Early Detection and Diagnosis of Memory Disorders and Alzheimer's Disease

NC Institute of Medicine – Task Force on Alzheimer's Disease and Related Dementia

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Duke University Medical Center
Joseph and Kathleen Bryan
Alzheimer's Disease Research Center


Here is Jane. Jane has been noticed some embarrassing problems with her memory for about a year now, ever since she retired and sold her business. She has difficulty tracking conversations and she is now more likely to repeat herself, unsure with whom she may have shared recent updates about her children and grandchildren.


Laboratory tests and even brain imaging studies all are normal. But Jane knows that Alzheimer's disease runs in her family. She has always been prepared for the possibility that this disease might also affect her one day.


Her family reassures her, pointing out how capable she is in all her activities. Her primary care doctor tells her that her concerns are normal and nothing more than age. Laboratory tests and even brain imaging studies all are normal.


Is that “one day” now here?
Do I have Alzheimer’s disease or is this just what I should expect with normal aging?
What can I do about it?

Alzheimer's disease (AD) is one of the most dreaded conditions, among the most feared diagnoses for adults over the age of 65

- Recent surveys indicate that 94% of physicians disclose diagnosis of terminal cancer
- Same group of physicians are reluctant to disclose the diagnosis of Alzheimer's disease to their patients

Blendon RJ. et al Key Findings from a Five-Country Survey of Public Attitudes about Alzheimer's Disease. Data from the Harvard School of Public Policy and Alzheimer's Europe study (2011)

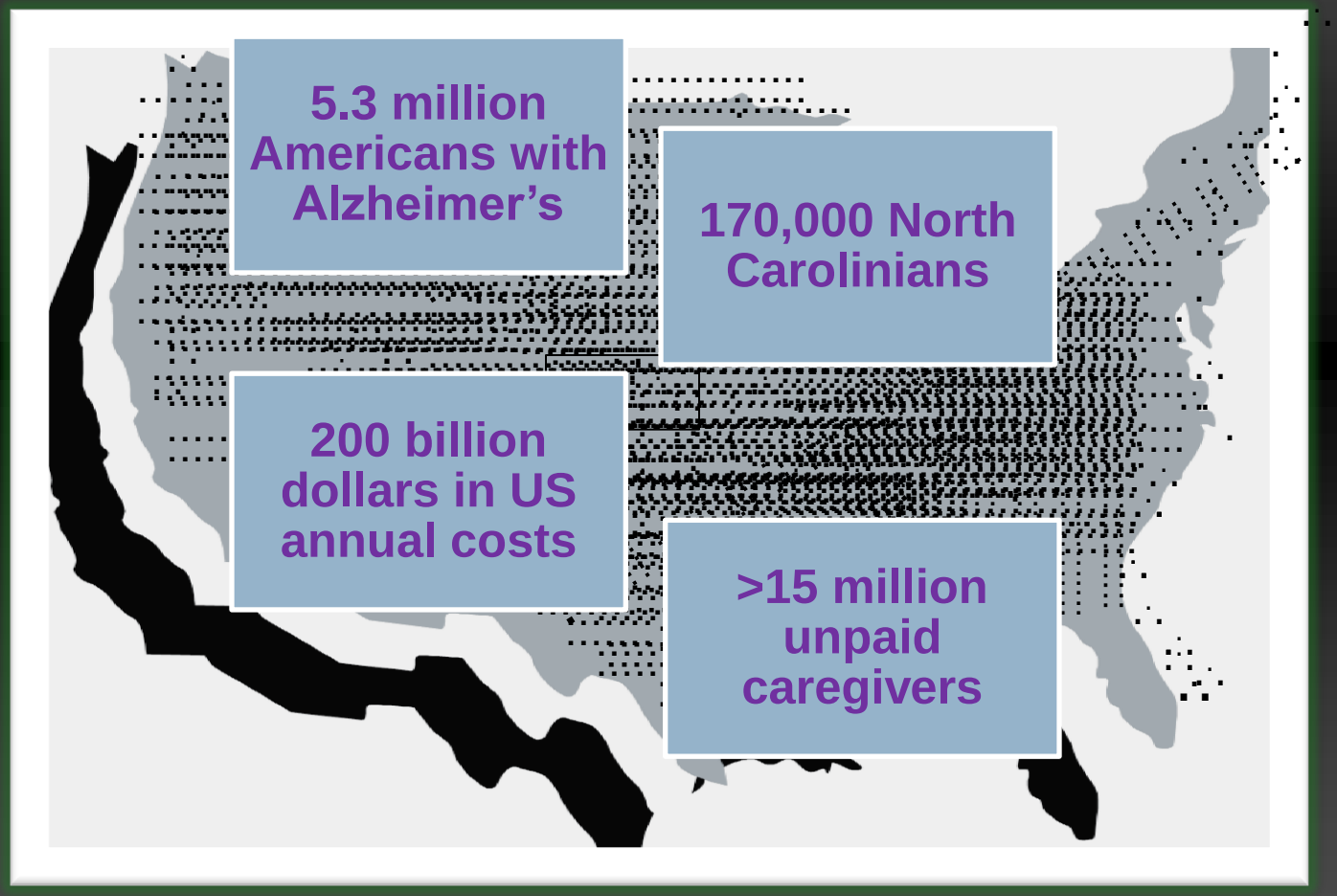
Barriers to routine screening & once identified then what?

Easing patient flow for positive screens

Because Alzheimer's disease affects thinking, memory, overall cognitive processing, the very essence of who we are…. it is frightening

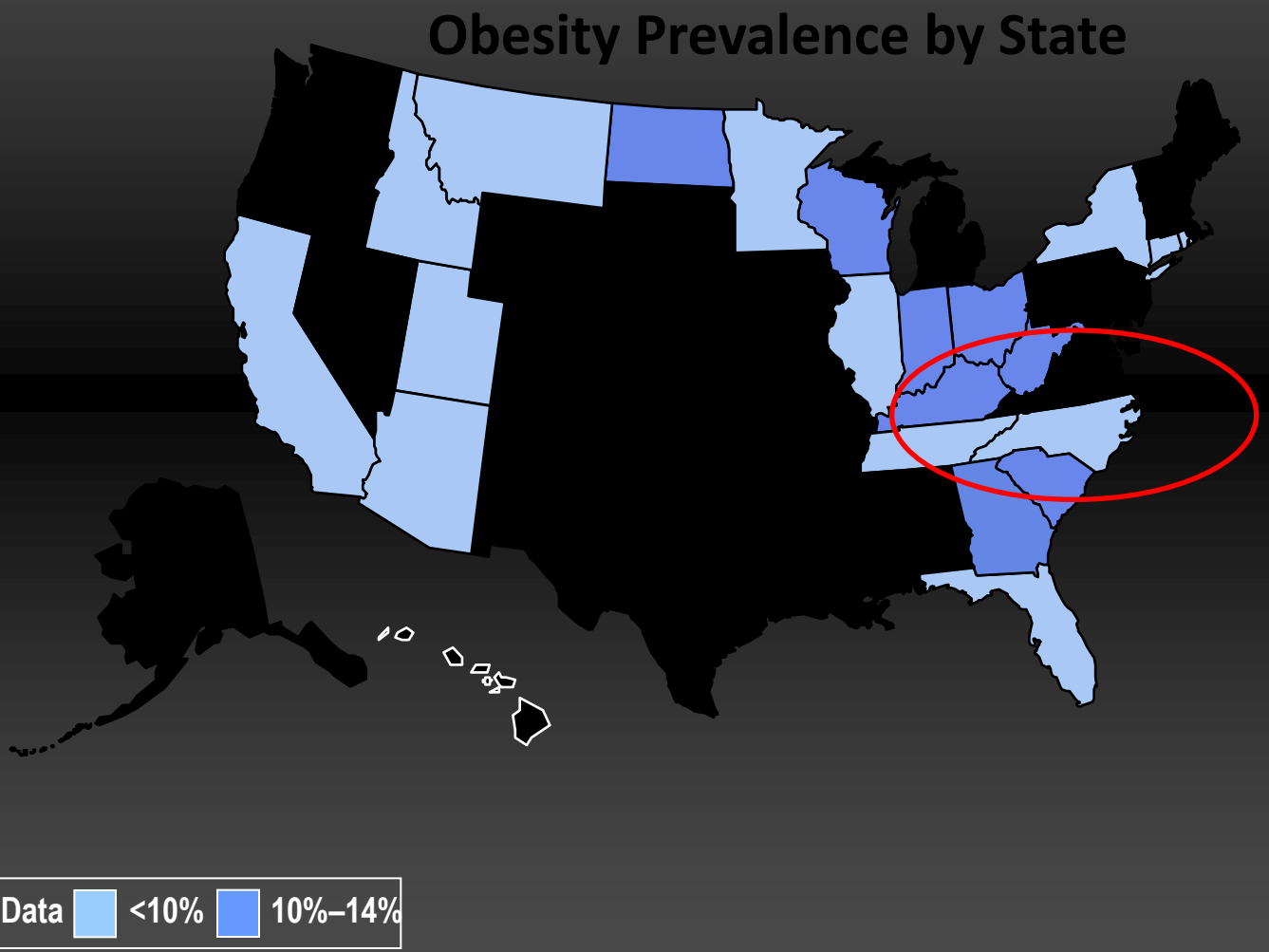
- Do all people have memory loss and AD if they live long enough?
- What benefit is there to diagnosis if there are no disease altering treatments?
- Are there things we can do to keep our brain healthy to prevent the disease?

Alzheimer's Disease: Current Projections & Economic Impact



CDC Behavioral Risk Factor Surveillance System

1985



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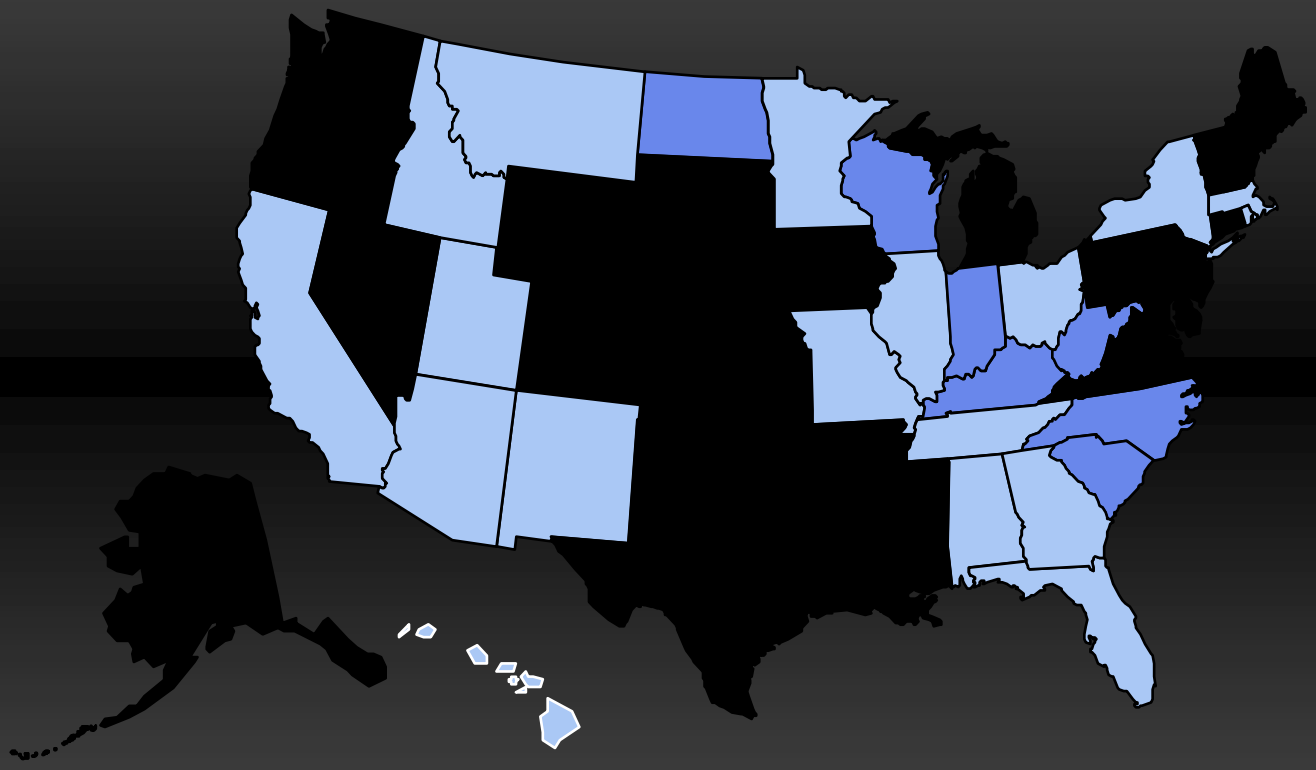

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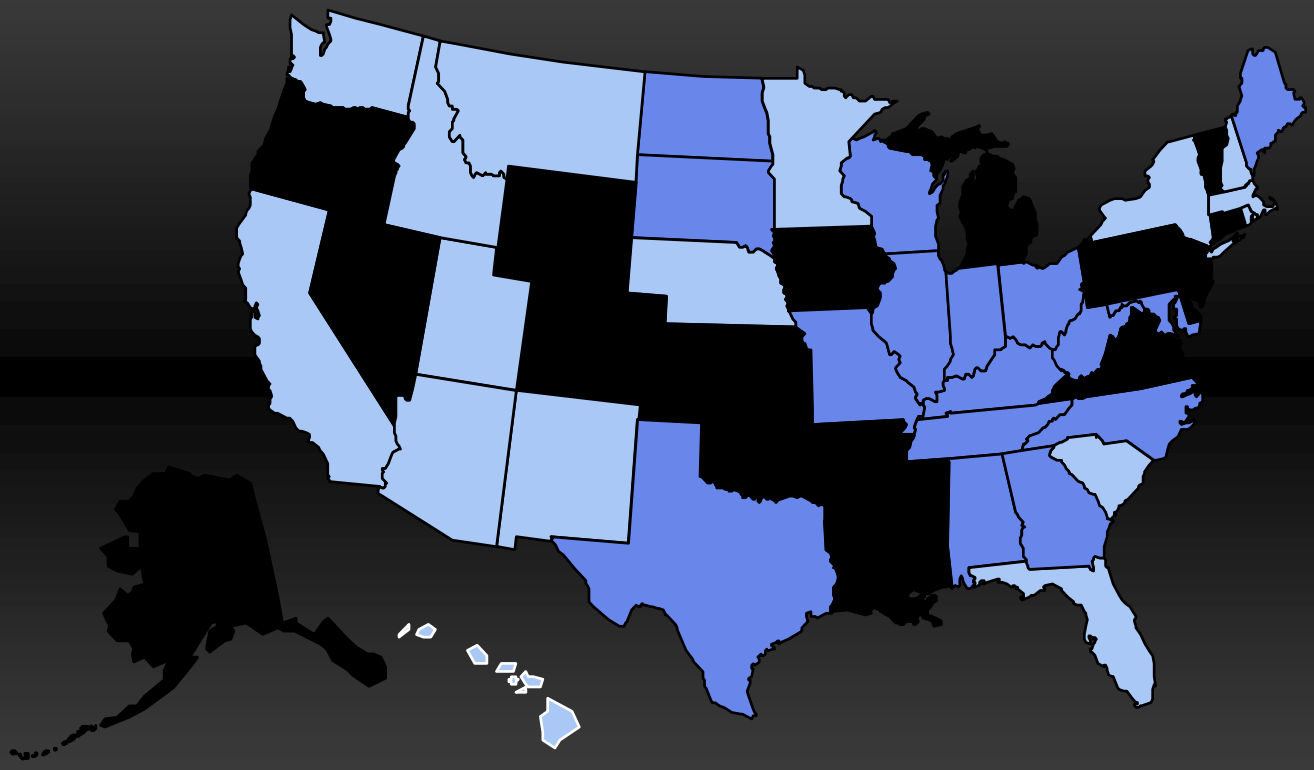

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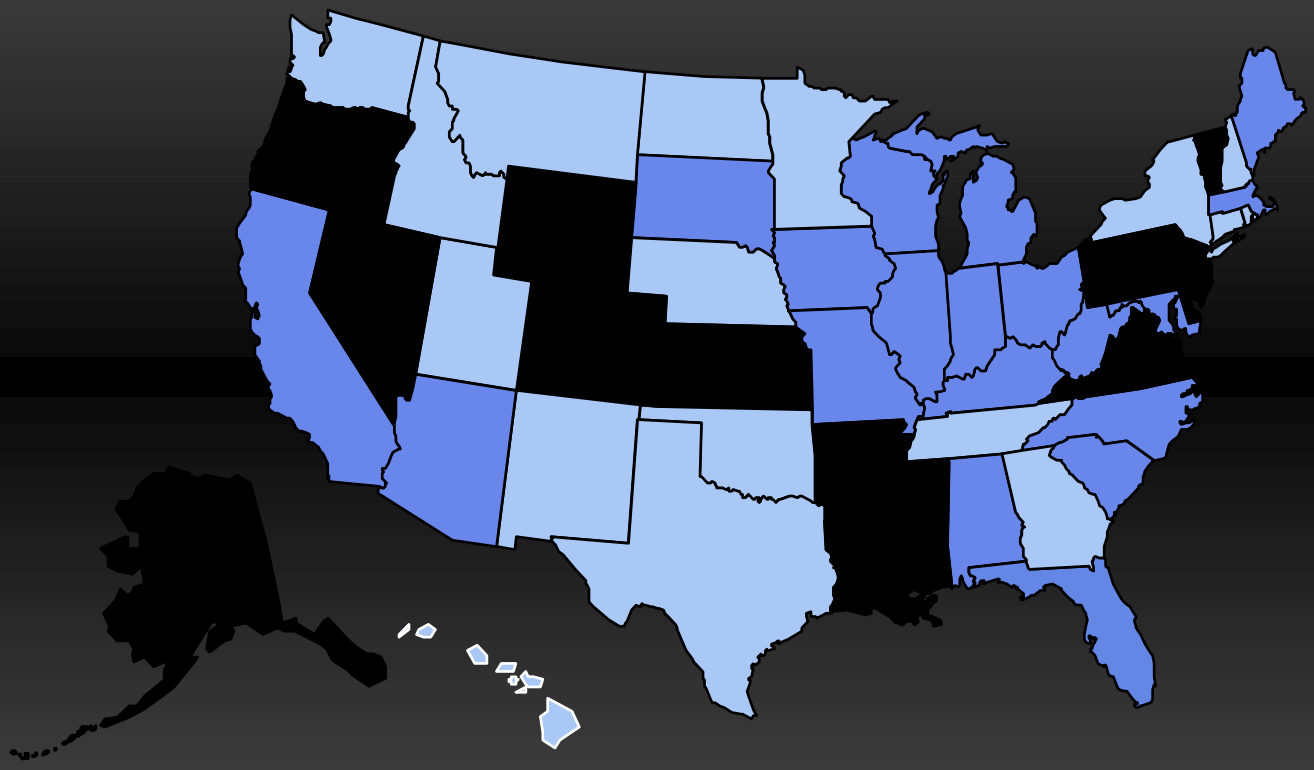

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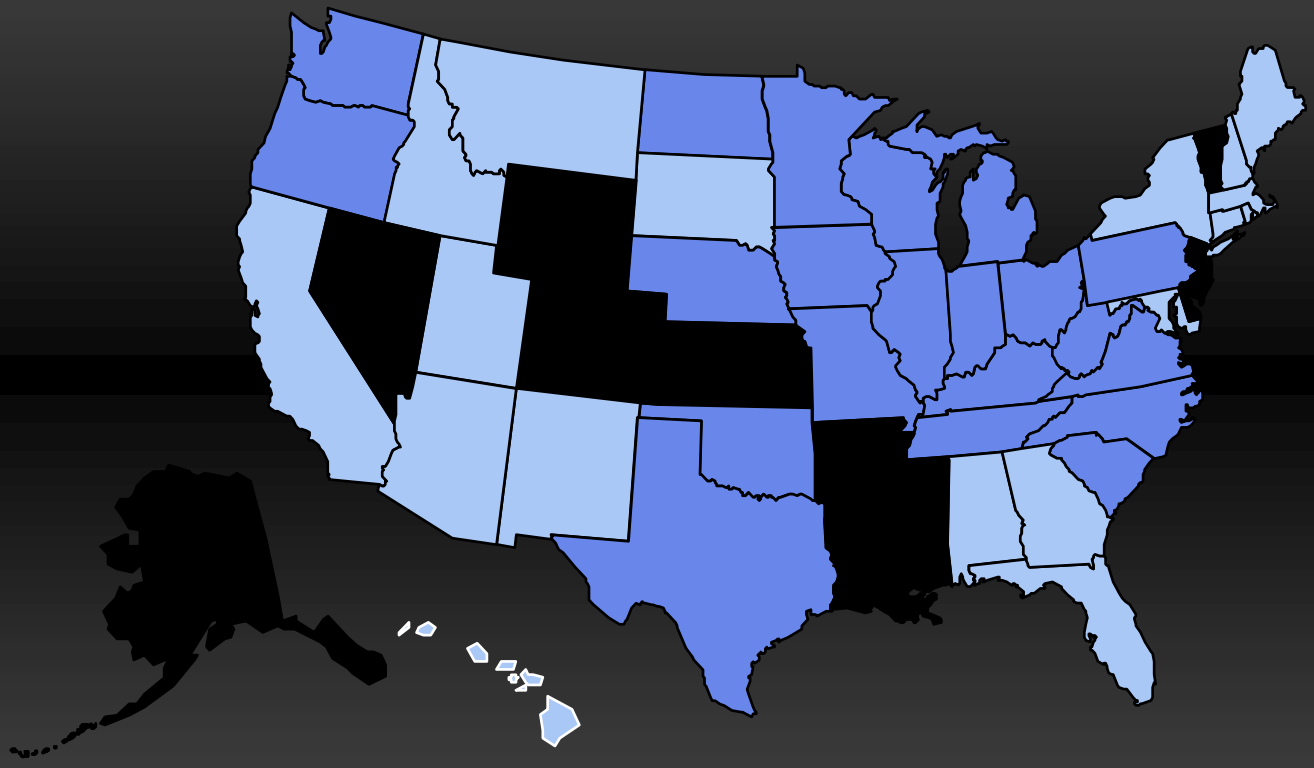

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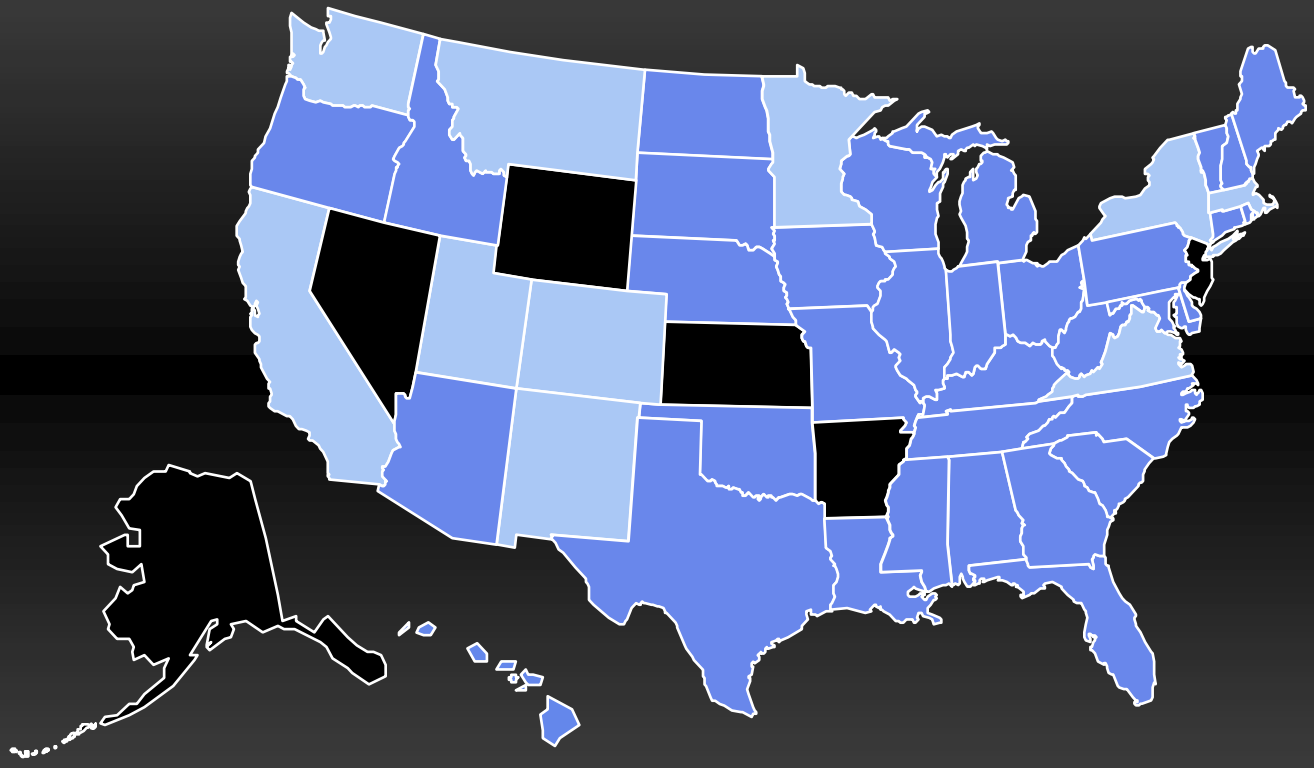

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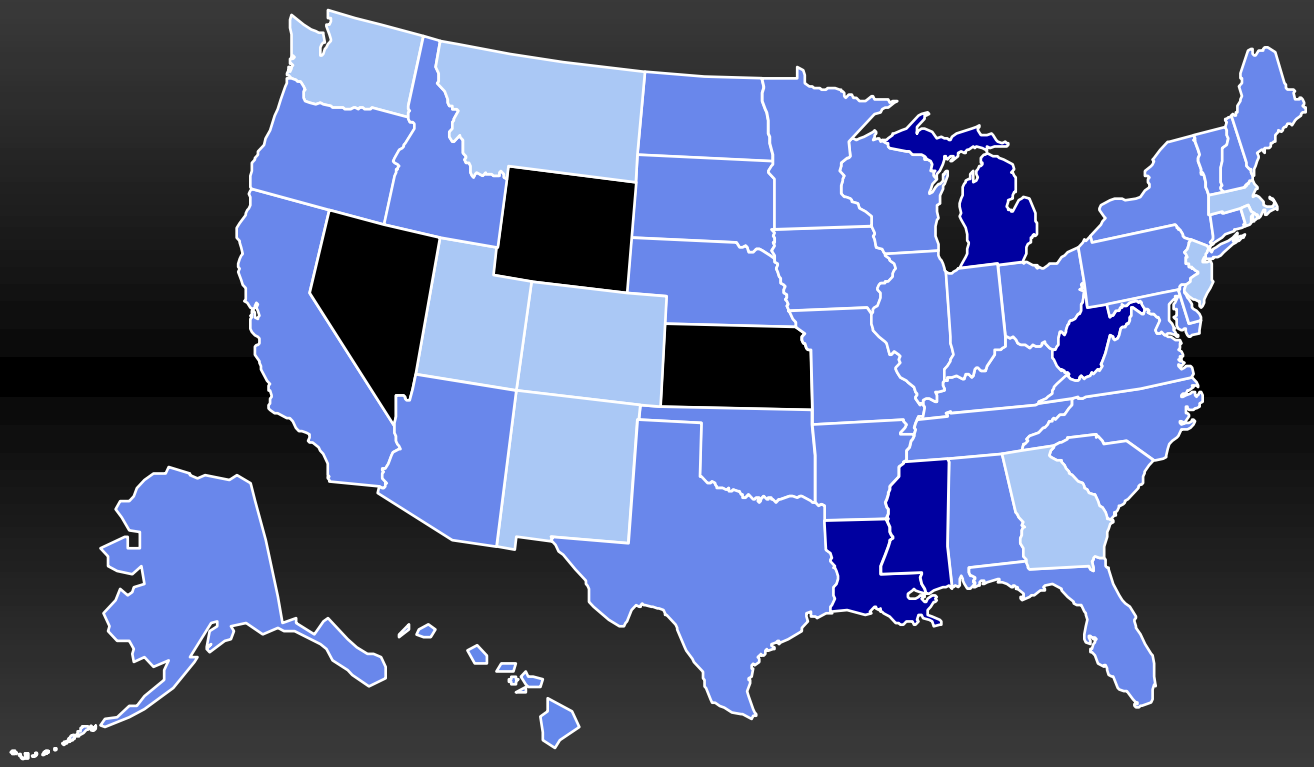

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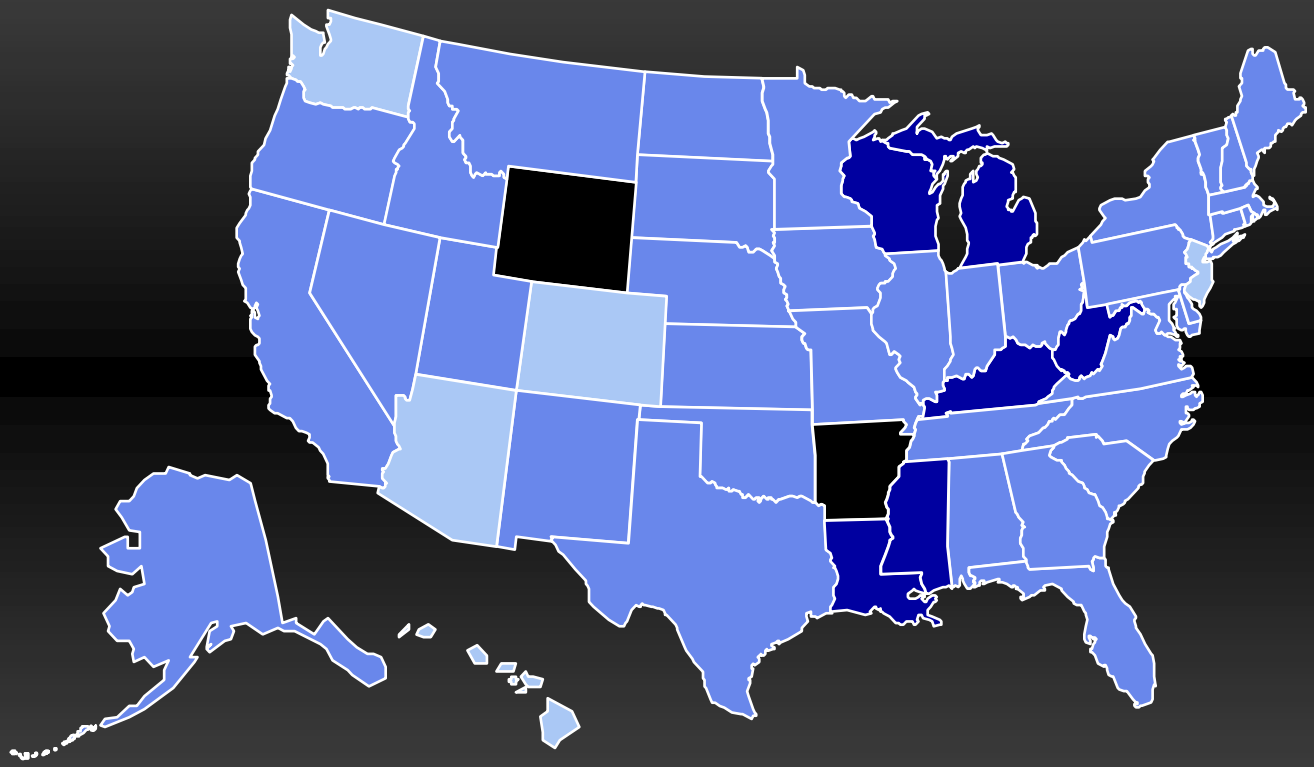

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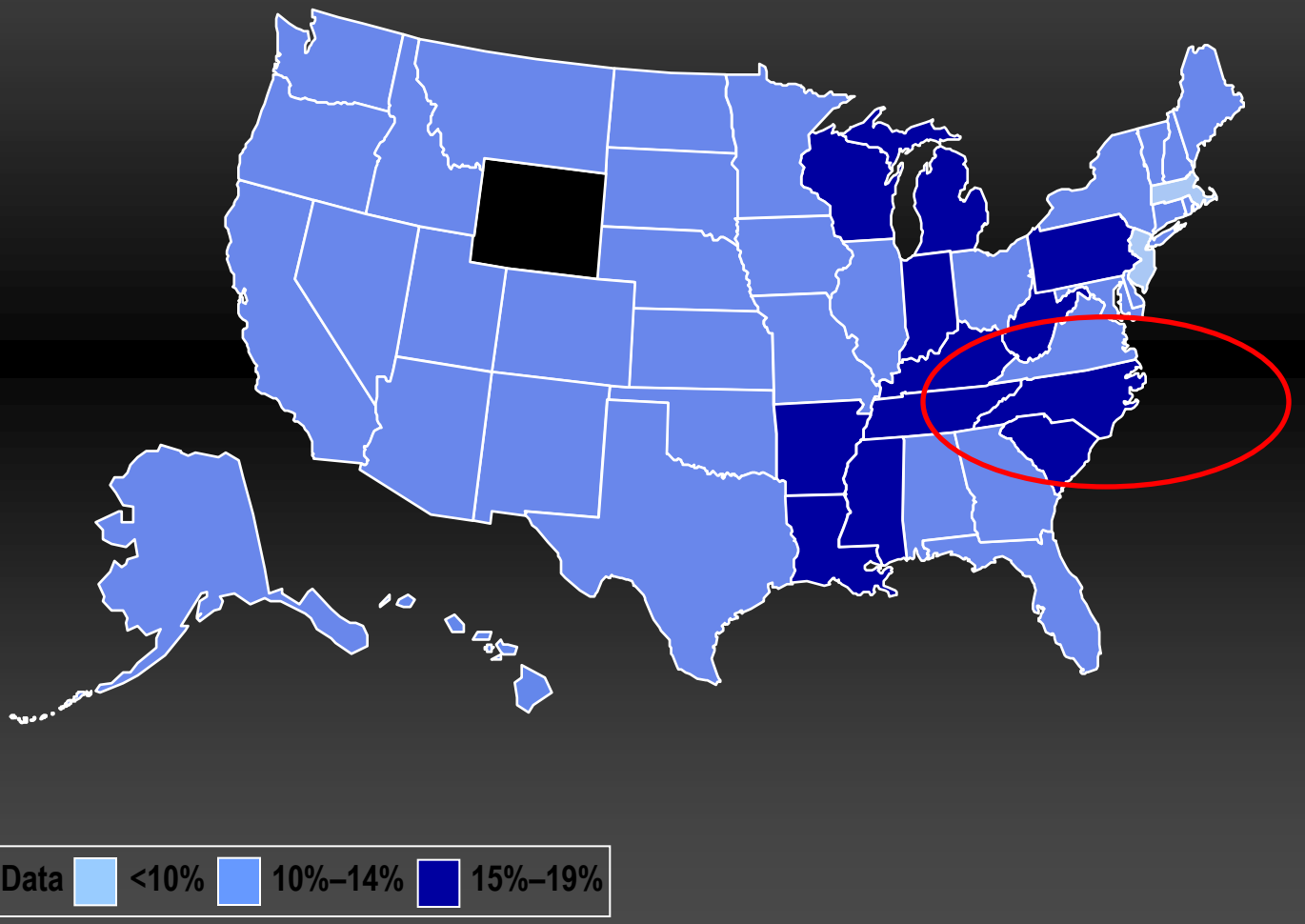

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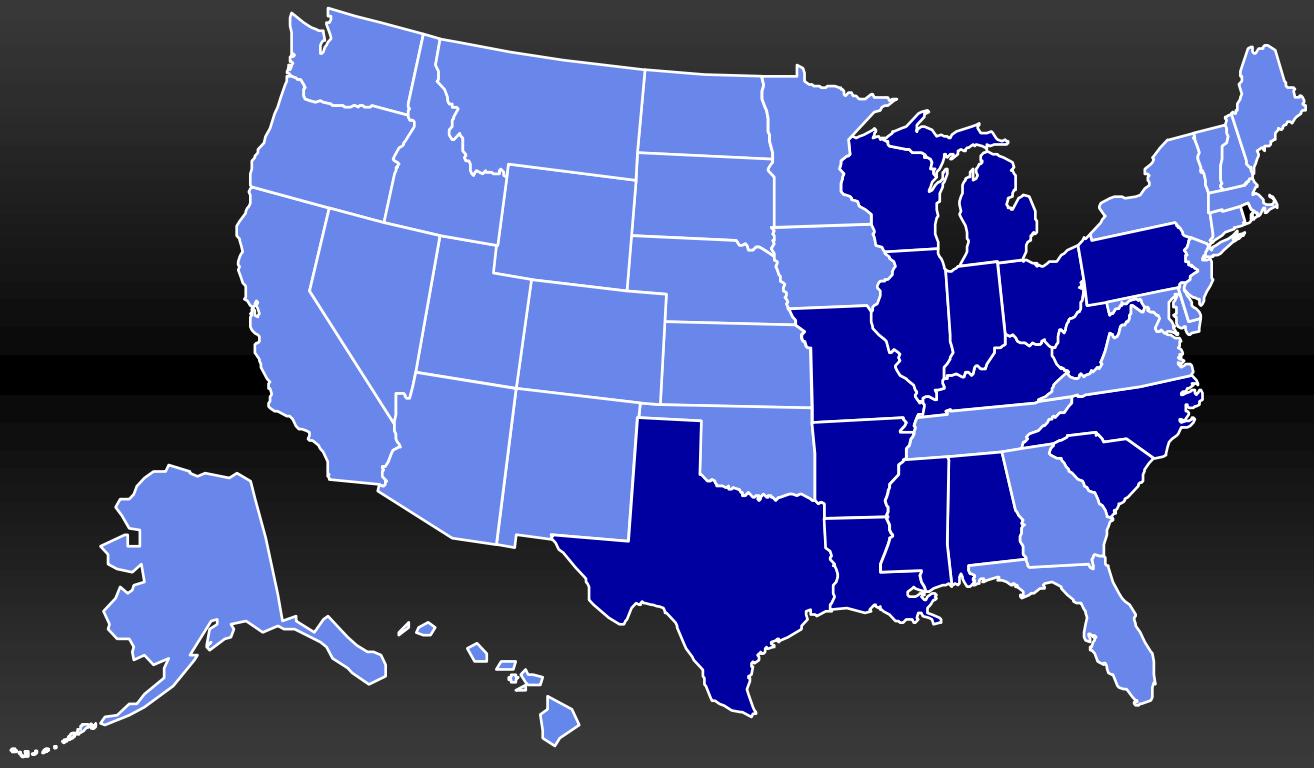

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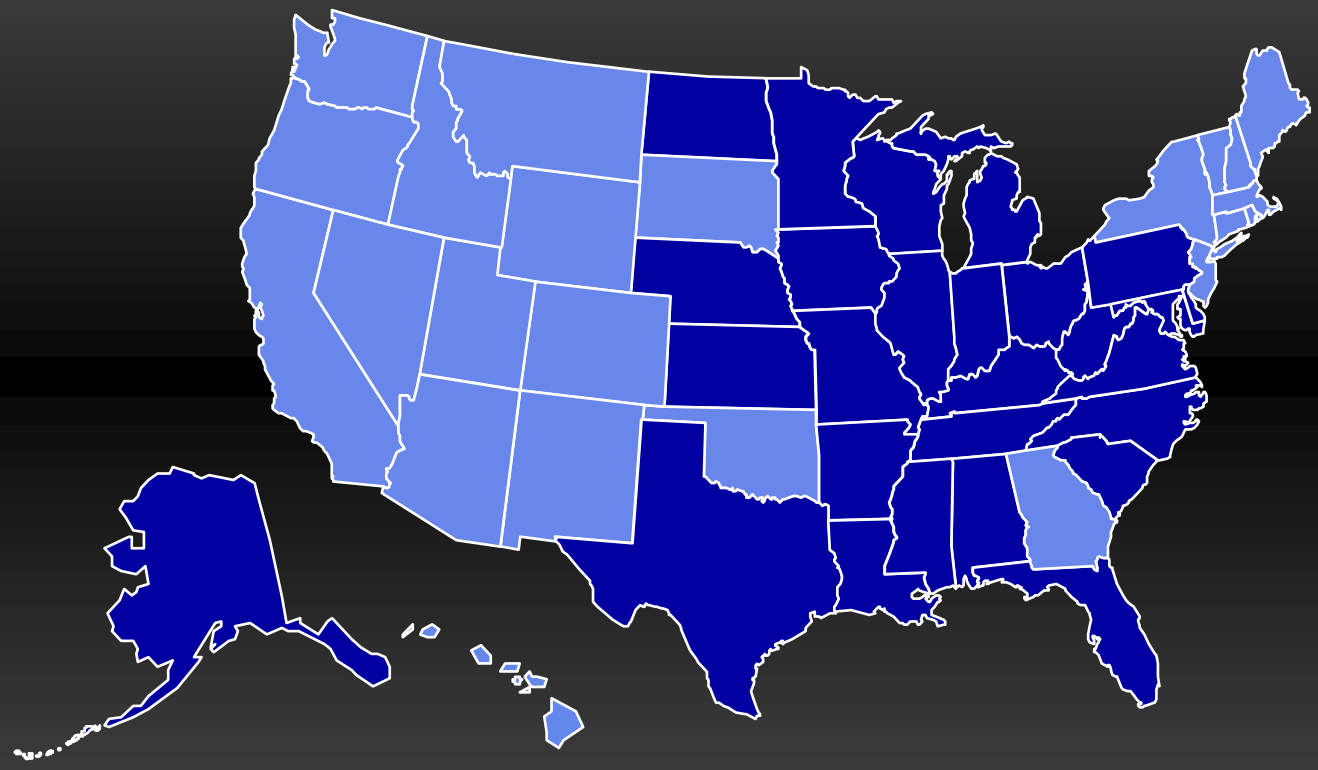

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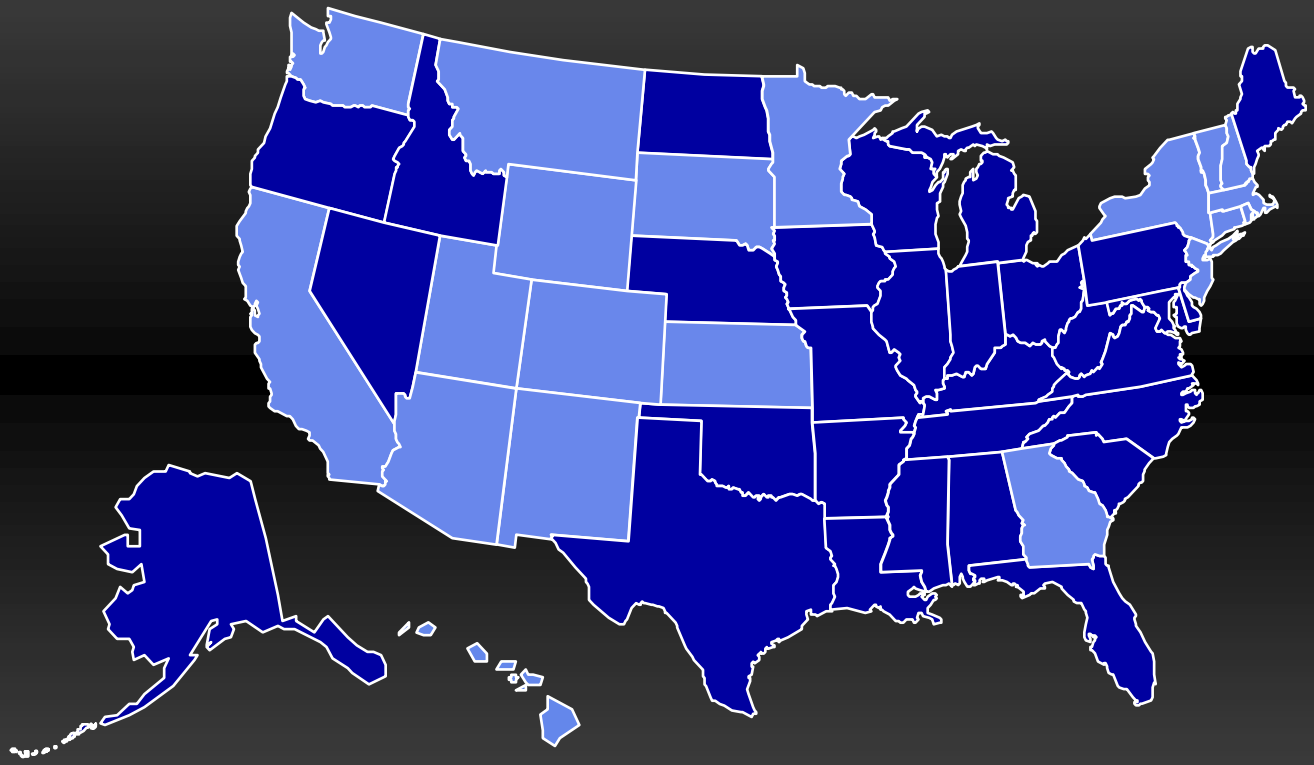

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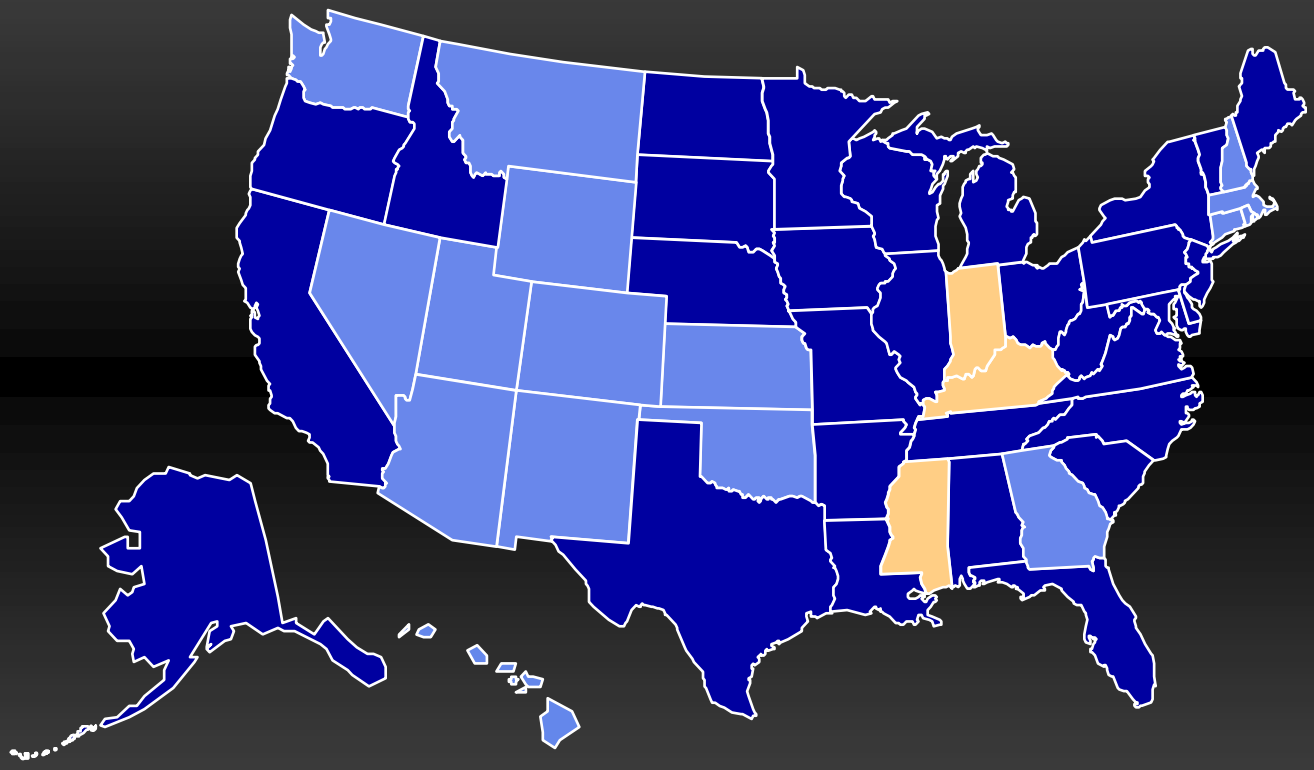

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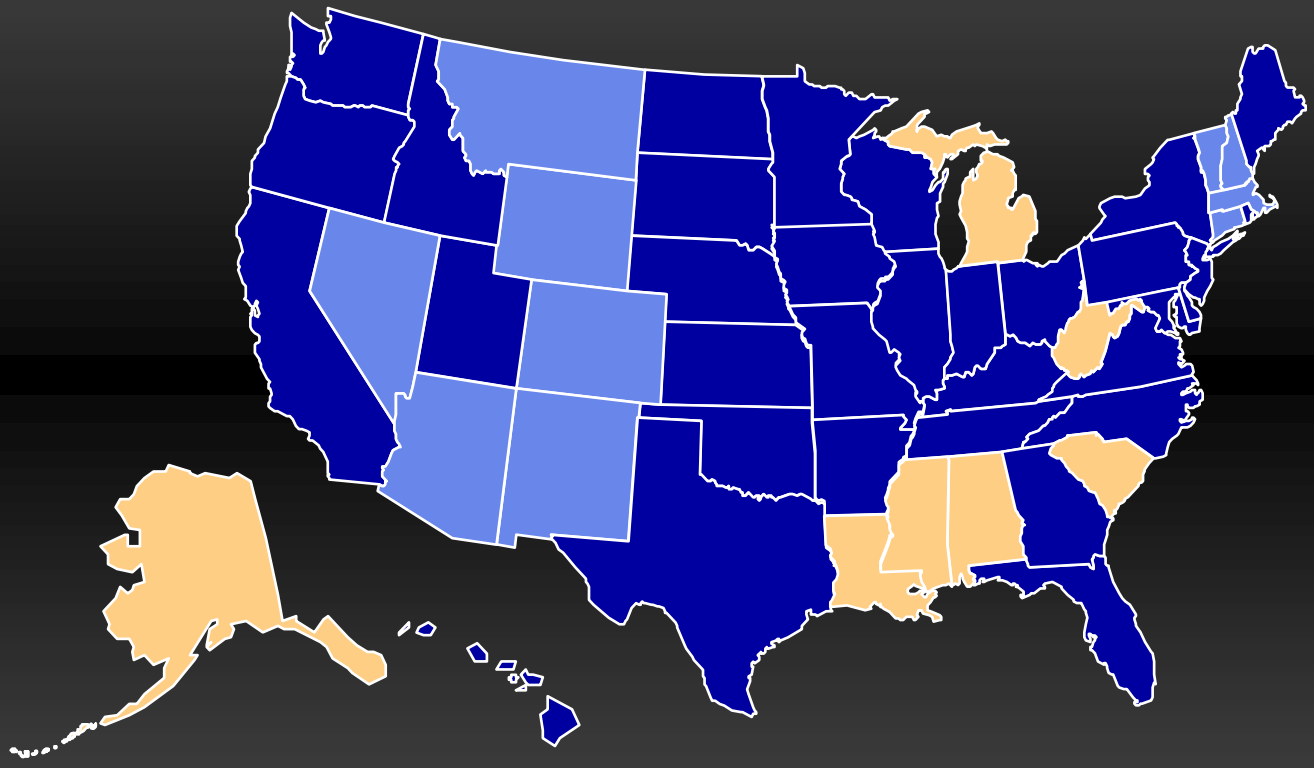

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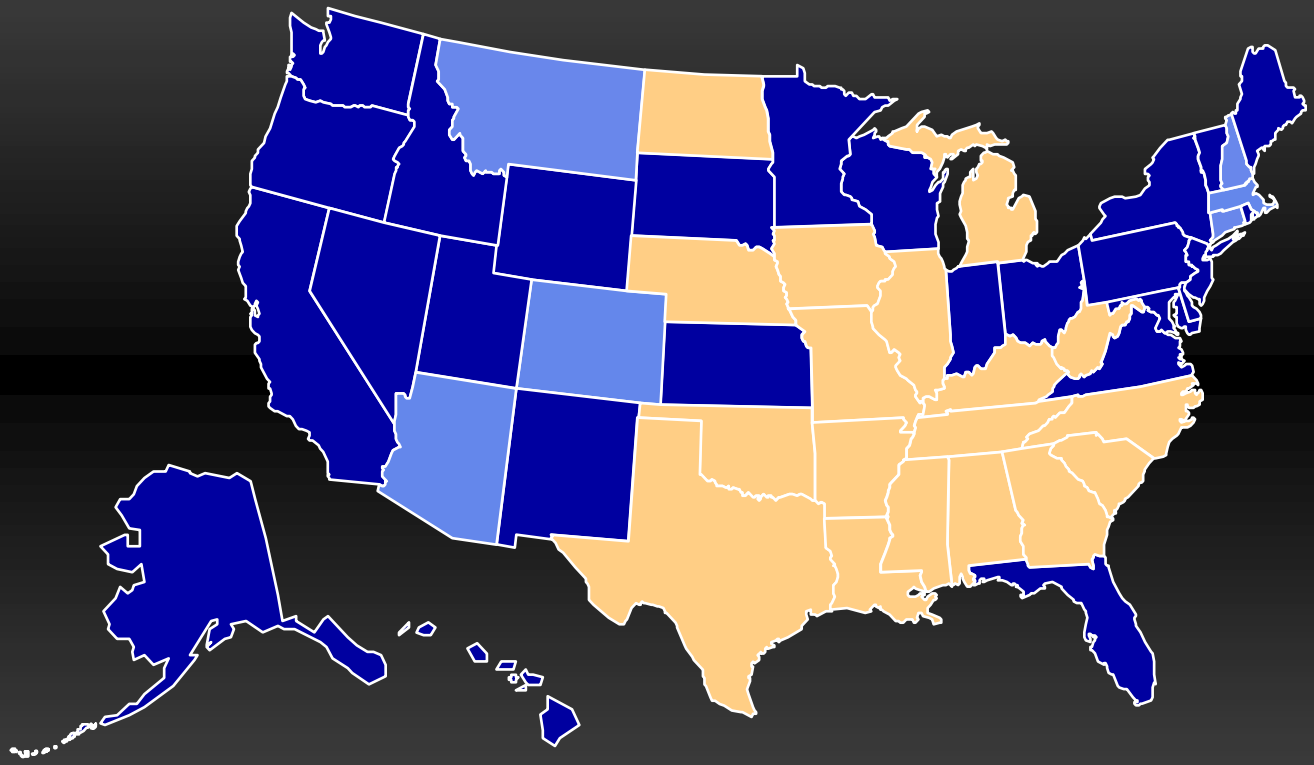

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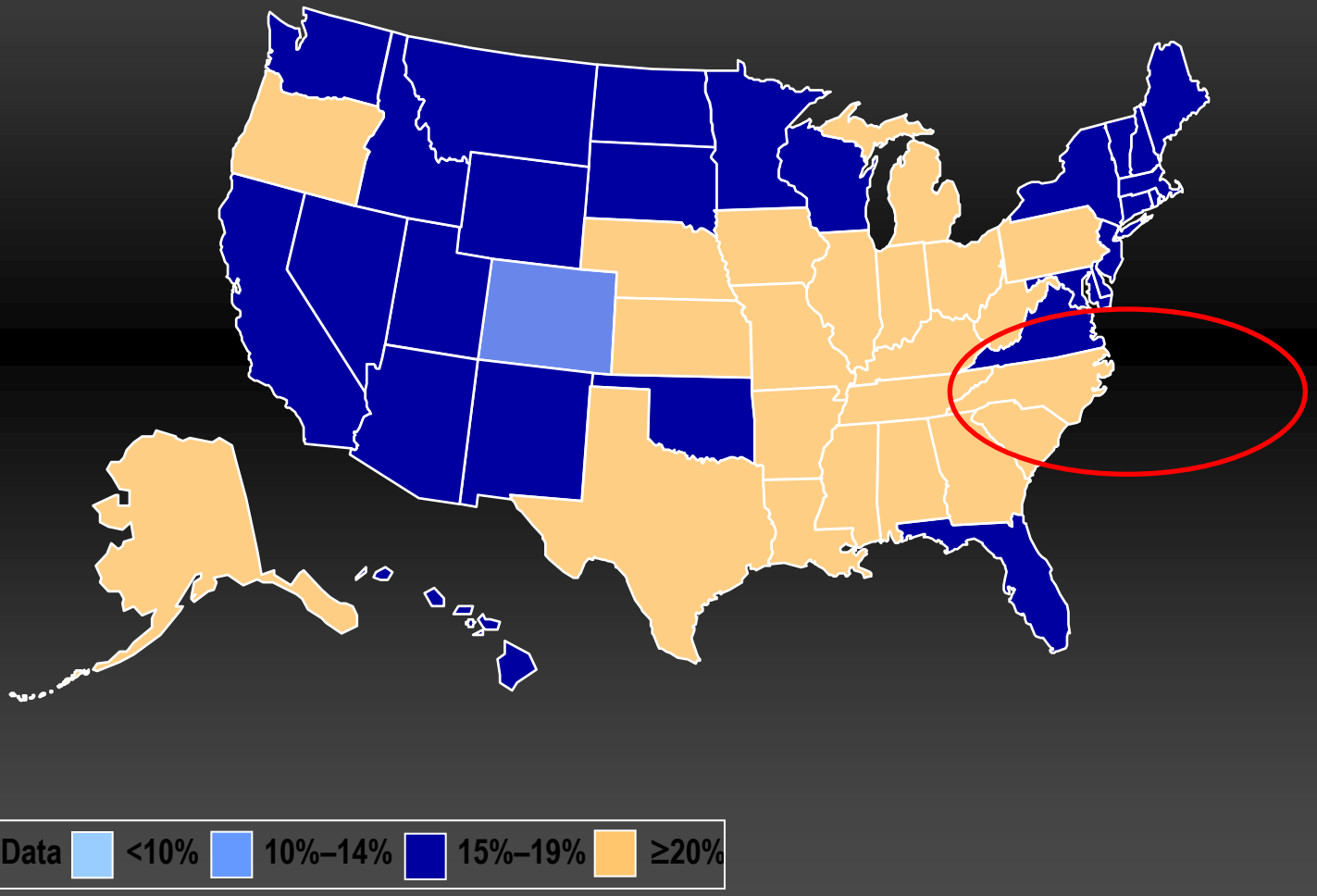

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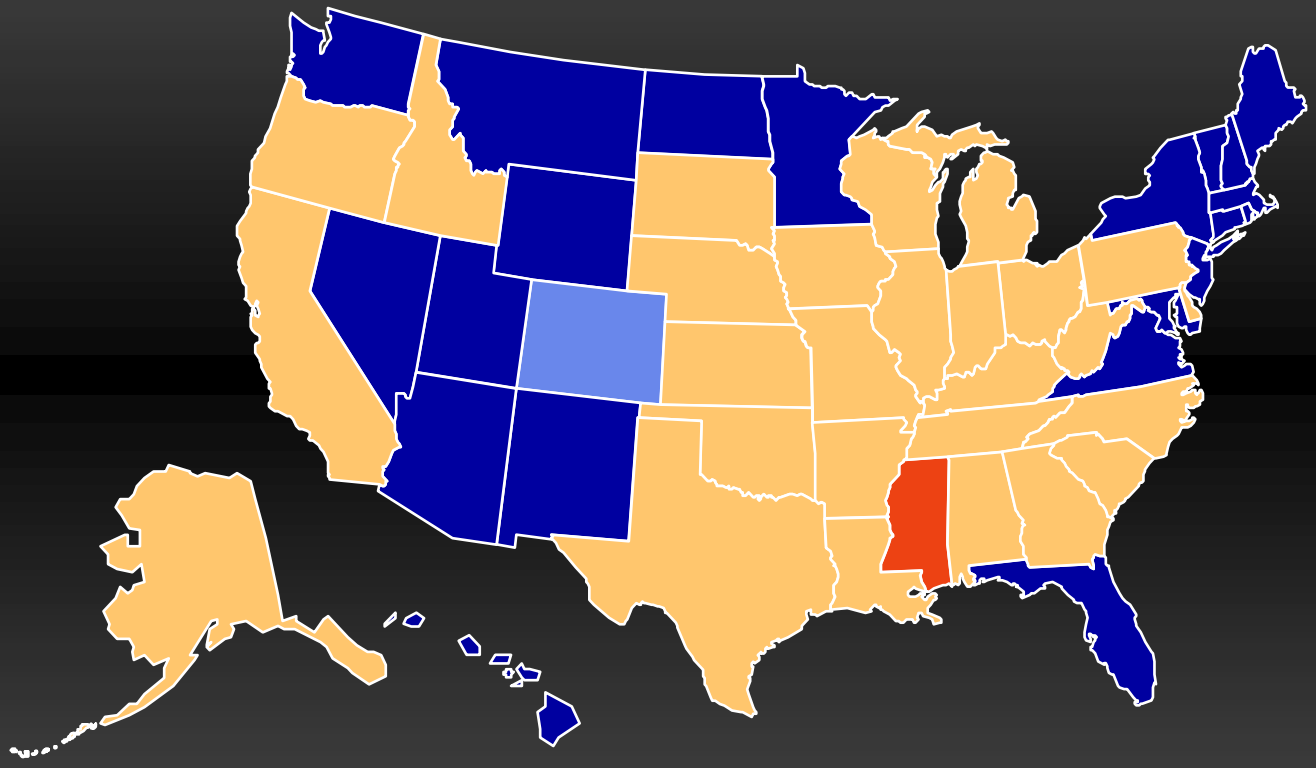

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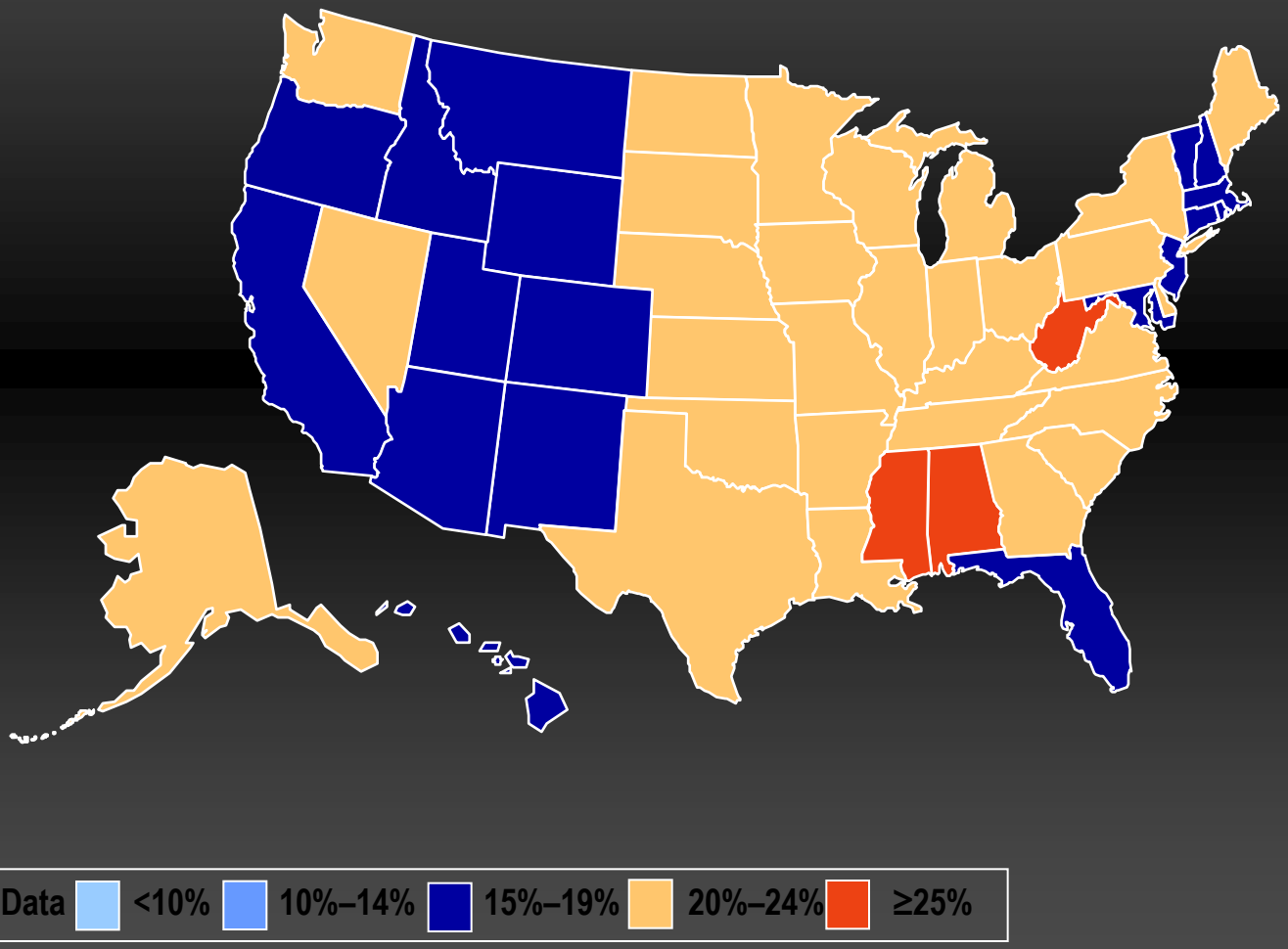

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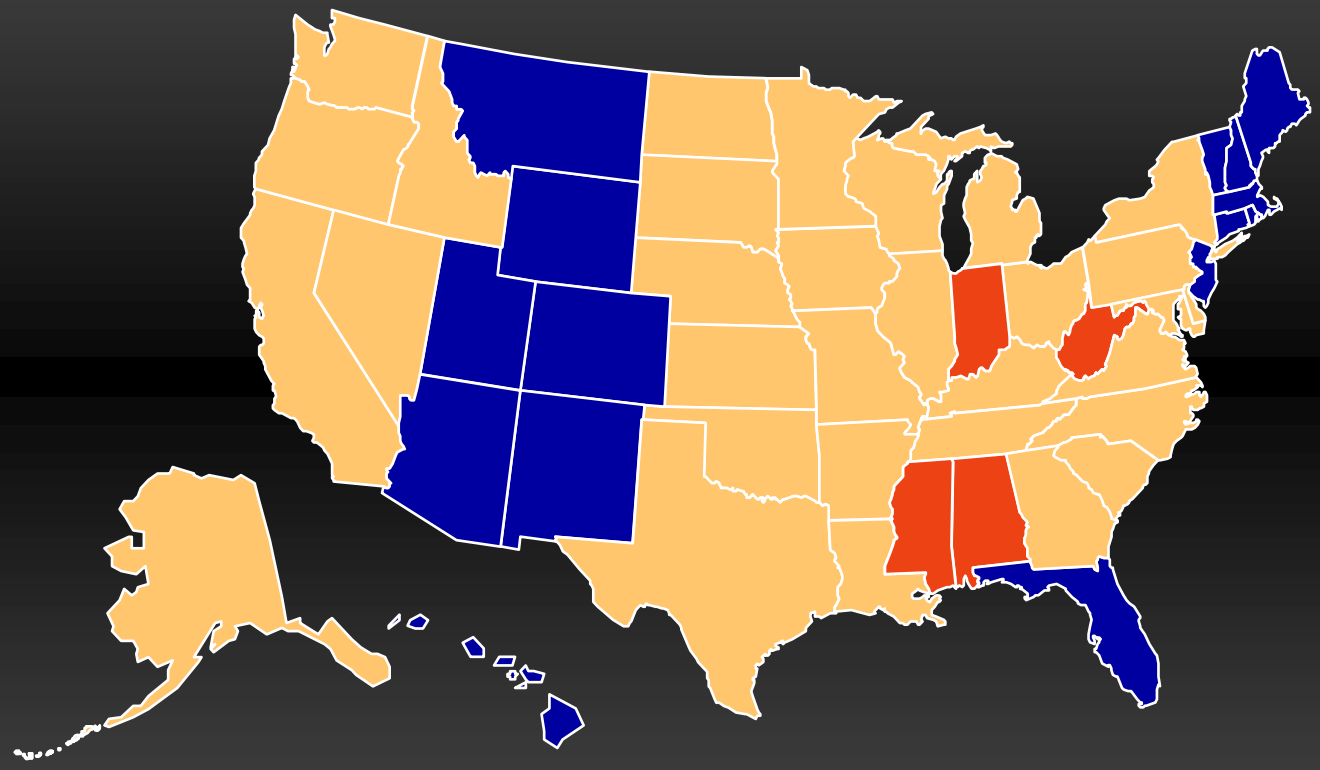

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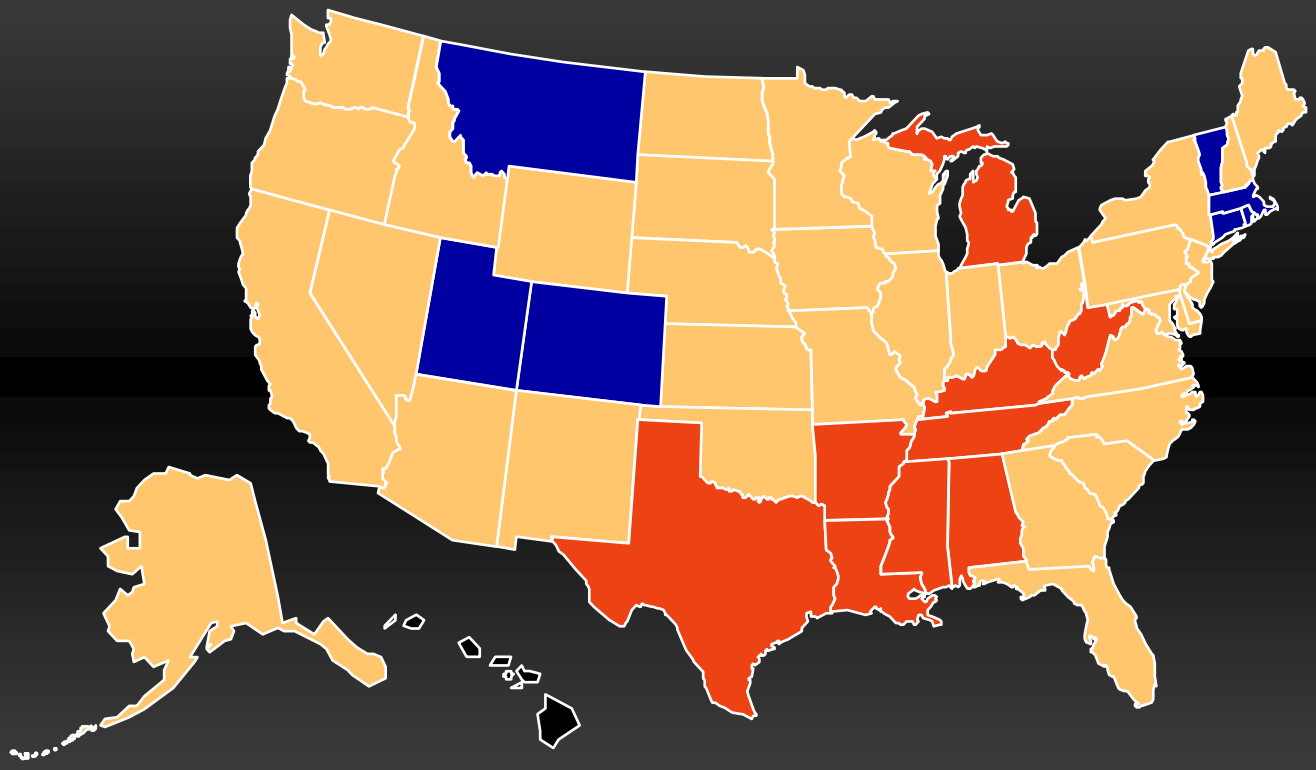

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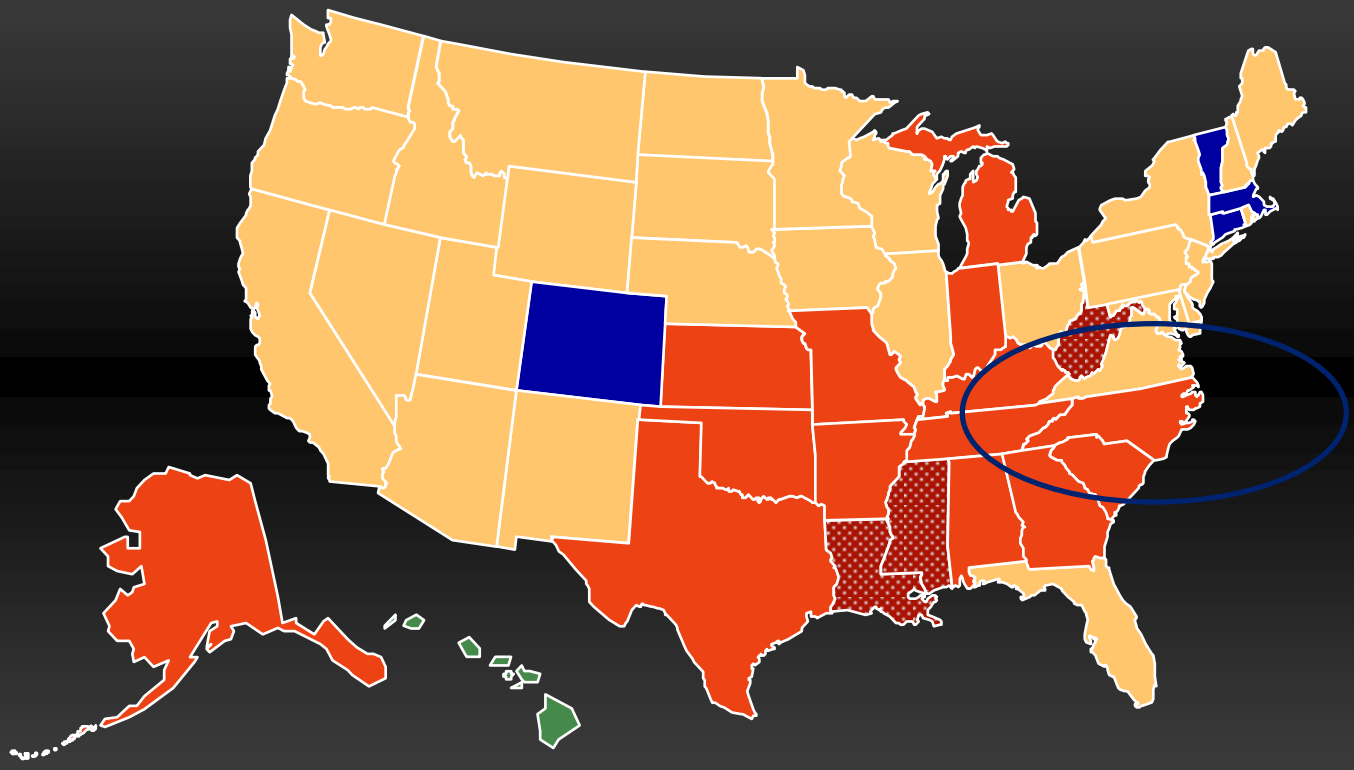

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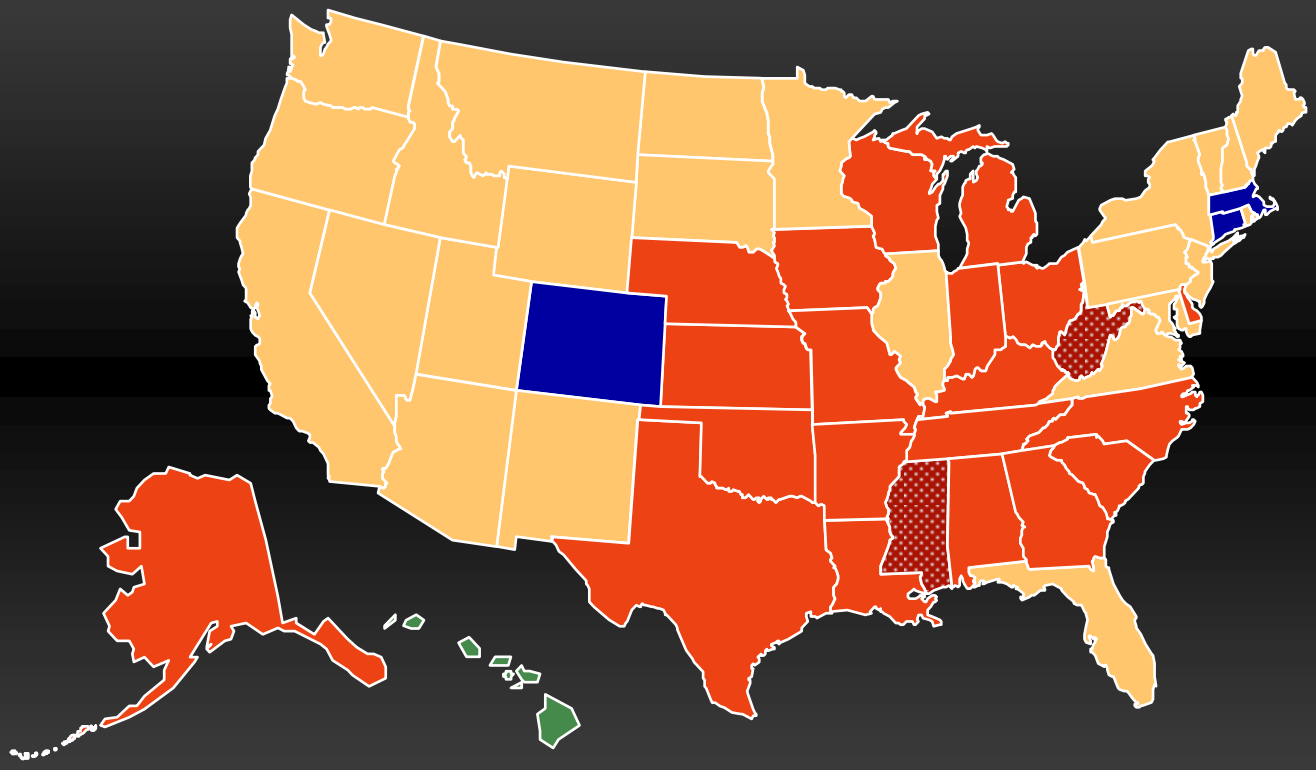

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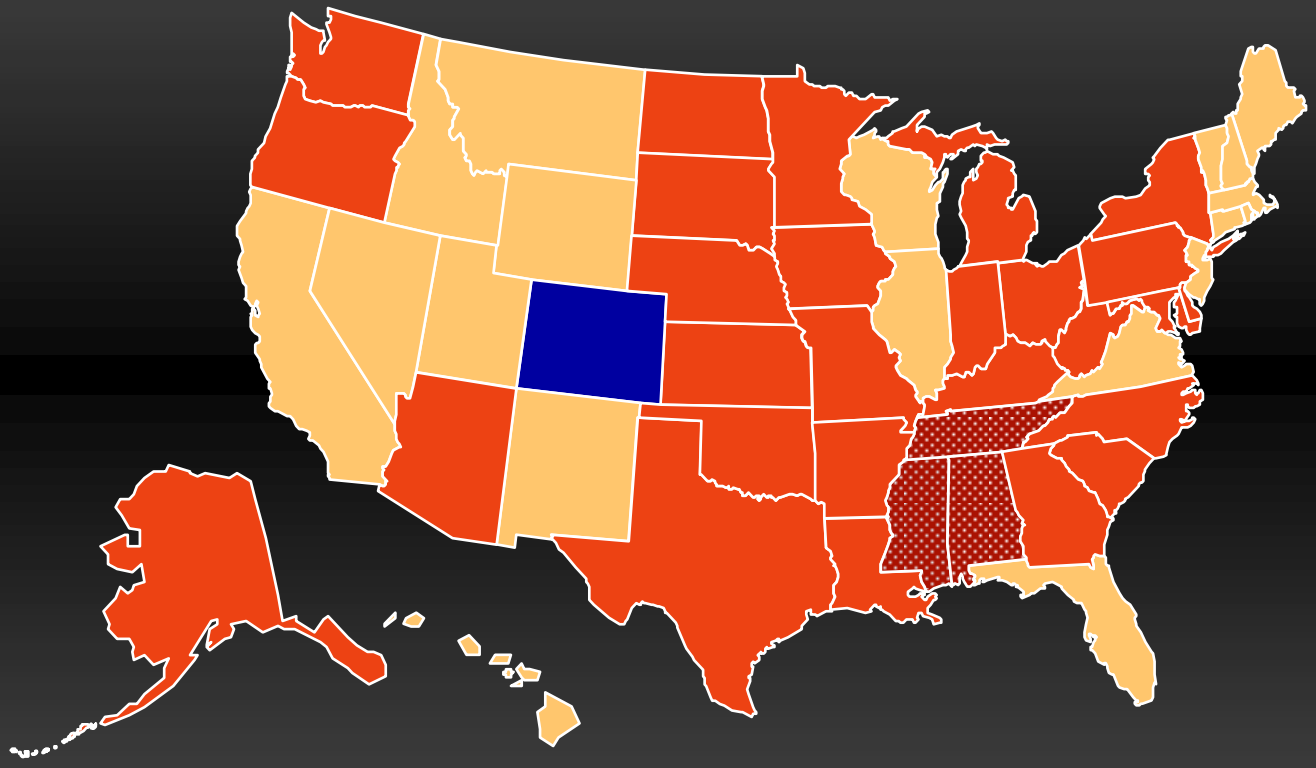

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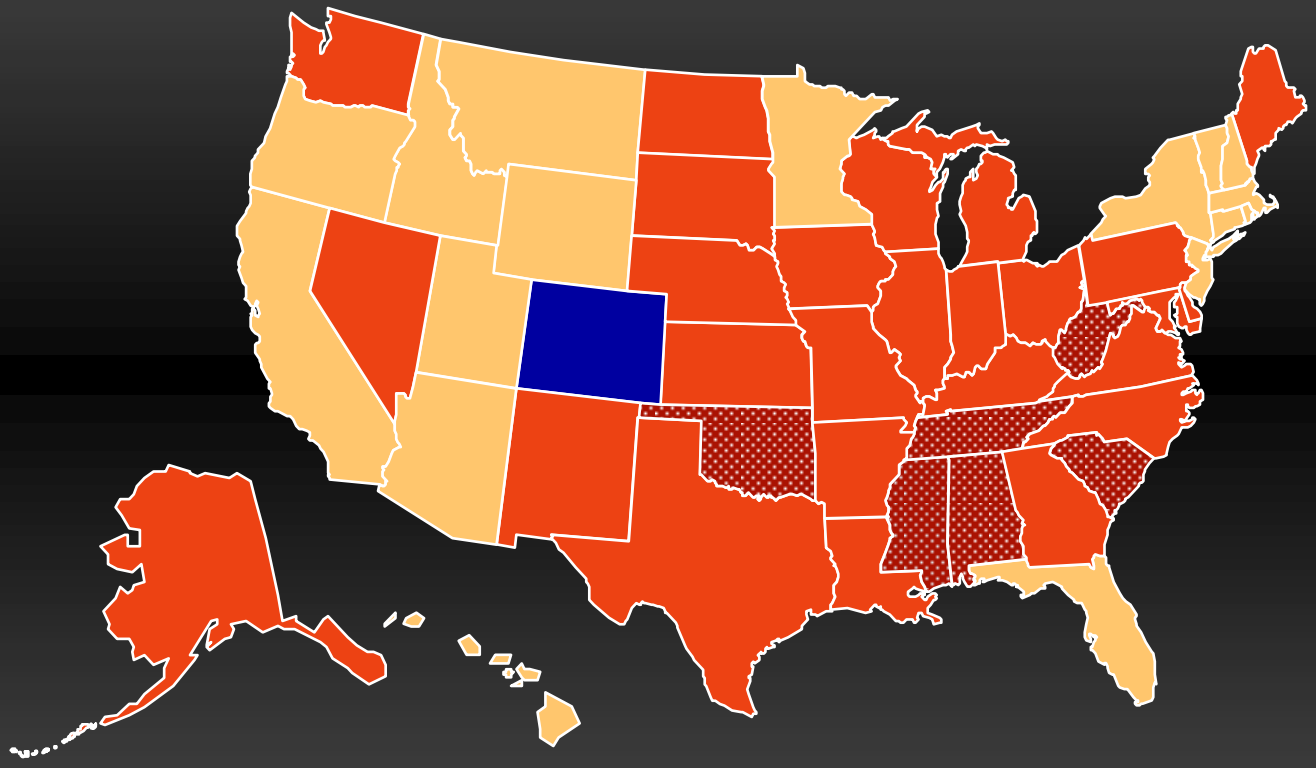

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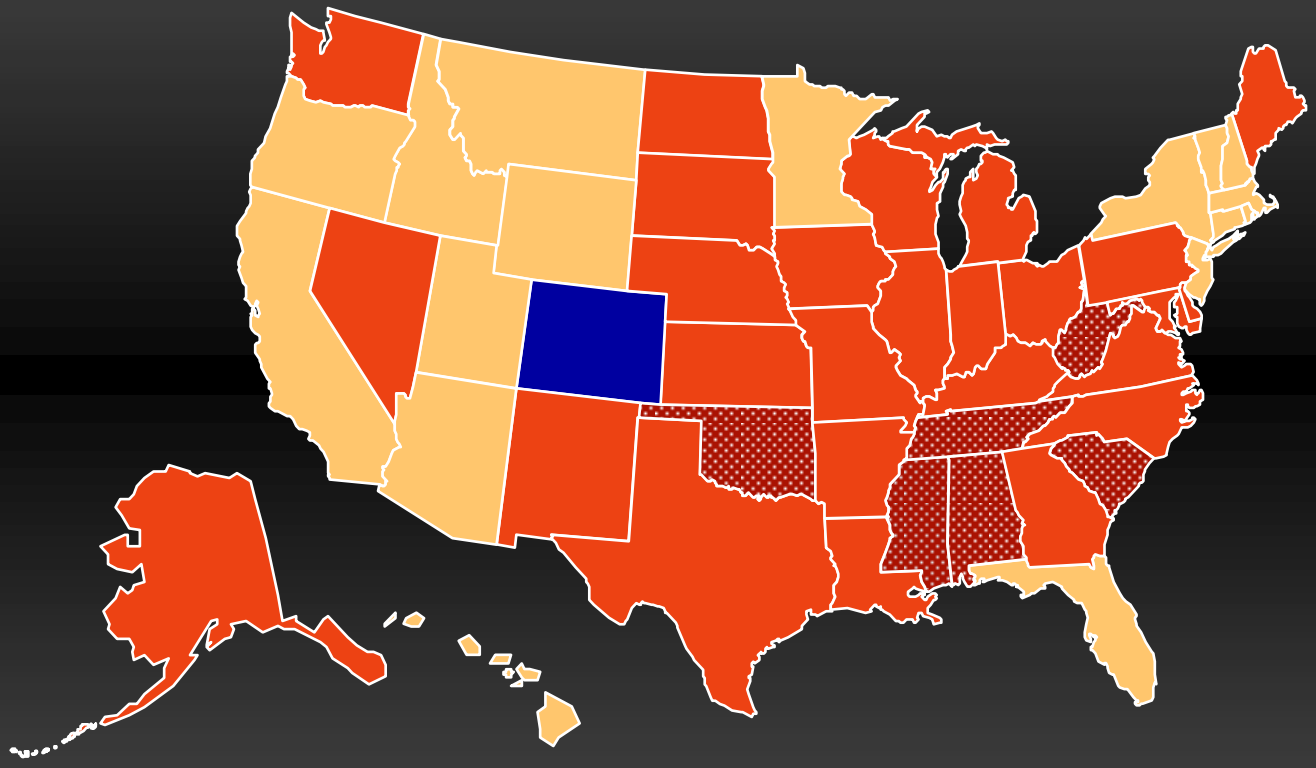
2008



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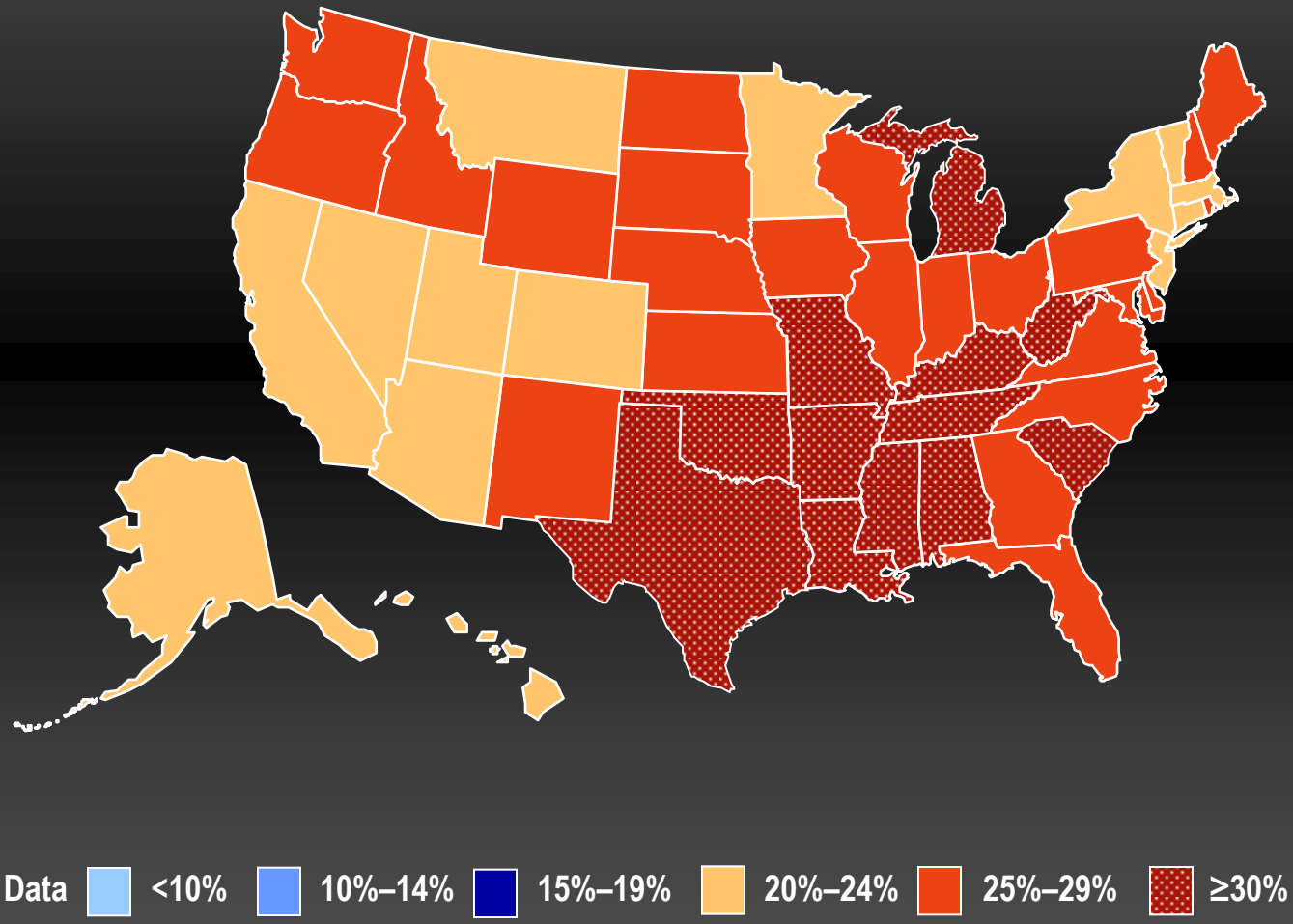
Obesity Trends* Among U.S. Adults
Behavioral Risk Factor Surveillance System, 2010



Alzheimer's Disease in NC

- NC is one of top 10 states with greatest increases in AD cases (Alzheimer's Association 2013)

- Why?????

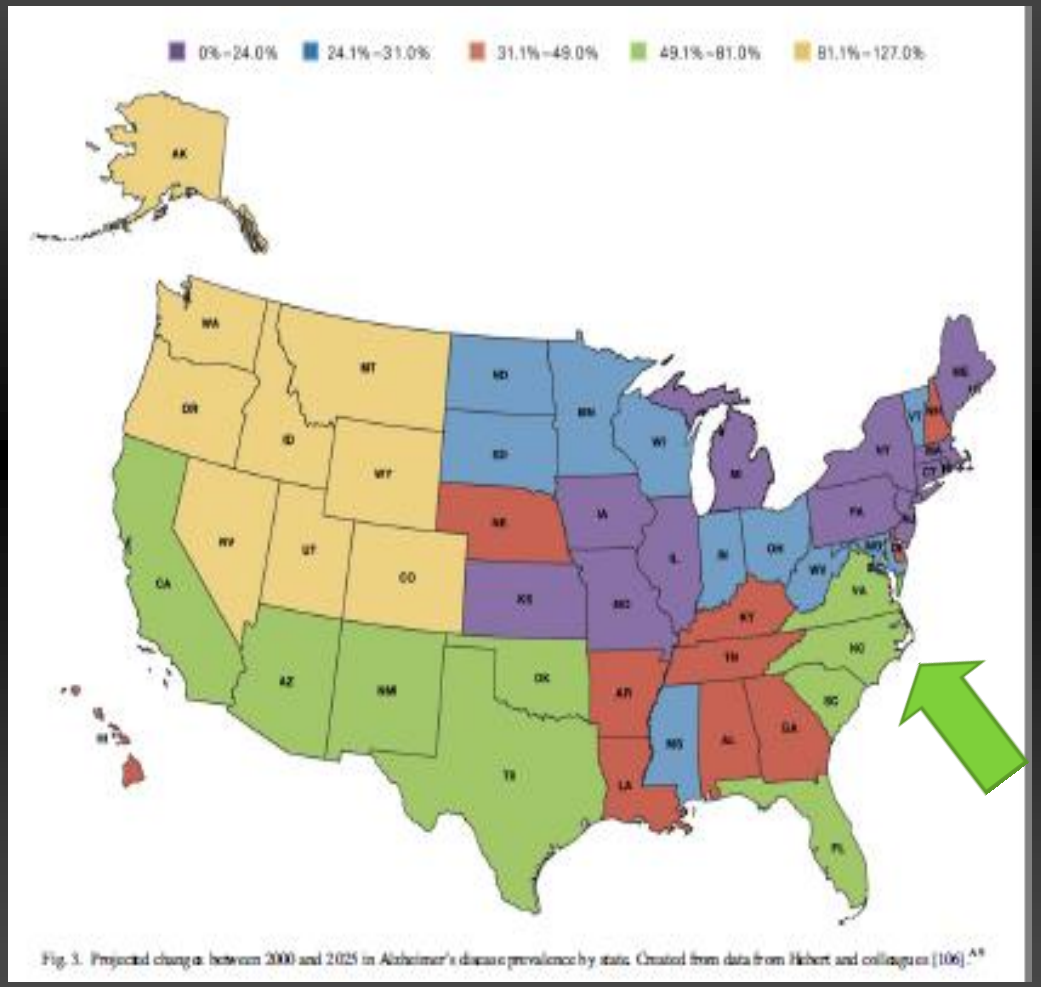


Fig. 3. Projected change between 2000 and 2025 in Alzheimer's disease prevalence by state. Created from data from Hebert and colleagues [106].[A9]

Alzheimer's Disease in NC

- Reasons:
- Age and minority demographics
- Other AD risk factors
  - Metabolic conditions: pre-diabetes, diabetes, obesity, dyslipidemia hypertension
- NC is in top 10 states for pre-diabetes, diabetes, and obesity (CDC)
  - 1.25 million North Carolinians have pre-diabetes or Type 2 Diabetes
  - 66% of North Carolinians >50 years of age are either overweight or obese

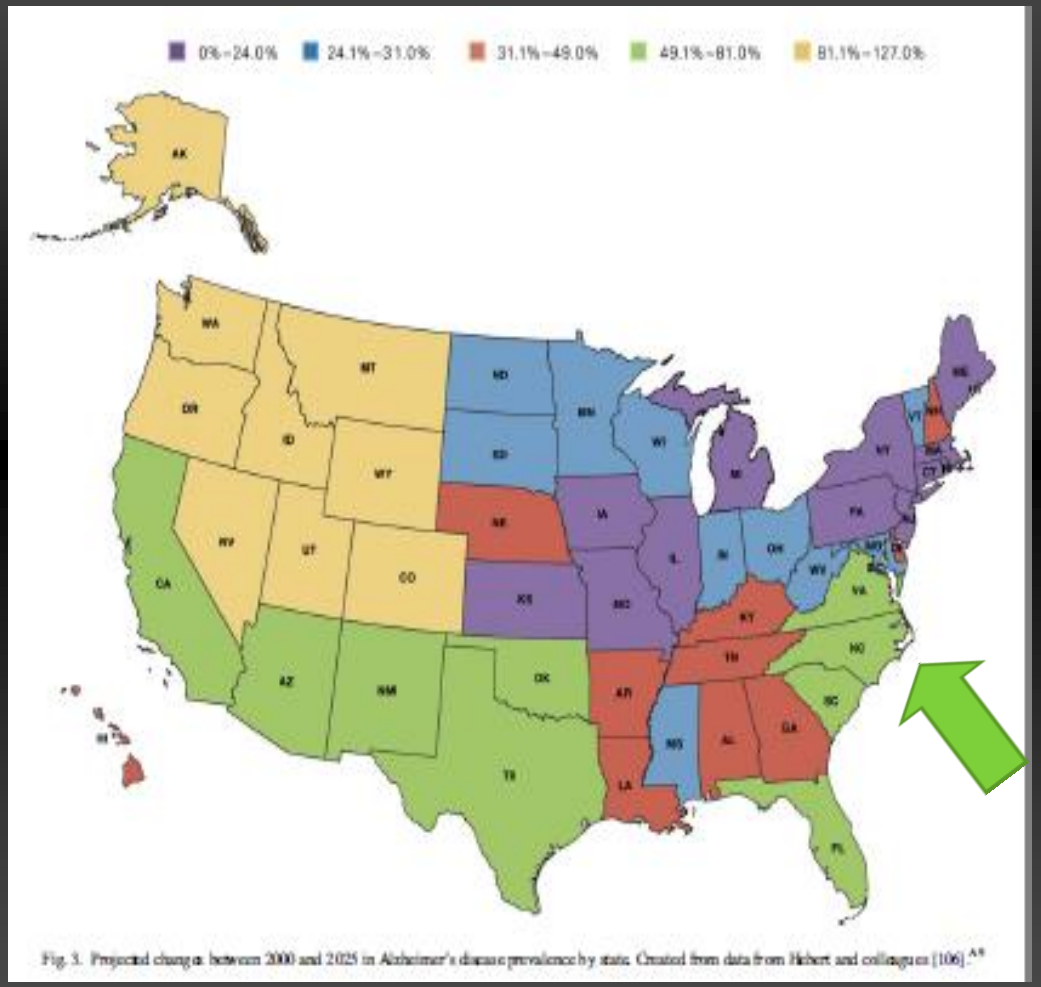


Fig. 3. Projected changes between 2000 and 2025 in Alzheimer's disease prevalence by state. Created from data from Hebert and colleagues [106].[A9]

Where we are today….

Bad News

- There is no treatment that will allow us to prevent the disease from occurring
- There is no treatment to stop the disease once it has started

Good news

- There is a lot we can do to lower risk of developing the disease
- And there are a lot of things we can do to promote successful aging

whether you are simply worried but still doing well

or whether you already have a memory condition

OBJECTIVES

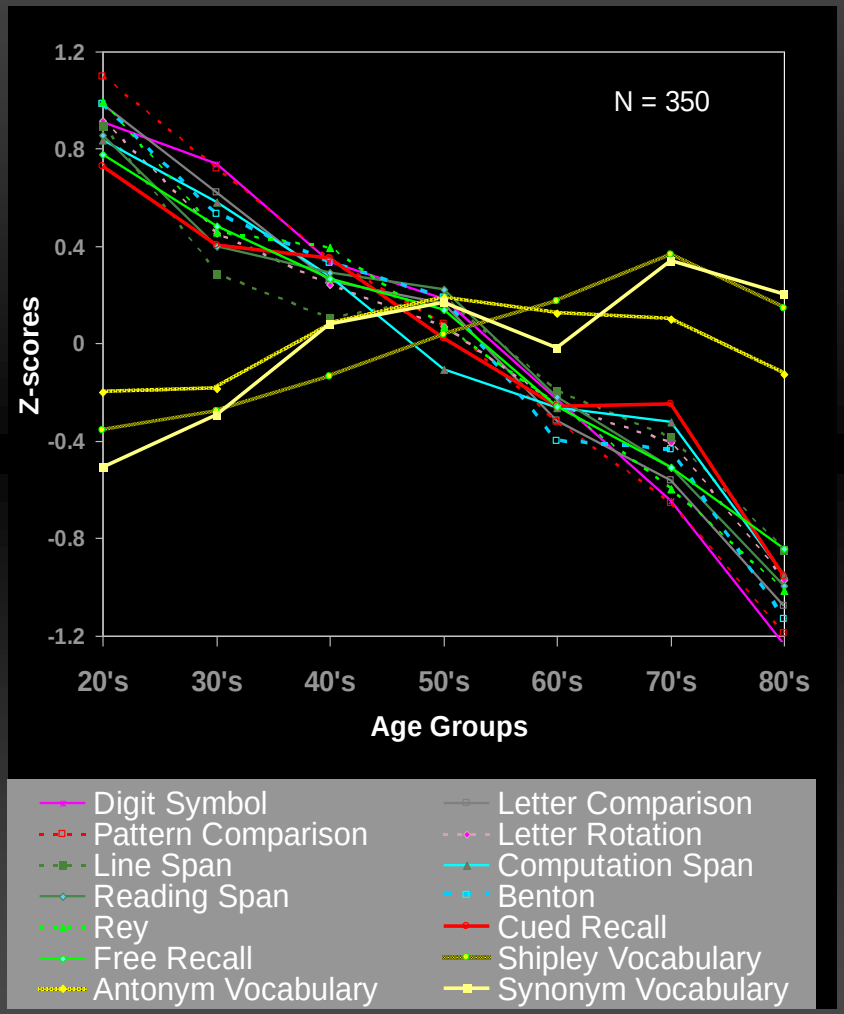
Answer the following questions:

- What are the differences between early Alzheimer's disease and forgetfulness with age? Are they the same thing?
- What is involved in early diagnosis and detection?
- Why is it important to diagnose early if no real disease modifying treatments?
- Set stage for discussion of barriers to diagnosis

Differentiating Alzheimer's disease from cognitive aging

Implications for Screening

What is Normal Cognitive Aging?



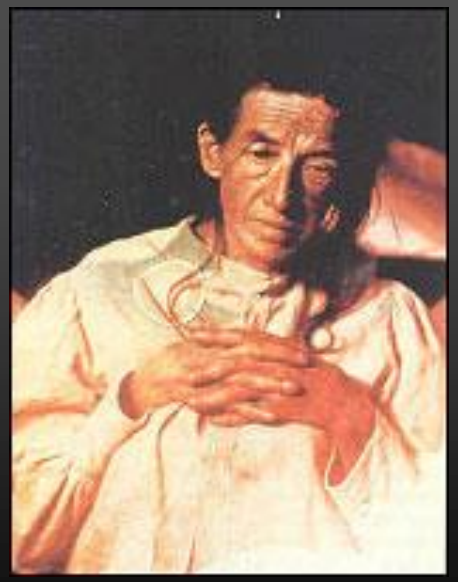
- Linear decline by age on measures of attention, concentration, rapid visuospatial analysis, episodic memory
- Resistant to age are aspects of semantic knowledge (vocabulary) and abstraction

From Park DC et al 2002, Psychology & Aging, 17, p. 305.

Normal Aging

- Most common cause of memory complaints in the elderly
- Specific areas of cognitive change are in selected aspects of recent memory (retrieval from long term storage)
- Leads to difficulty across memory retrieval tasks including name recall
- Can be facilitated with retrieval support (e.g. recognition cueing; context)

Alzheimer's disease



"Auguste D" - Alzheimer's Original Case

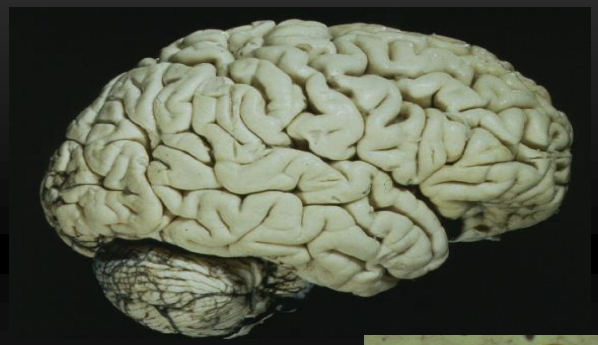
Admitted to Frankfurt Asylum Nov 26, 1901

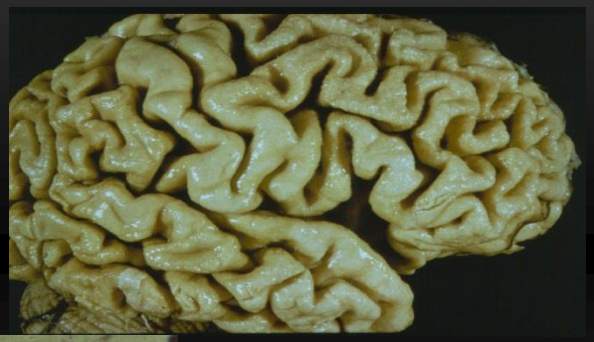
age 51y

- Mistrust of husband and female neighbor
- Mistakes in food preparation; neglected housework; could not find way around apartment; hid objects, then could not find them
- Delusions of harm
- Memory deficits, perseverative, aphasic
- Agitated, screaming, strikes other patients

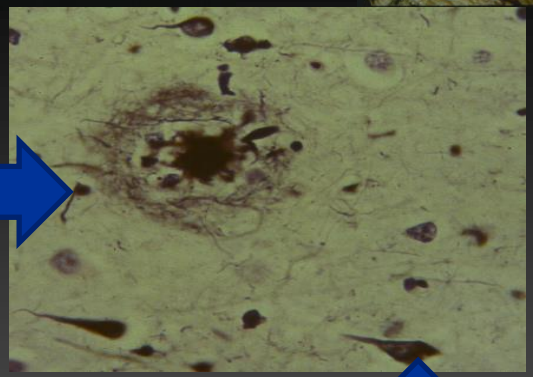
Died at age 55y in April 1906; bedridden, decubitus, 74 lbs

Hallmark Brain Pathology of Alzheimer Disease:
Amyloid Plaques & Neurofibrillary Tangles





Beta amyloid "plaques"



Atrophy

Neurofibrillary Tangles (*p-Tau protein*)

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Alzheimer's Disease Research Center

Alzheimer's Disease

- More common than originally appreciated
- Age-associated problem with nearly 50% over age 85 having the illness
- Characteristic problem is different from normal age-related memory loss
  - *profound forgetfulness for recent events- rapid forgetting of new events*
  - *Benefits very little from cuing (recognition)*
- *Gradual but* inexorable progressive impairment
- Leads to functional disability

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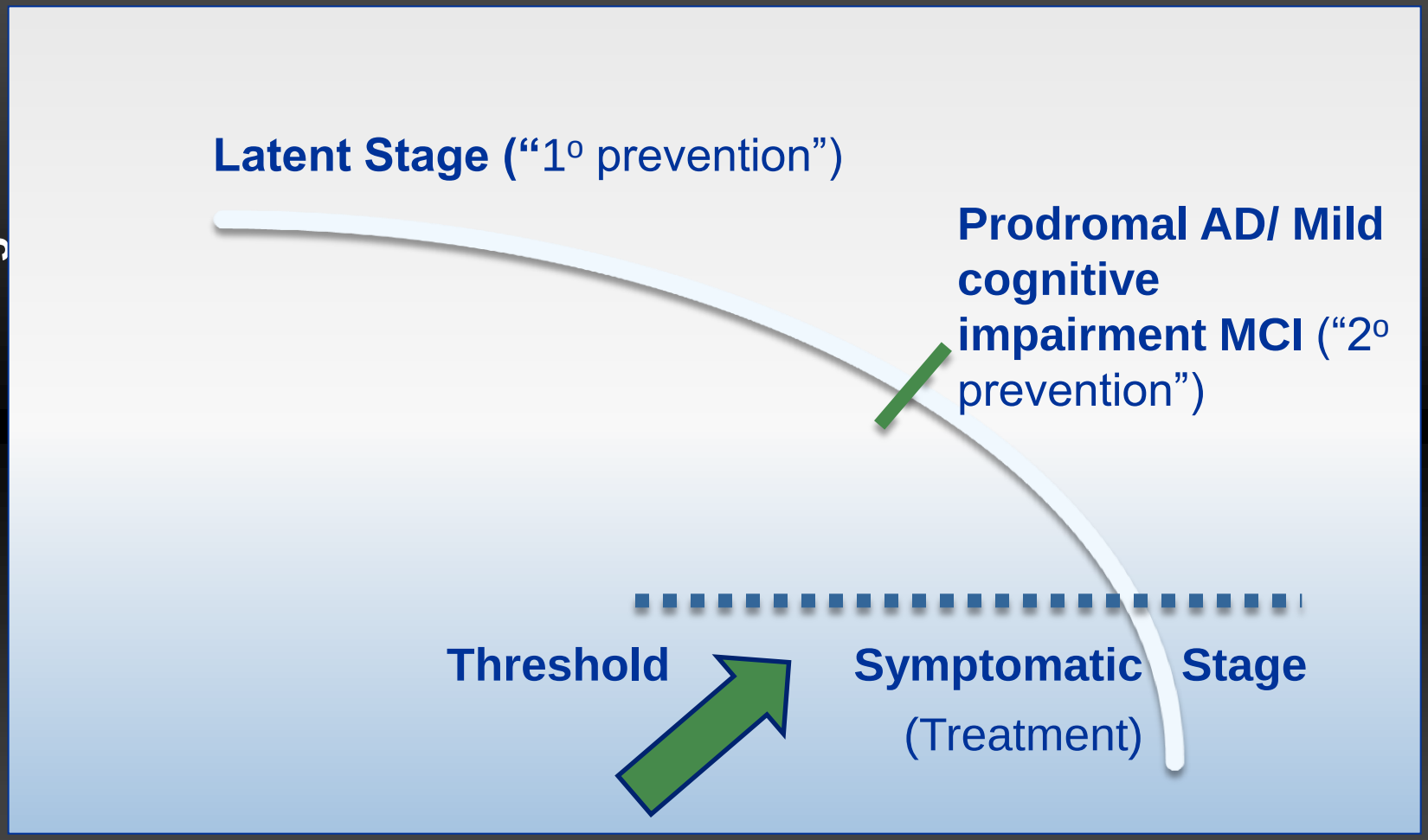
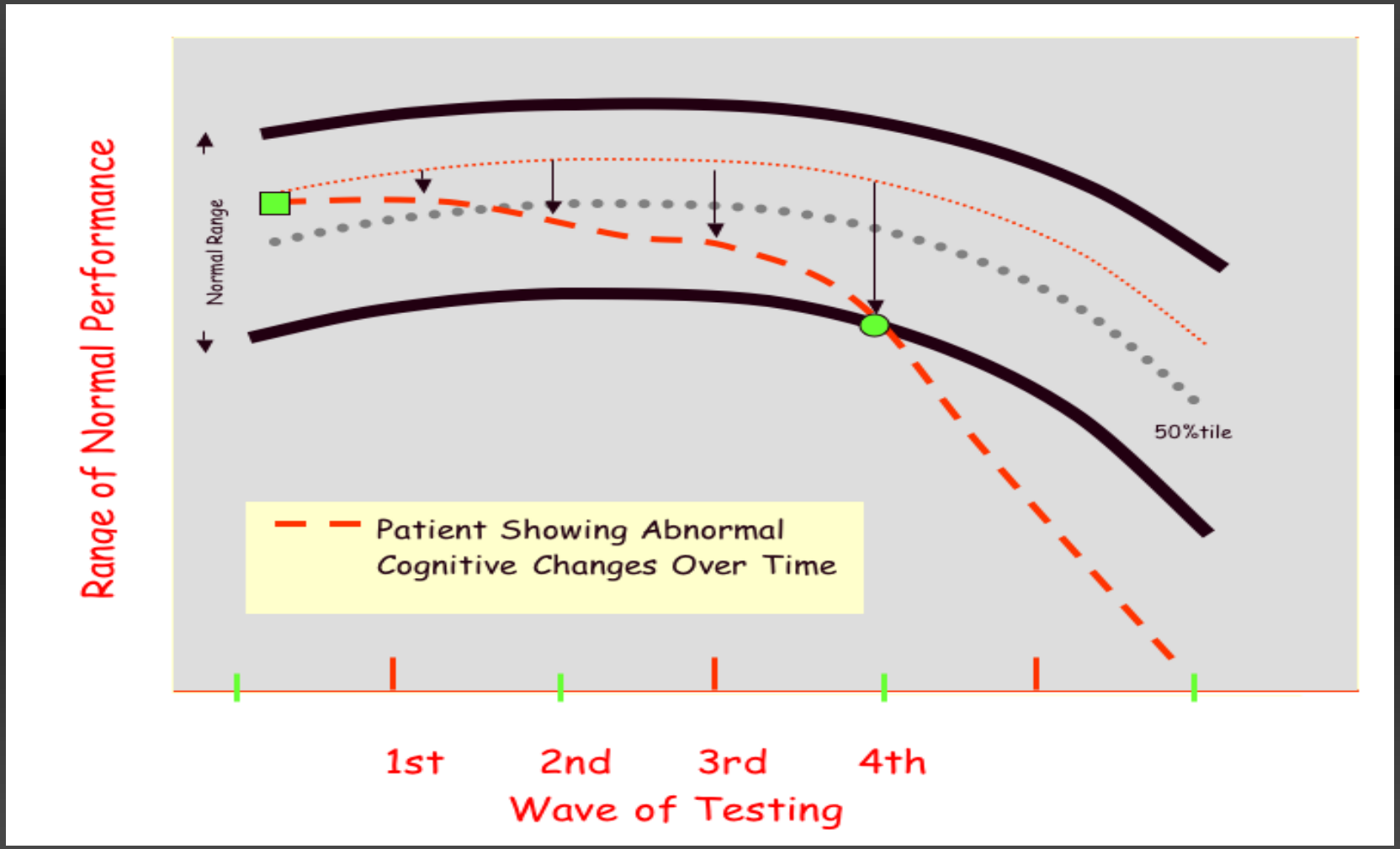
Joseph and Kathleen Bryan
Alzheimer's Disease Research Center

Alzheimer's- Chronic disease



Welsh-Bohmer, KA. *Neuropsychol Rev.* 2008;18(1):70-2.

Inter-individual variability in change over time
"Who is Who" – Normal Aging vs Early AD



Chelune & Foster, CCMS 2007

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PRESCREENING FOR MCI and AD

Test	Dementia *vs.* and ProdAD		ProdAD *vs.*	
	Raw	Adjusted	Raw	Adjusted
3MS	0.894	0.913	0.765	0.810
Verbal Learning Test	0.849	0.869	0.752	0.789
Clock Drawing Test	0.625	0.720	0.597	0.695
Digits Forward	0.575	0.705	0.584	0.706
Digits Backward	0.565	0.702	0.582	0.698
False Alarm rate	0.738	0.804	0.648	0.729
IADLs	0.674	0.742	0.461	0.691

Table: Cache County Data- Areas under the curve(AUC) for each neurocognitive test considered individually (n=474)

* Adjusted models include age, sex, and education level in years

Abbreviations: 3MS, Modified Mini-Mental State Examination; IADLs, Instrumental Activities of Daily Living

PRESCREENING FOR MCI and AD

Dementia *vs*. and ProdAD	**AUC**	**-2LL**	**Difference**
3MS	**0.913**	183.43	
+ Verbal Learning Test	**0.926**	169.08	14.35*
+ False Alarm Rate	0.928	167.90	1.18
+ IADLs	0.928	166.77	1.13
+ Clock Drawing	0.927	166.76	0.01
+ Digits Forward	0.927	165.57	1.19
+ Digits Backward	0.930	164.08	1.49
ProdAD *vs.*			
3MS	**0.810**	227.72	
+ Verbal Learning Test	**0.829**	213.96	13.76*
+ False Alarm Rate	**0.849**	203.38	10.58*
+ Digits Forward	0.852	201.69	1.69
+ Digits Backward	0.851	201.63	0.06
+ Clock Drawing	0.857	200.53	1.10
+ IADLs	0.857	194.79	5.74*

Table 3. Areas under the curve (AUC) for series of neurocognitive tests†‡

*p-value < 0.05

† All models include age at follow-up, sex, and education level in years

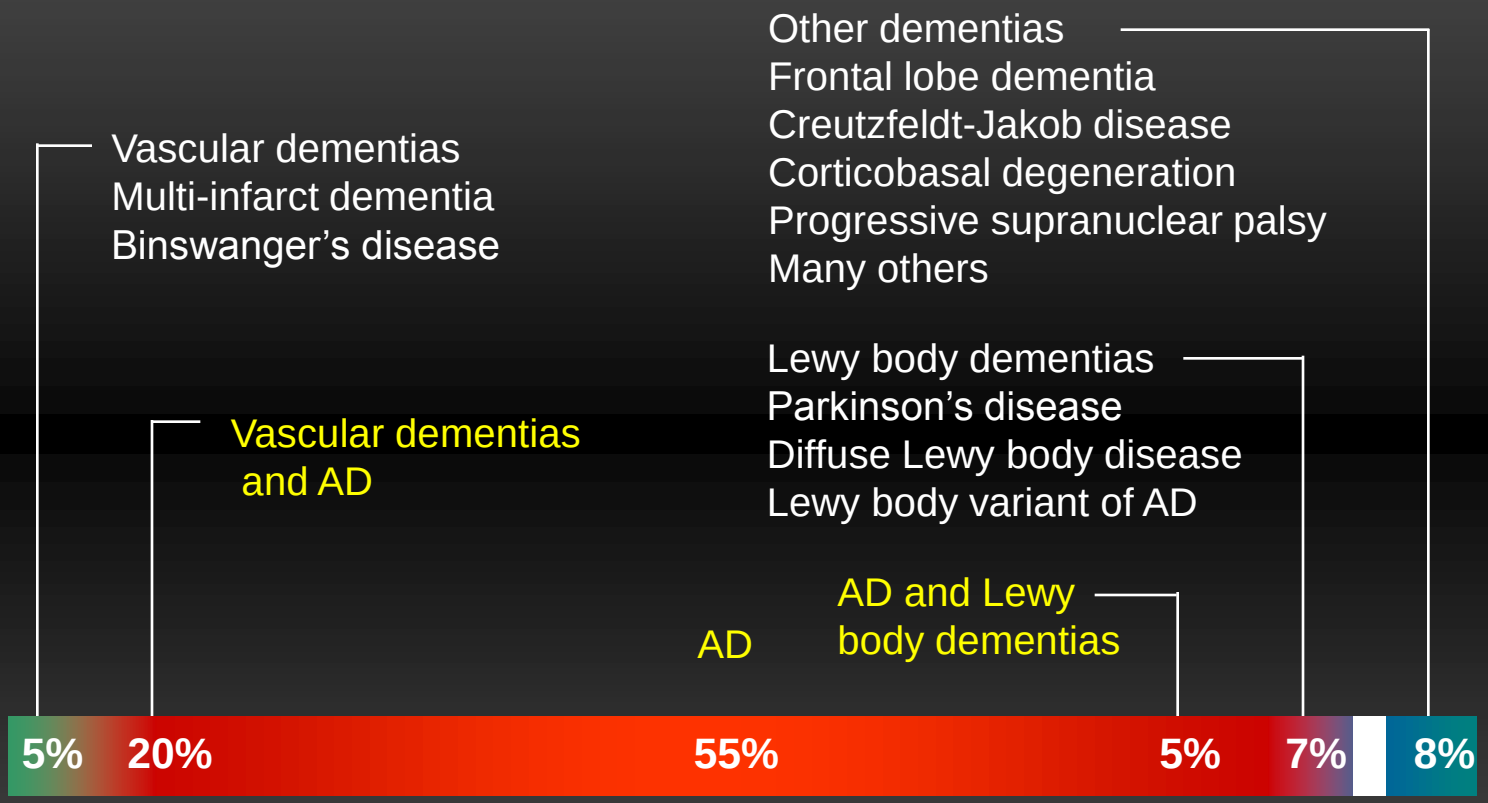
‡Series ordered by strength of individual AUCs (see Table 2 above); each successive model includes all the tests listed above.

Abbreviations: 3MS, Modified Mini-Mental State Examination; IADLs, Instrumental Activities of Daily Living; -2LL, -2 Log Likelihood

Diagnosing MCI and Alzheimer's

- Positive cognitive screens require follow-up:
  - verification over 6 months of persistent problem
- Full diagnostic evaluation:
  - Verification of the clinical syndrome (mental status testing & information from patient and collateral)
  - Laboratory tests to rule out treatable conditions, neurological examination, neuropsychological evaluation when appropriate, neuroimaging

Differential Diagnosis



Small GW, et al. *JAMA*. 1997;278:1363-1371.
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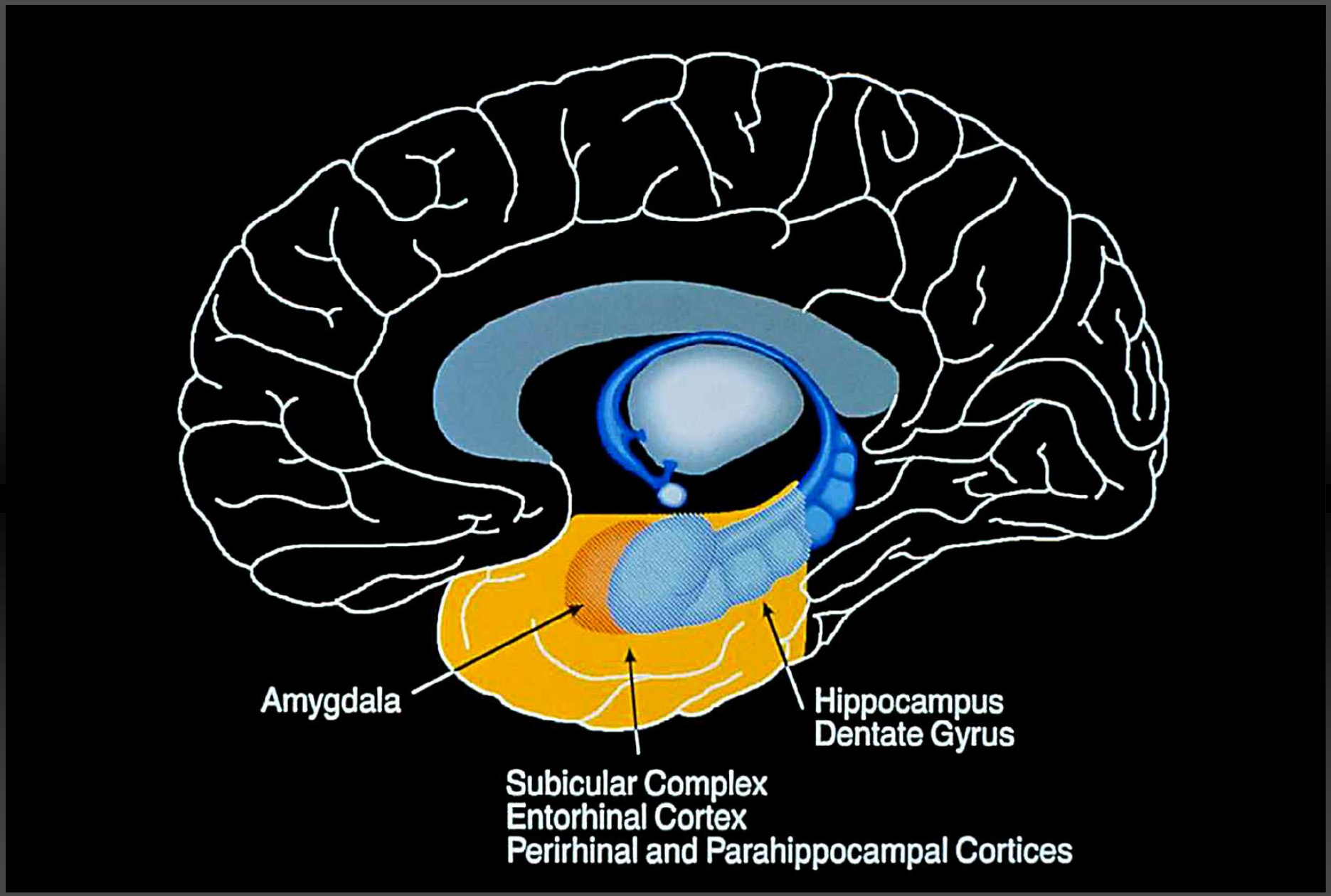
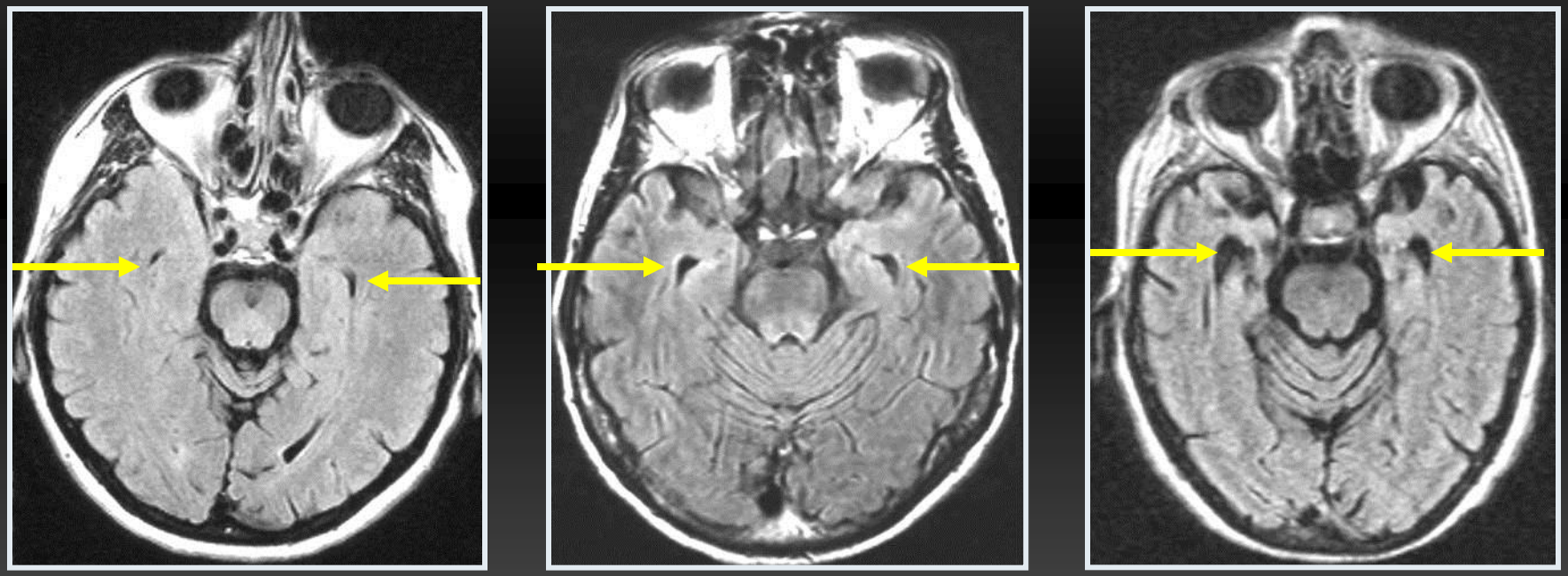
Morris JC. *Clin Geriatr Med*. 1994;10:257-276.


Amygdala
Hippocampus
Dentate Gyrus
Subicular Complex
Entorhinal Cortex
Perirhinal and Parahippocampal Cortices

Neuroimaging Biomarkers

MRI Progressive Hippocampal Atrophy

Normal MCI AD

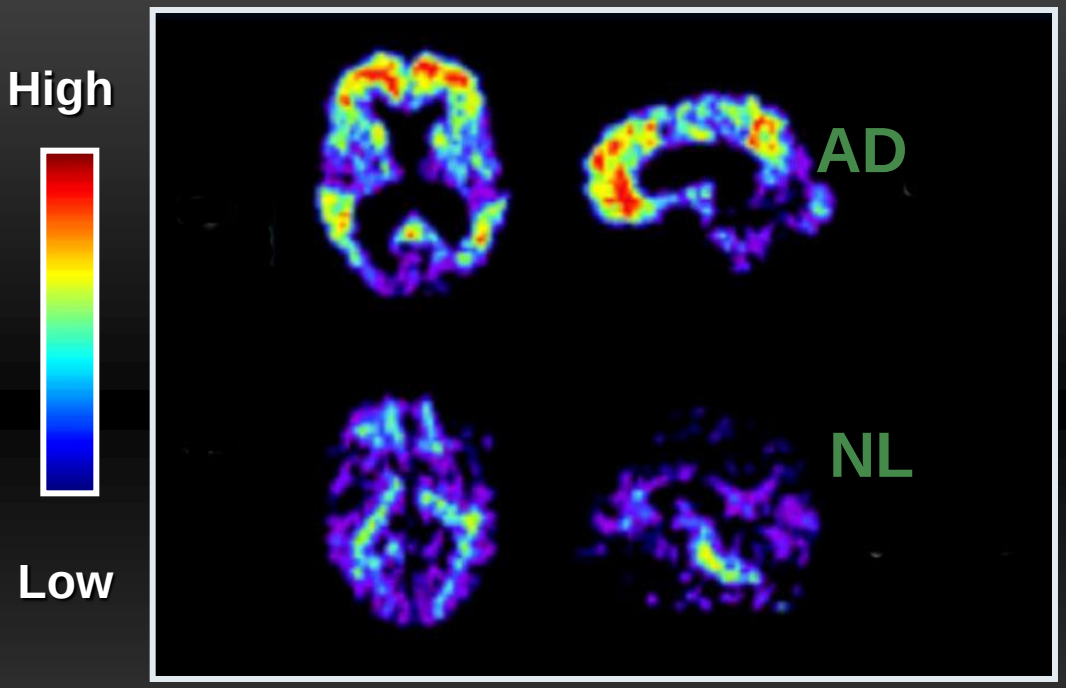


Structural MRI captures disease related changes in brain by measuring volume

Visser et al., 1999 J Neurol 246: 477-85; Jack et al, 1999 Neurology 52:1397-1403;
DeLeon et al., 2007, Annals NYAcadSci 1097: 114-146.

Figure from Jeffrey Browndyke, Ph.D.

β-Amyloid Imaging in AD



PET probes

- 11C-PIB, 18F-FDNP, 11C-BTA-1, AV144

MRI probes

- PUT-Gd-Aβ, Gd-DTPA-$Aβ_{1-40}$, MION-$Aβ_{1-40}$
- MR microscopy (7 Tesla)

SPECT probes

- 99Tc-10H3

Klunk et al. Ann Neurol. 2004;55:306-319.
Sair et al. *Neuroradiology.* 2004
Poduslo et al. *Neurobiol Dis.* 2002

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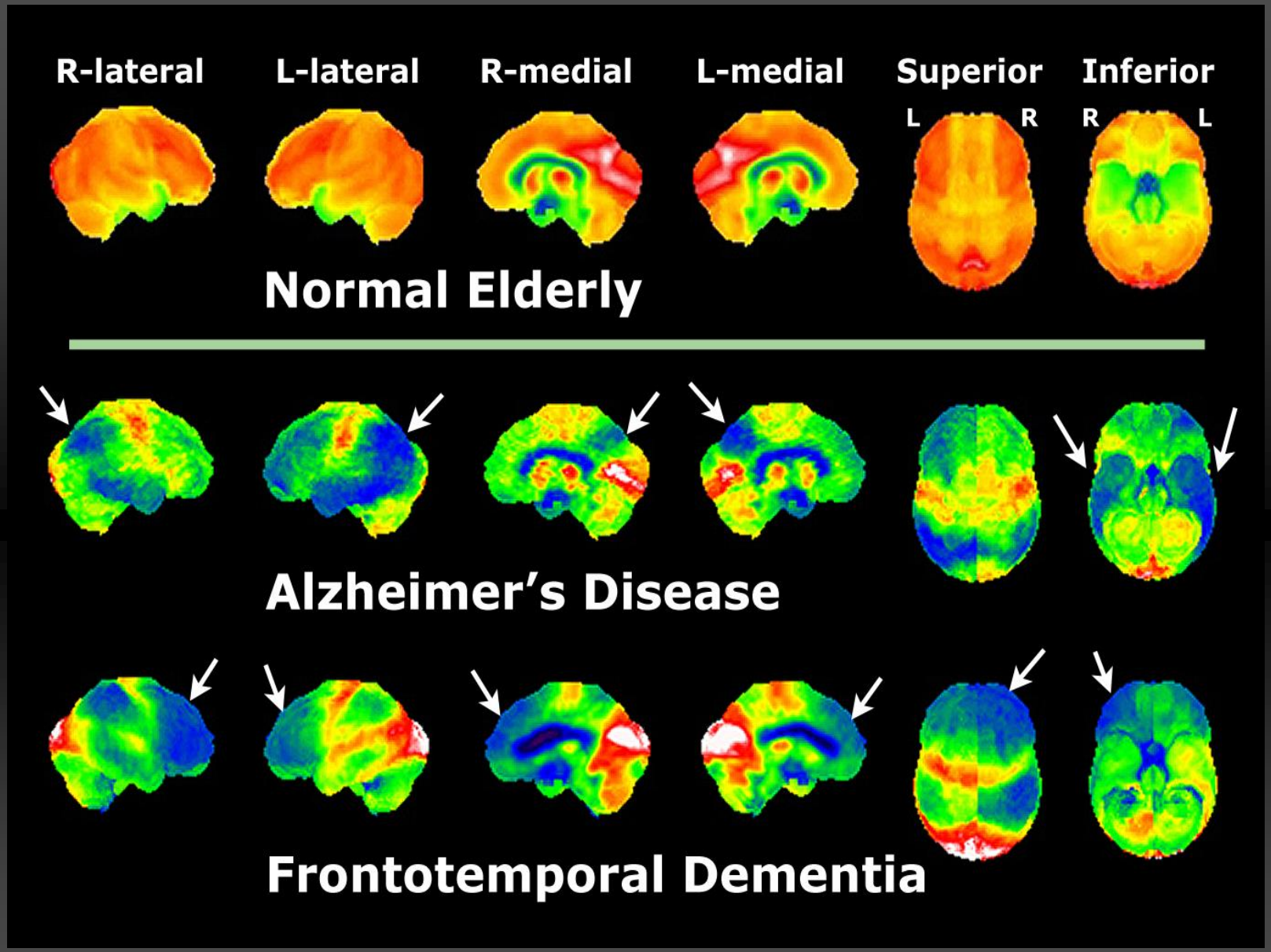

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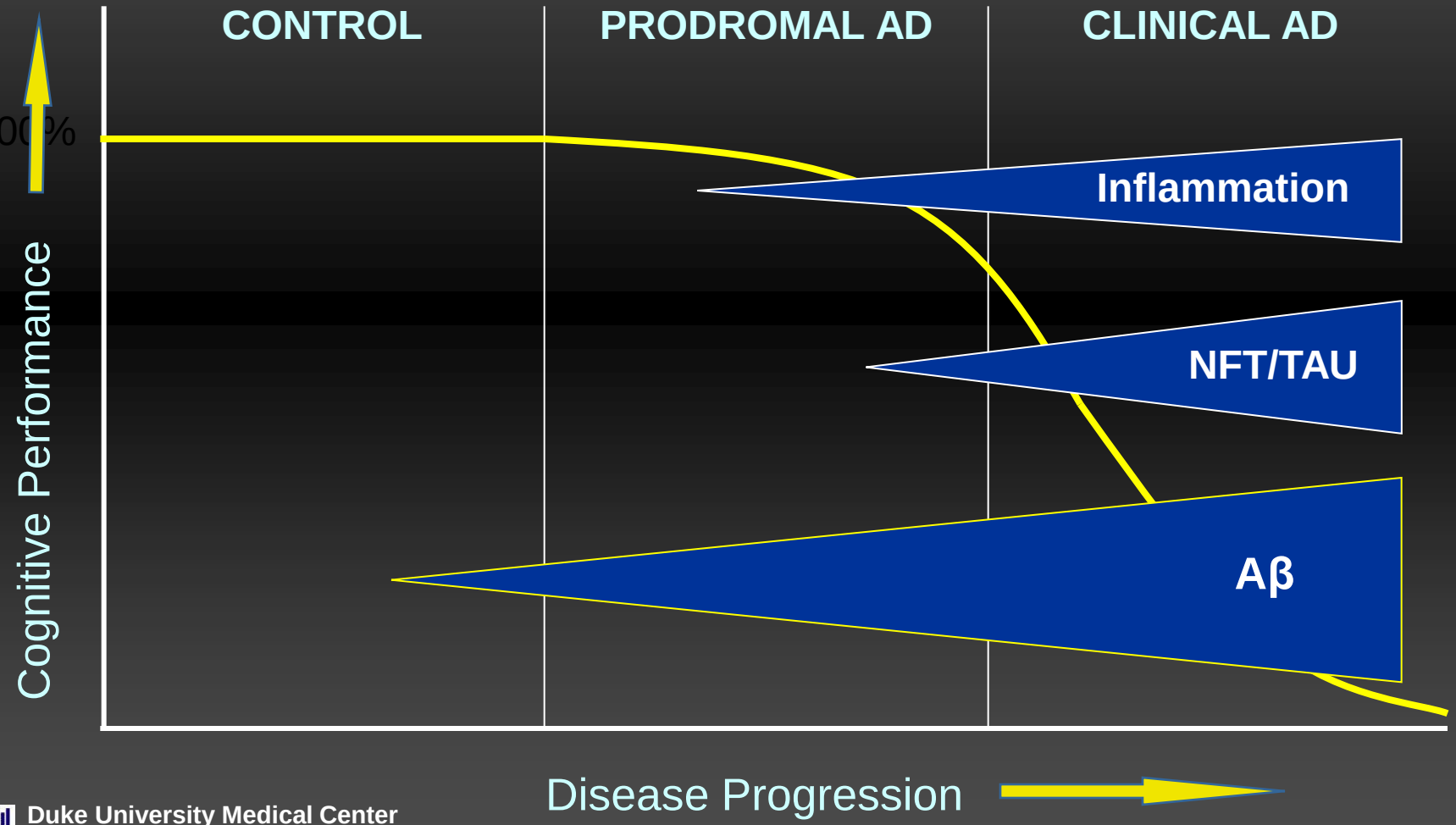
Evolution of Pathology Associated with Alzheimer's Disease



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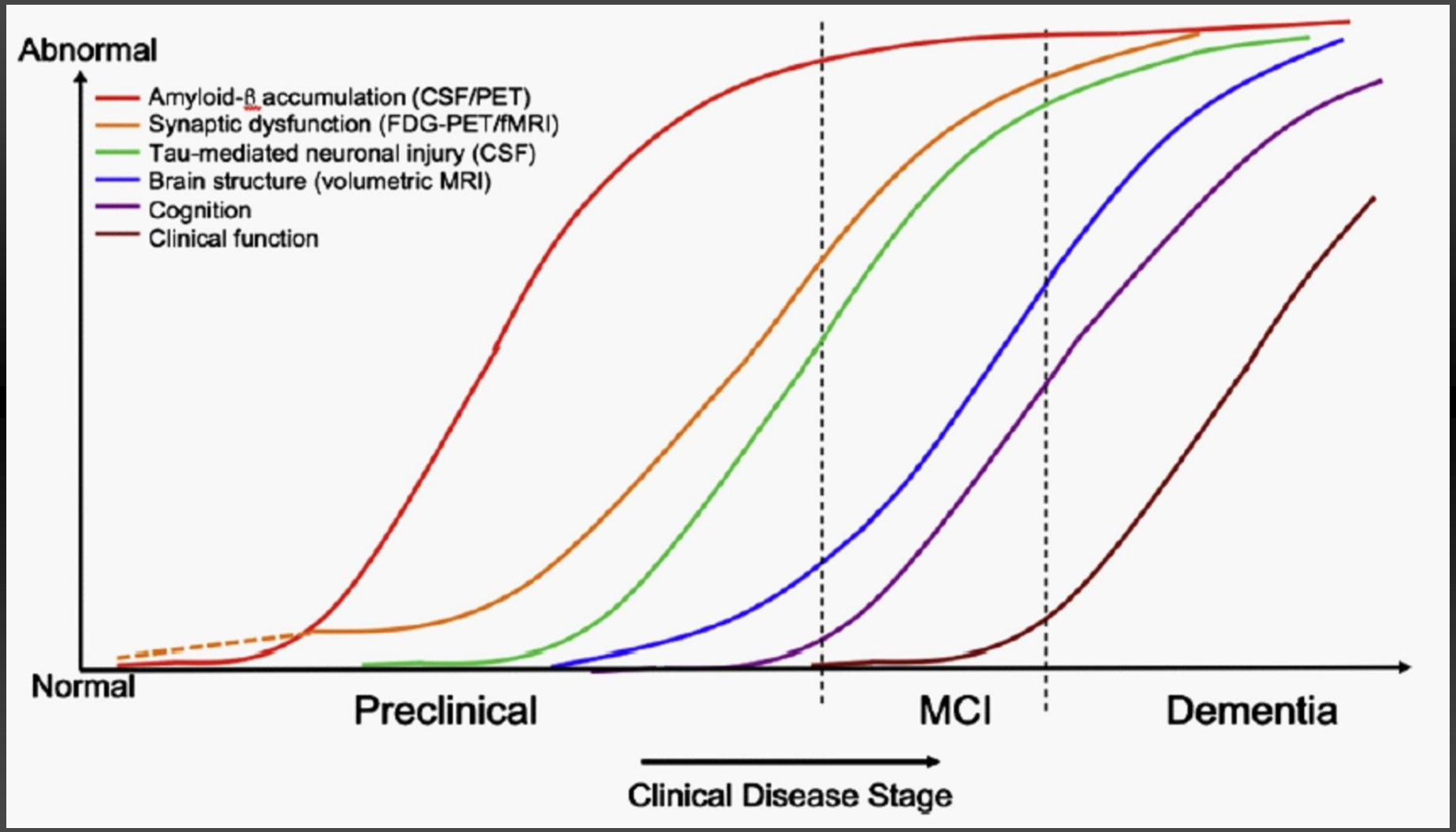
Hypothetical Model of AD Biomarkers



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Sperling et al. Alz. And Dementia (2011) 7: 280-92

2011 AD DIAGNOSTIC CRITERIA

Combines advances in clinical medicine & AD biomarkers

AD DEMENTIA

ELSEVIER

Alzheimer's & Dementia 7 (2011) 263–269

Alzheimer's & Dementia

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Guy M. McKhann[a,b,*], David S. Knopman[c], Howard Chertkow[d,e], Bradley T. Hyman[f]
Clifford R. Ja
Jennifer J. M
Martin N. Ross

PRODROME/ MCI

ELSEVIER

Alzheimer's & Dementia 7 (2011) 270–279

Alzheimer's & Dementia

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Marilyn S. Albert[a,*], Steven T. DeKosky[b,c], Dennis Dickson[d], Bruno Dubois[e],
Howard H. Feldman[f], Nick C. Fox[g], Antl
Ronald C. Petersen[l], Peter J. Snyder[m,n]

PRE-CLINICAL

ELSEVIER

Alzheimer's & Dementia 7 (2011) 280–292

Alzheimer's & Dementia

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Reisa A. Sperling[a,*], Paul S. Aisen[b], Laurel A. Beckett[c], David A. Bennett[d], Suzanne Craft[e], Anne M. Fagan[f], Takeshi Iwatsubo[g], Clifford R. Jack, Jr.[h], Jeffrey Kaye[i], Thomas J. Montine[j], Denise C. Park[k], Eric M. Reiman[l], Christopher C. Rowe[m], Eric Siemers[n], Yaakov Stern[o], Kristine Yaffe[p], Maria C. Carrillo[q], Bill Thies[q], Marcelle Morrison-Bogorad[r], Molly V. Wagster[r], Creighton H. Phelps[r]

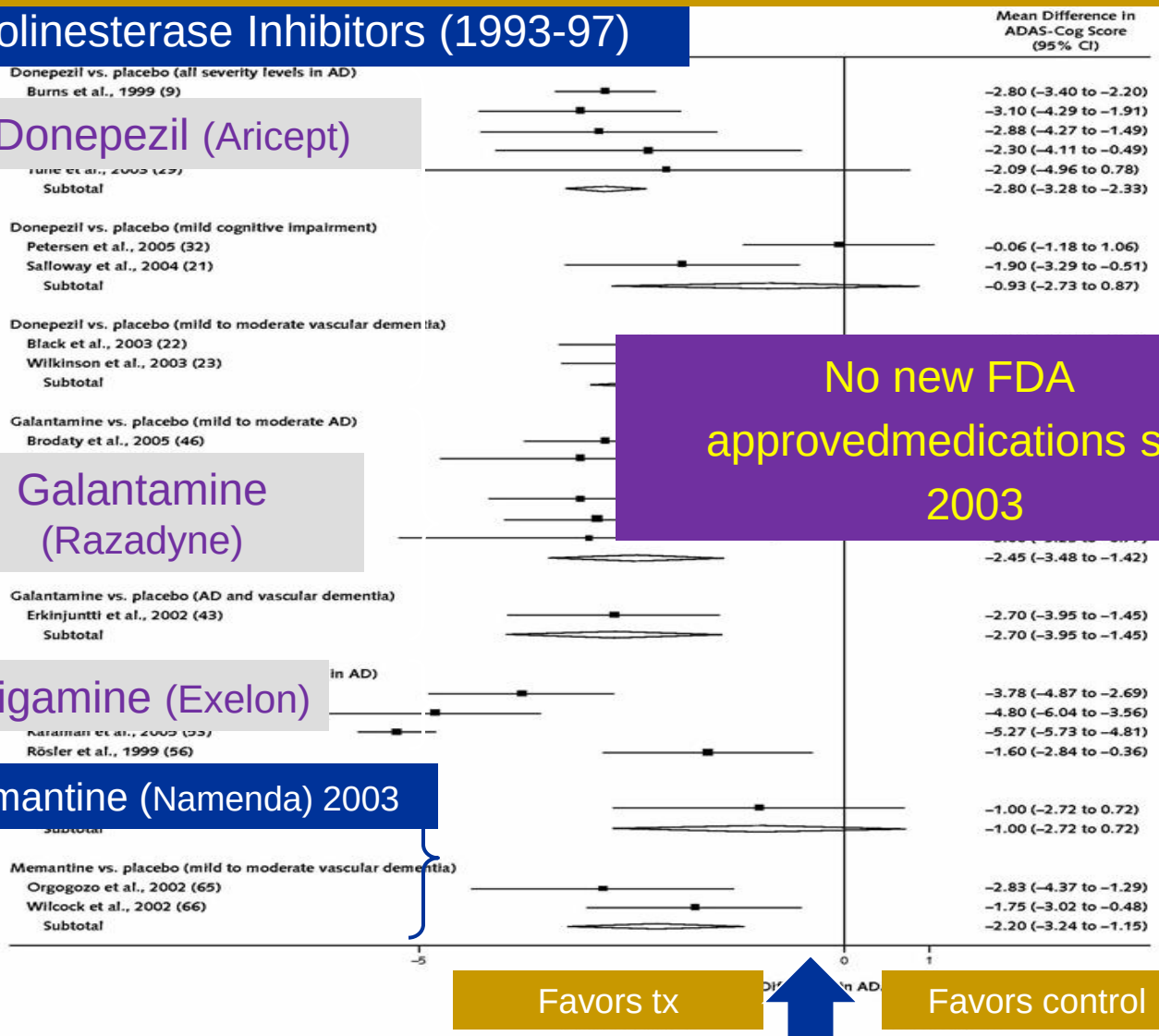
Therapeutic Strategies for Alzheimer's Disease

The two major treatment approaches:

- Symptomatic treatment
- Disease-modifying treatment

CURRENT FDA APPROVED DRUGS FOR AD & THEIR EFFECTS

Cholinesterase Inhibitors (1993-97)



Donepezil (Aricept)

Galantamine (Razadyne)

Rivistigamine (Exelon)

Glu inhib:Memantine (Namenda) 2003

No new FDA approvedmedications since 2003

For donepezil (10 mg/d) versus placebo (Alzheimer disease [*AD*], all severity levels), the estimate v…tistically significant ($P < 0.001$) and tests for heterogeneity were not significant ($I^2 = 0.0\%$; $P = 0.94$). For donepezil (10 mg/d) versus placebo…d cognitive impairment), the estimate was not significant ($P = 0.31$) and tests for heterogeneity were significant ($I^2 = 75.5\%$; $P = 0.043$). For do…il (10 mg/d) versus placebo (mild to moderate vascular dementia), the estimate was significant ($P < 0.001$) and tests for heterogeneity were not sig…t ($I^2 = 0.0\%$; $P = 0.84$). For galantamine (24 mg) versus placebo (mild to moderate AD), the estimate was significant ($P < 0.001$) and tests fo…erogeneity were significant ($I^2 = 75.5\%$; $P = 0.001$). For galantamine (24 mg) versus placebo (mild to moderate AD and vascular dementia), the es…e was significant ($P < 0.001$). For rivastigmine (6 mg and 12 mg) versus placebo (AD, all severity levels), the estimate was significant ($P < 0.001$) and tests for heterogeneity were significant ($I^2 = 90.8\%$; $P < 0.001$). For memantine (20 mg) versus placebo (mild to moderate AD), the estimate was not significant ($P = 0.25$). For memantine (20 mg) versus placebo (mild to moderate vascular dementia), the estimate was significant ($P < 0.001$) and tests for heterogeneity were not significant ($I^2 = 11.4\%$; $P = 0.29$).

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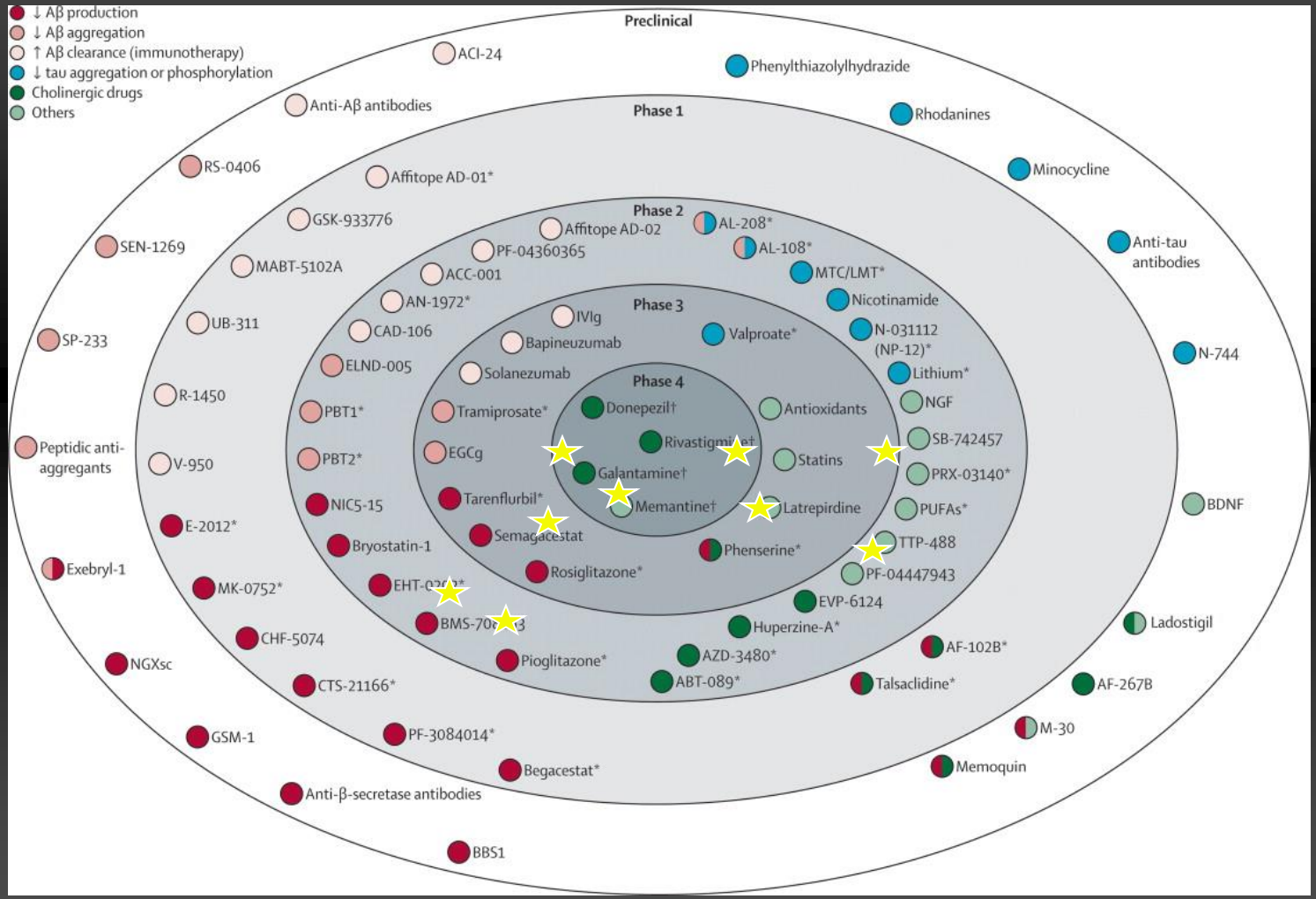
AD Drugs in Development



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Mangialasche et al. Lancet Neurology (2010) 9:702-16

2014 Launching Alzheimer's Disease Prevention Studies

- Dominantly Inherited Alzheimers Network (**DIAN**) Trial Unit (DIAN-TU), and
- Alzheimer's Prevention Initiative (**API**) examine compounds to prevent AD onset and cognitive decline in genetic forms of the disease (young age of onset)

- Alzheimer's Disease Cooperative Study *A*nti-*A*myloid Treatment in *A*symptomatic *A*D (**ADCS- A4 Study**) will examine treatments in individuals who show increased amyloid accumulation in their brains on amyloid imaging studies
- ***TOMM*ORROW** Study examines individuals at high and low genetic risk (algorithm: age, APOE, TOMM40)

What can we do now????

- Seven things that can be done now to reduce risk of disease and
- Potentially have a positive impact on memory decline & dementia progression


Is it Alzheimer's? What can I do about it?
A lot you can do about it:
1) Mindset shift- you matter
2) Treat what you can treat
3) Get active
4) Watch your weight & diet
5) Keep mind active with new things
6) Stress reduction & sleep
7) Help in research

Practical Reality: Diagnostic Nihilism

Why Diagnose if no Disease Modifying Treatment?

Early Detection: Benefits to Physicians

- Whether diagnosis or “risk” detection- earlier identification allows focus on treatable or reversible disorders that may cause further medical or psychosocial complications
- Reduction in possible errors or poor compliance when gauging self-care abilities of the patient
- Better ability to manage patient’s coexisting conditions
- Respect for a patient’s right of self-determination and ability to make healthcare decisions whenever possible
- More time to address safety issues before accidents or emergencies occur

Alzheimer’s Association. Available at: http://www.alz.org/professionals_and_researchers_14897.asp.

Early Detection: Benefits to Patients

- Better ability to understand the disease and make choices about treatment options
- Greater possible benefits from treatment
- Ability to participate in building a care team
- More opportunity to participate in clinical trials
- More time to make plans for employment and future financial security

Alzheimer's Association. Available at: http://www.alz.org/professionals_and_researchers_14897.asp.

Practical Consequences of Improved Diagnostic Accuracy

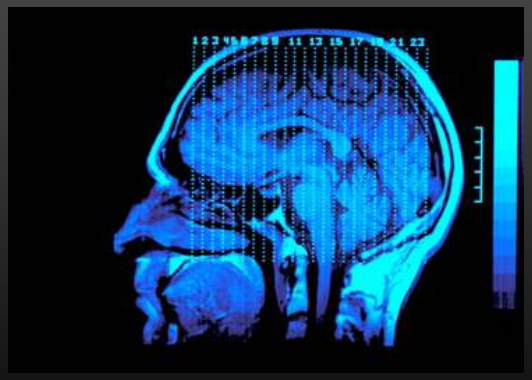
- Accurate diagnostic information and education reduce family/caregiver burden[1]
- "AD" label can improve caregiver attitudes and compassion[1]
- Information about the disease improves quality of life for family/patient and delays nursing home placement [2]

1. Wadley VG, Haley WE. *J Gerontol B Psychol Sci Soc Sci.* 2001;56:P244-P252.
2. Mittleman M, et al. *JAMA.* 1996;276:1725-1731.

Future Options- Research Opportunities

- As in other diseases, partnership between patient, managing physician, and research groups are critical to find treatments
- In Brain Tumor, research protocol involvement is standard. Option should be discussed routinely in AD.

Bryan ADRC- ADPR
Alzheimer's Disease Prevention Registry



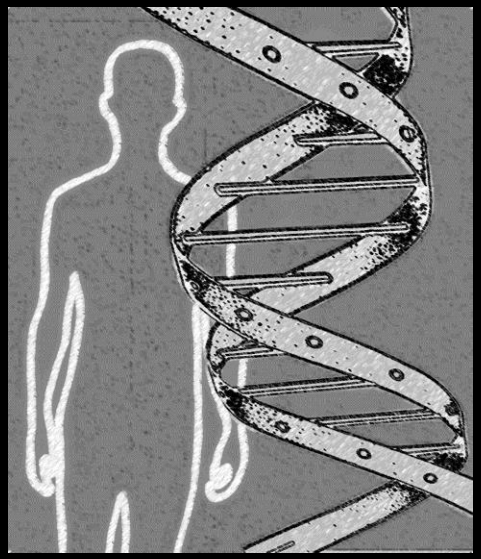
Discovery, Prevention, Treatment

- Goal is to mobilize the community to help in Alzheimer's disease research
- The *ADPR* is a registry of community members who:
  - do ***not*** have a diagnosis of Alzheimer's disease
  - are interested in possibly being involved in research in the future
  - and are registering to be informed of studies in the Bryan ADRC as they become available

Bryan ADRC
AD Prevention Registry

Be a part of the solution!

Every participant makes a difference!



866-444-ADRC or visit our website:

http://adrc.mc.duke.edu/

What to when patients and families need assistance?

- Useful resources:
  - Alzheimer's Association
    www.alz.org *800.272.3900*
  - Family Support Program at Duke University
    800 672 4213
  - AlzNC-Inc
    www.alznc.org
    919.832.3732 or 800.228.8738
  - Bryan Alzheimer's Disease Research Center
    ***adrc**.mc.duke.edu*