impaired.
  - Identify those who progress to dementia and those who remain free of dementia.
  - Identify predictors of progressing to dementia vs. predictors of remaining dementia-free.

R01 AG02365

MYHAT Cohort recruitment

- Age-stratified random sample from publicly available 2004 voter registration list.
- Entry criteria:
  - Age 65+;
  - Not currently in long-term care institution;
  - Not severely impaired in vision or hearing;
  - No decisional incapacity.

MYHAT Design

- Recruited 2036 individuals.
- Triaged out 54 individuals with age-education corrected MMSE score <21.
- Full assessment of 1982 participants recruited between 2006-2008 (baseline wave/cycle).
- Annual reassessment waves.

MYHAT MCI Outcomes study

- In a population-based cohort, during 2006-2017:
- Excluding those who had dementia at study entry, and those who had less than 5 years' followup after study entry.
- We followed participants for at least 5 years, identifying those who developed MCI (CDR=0.5) and dementia (CDR>=1) at any point.

Mild Cognitive Impairment (MCI) over at least 5 years				Remained Normal
Reverted to Normal	Stable MCI	Progressed to Dementia	(Total MCI)	
252	384	86	(722)	881
34%	*53%*	*12%*	(100%)	

MCI outcomes over > 5-year followup

- Defining MCI as CDR = 0.5 and dementia as CDR≥1.
- We **compared** 3 MCI subgroups:

  (1) those who **progressed** to dementia (n=86),

  (2) those who **stabilized** at MCI (n=384),

  (3) those who **reverted** to normal (n=252),

- **to** :

  (4) those who **remained consistently normal** (n=881).

- Using multinomial logistic regression models adjusted for demographics, we examined the associations of each group with selected baseline characteristics.

"Baseline" characteristics of entire sample and of MCI subgroups: N=1603

	Normal N=881	**Reverters** N=252	**StableMCI** N=384	**Progressors** N=86	*P value*
Age (Mean/SD)	75.2 (7.0)	77.5 (7.0)	82.3 (6.9)	83.6 (5.7)	*0.0001*
Sex (% female)	62.1	58.7	64.1	61.6	*NS*
Education (%) <HS,	8.3	12.7	20.3	29.1	
=HS,	44.6	45.2	47.40	33.7	*<0.001*
>HS	47.1	42.1	32.3	37.2	
>0 subjective memory concerns (SMC)	51.4	96.0	94.5	93.0	*<0.001*
Number of SMC (median, IQR)	1 (2)	4 (2)	4 (3)	5 (4)	*0.0001*
Self-rated health (% poor +fair)	11.8	23.4	24.2	20.9	*<0.001*
>0 IADL impairments (%)	8.2	21.0	38.3	48.0	*<0.001*
>3 Depressive symptoms (%)	4.7	12.3	11.5	15.1	*<0.001*
*APOE*4* genotype % E4 (%)	19.2	21.4	21.9	34.2	*NS*
Systolic blood pressure >130 (%)	51.8	48.0	51.0	53.5	*NS*
Diastolic blood pressure >70 (%)	64.7	61.9	49.0	47.7	*<0.001*
H/o Stroke/TIA (%)	8.5	12.3	18.2	22.1	*<0.001*
H/o Heart attack (%)	35.3	39.3	37.8	36.1	*NS*
H/o Diabetes (%)	20.4	20.2	27.3	23.3	*0.044*
Current Smoking (%)	8.5	6.4	3.4	7.0	*0.011*
Current Alcohol consumption (%)	88.3	79.4	66.7	62.8	*<0.001*
Number of prescription medications (%)	3 (4)	5 (4)	5 (5)	4 (3)	*0.0001*
Exercise % any (%)	63.2	56.8	55.5	48.8	*0.006*

Comparing MCI subgroups to normal group,

(multinomial logistic regression adjusting for demographics)

POTENTIAL PREDICTORS	Reverters vs. Consistently Normal		Stable MCI vs. Consistently Normal		Progressor vs. Consistently Normal	
	RRR	p-value	RRR	p-value	RRR	p-value
>0 Subjective cognitive concerns	**22.58**	**<0.001**	**16.33**	**<0.001**	**12.79**	**<0.001**
Number of subjective concerns	**2.52**	**<0.001**	**2.73**	**<0.001**	**3.02**	**<0.001**
Self-rated health – good/very good/ excellent (ref: poor/fair)	**0.417**	**<0.001**	**0.364**	**<0.001**	**0.424**	**0.004**
>0 IADL impairments	**2.629**	**<0.001**	**4.174**	**<0.001**	**6.150**	**<0.001**
≥ 3 depressive symptoms	**2.872**	**<0.001**	**2.557**	**<0.001**	**3.55**	**<0.001**
*APOE *4* genotype	1.221	NS	**1.535**	**0.012**	**3.062**	**<0.001**
Systolic blood pressure (SBP)	0.844	NS	0.925	NS	0.976	NS
Diastolic blood pressure (DBP)	0.993	NS	**0.74**	**0.026**	0.757	NS
H/o Stroke/TIA	1.518	NS	**2.556**	**<0.001**	**1.967**	**0.047**
H/o Heart attack	1.088	NS	0.924	NS	0.826	NS
H/o Diabetes	1.002	NS	1.605	0.002	1.312	NS
Smoking	0.846	NS	0.615	NS	1.575	NS
Alcohol	**0.543**	**0.002**	**0.362**	**<0.001**	**0.306**	**<0.001**
Number of Prescription medications	**1.13**	**<0.001**	**1.15**	**<0.001**	1.02	NS

3 MCI outcome groups

MCI subgroups with different 5-year outcomes had *some similar and some distinct* characteristics, suggesting different underlying causes.

Compared to those who remained consistently normal:

- The **progressors** to dementia had profiles broadly typical of Alzheimer's disease; objective memory deficits, *APOE*4*, and also history of stroke.
- The **reverters** to normal did *not* have memory deficits or *APOE*4*; they had more subjective complaints; they took more prescription medications.
- **Stable MCIs** *(biggest group!)*had diabetes, low diastolic pressure, took more prescription meds, and also had *APOE*4* genotype.
- Demonstrates heterogeneity of MCI in the population at large.

J Am Geriatr Soc. 2019 Feb;67(2):232-238

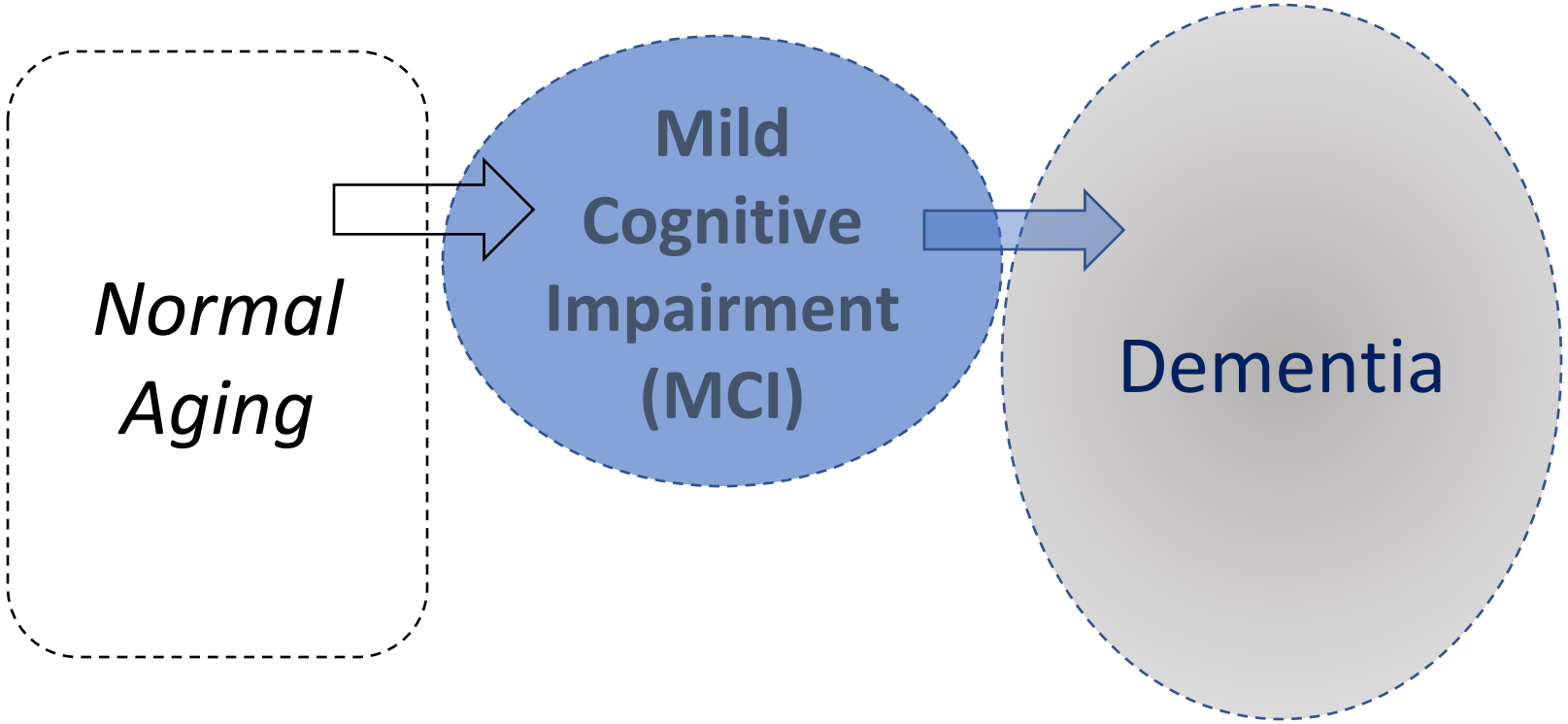
In conclusion

- MCI is not always prodromal dementia.
- "Intermediate" ≠ "Transitional"
- The majority of people with MCI in the community do not progress to dementia.
- MCI is even more heterogeneous than dementia.
- Several potentially treatable conditions are associated with MCI that does not progress to dementia.
- Till biomarker-based diagnosis becomes readily available, we should consider non-progressive causes; we should not routinely prescribe anti-AD drugs for everyone with MCI.

For more information about our projects, please visit our website.

www.dementia-epidemiology.pitt.edu

The Cognitive Continuum in the Dementia Research Clinic



SUMMARY

The Cognitive Continuum in the Community