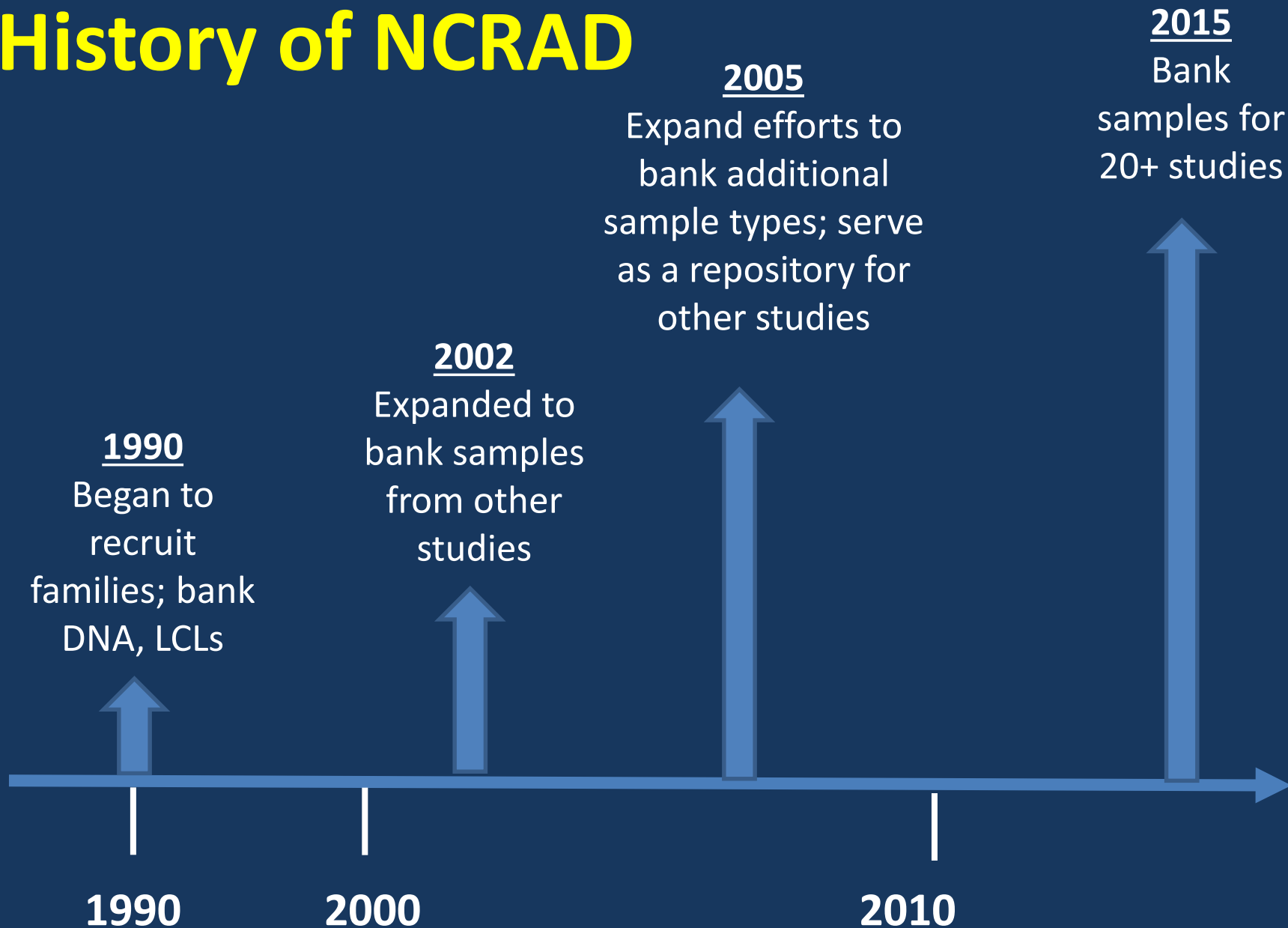


# National Cell Repository for Alzheimer Disease (NCRAD)

Tatiana Foroud, Ph.D.  
Principal Investigator  
Indiana University School of Medicine

U24AG21886

# History of NCRAD



1990

Began to recruit families; bank DNA, LCLs

1990

2002

Expanded to bank samples from other studies

2000

2005

Expand efforts to bank additional sample types; serve as a repository for other studies

2010

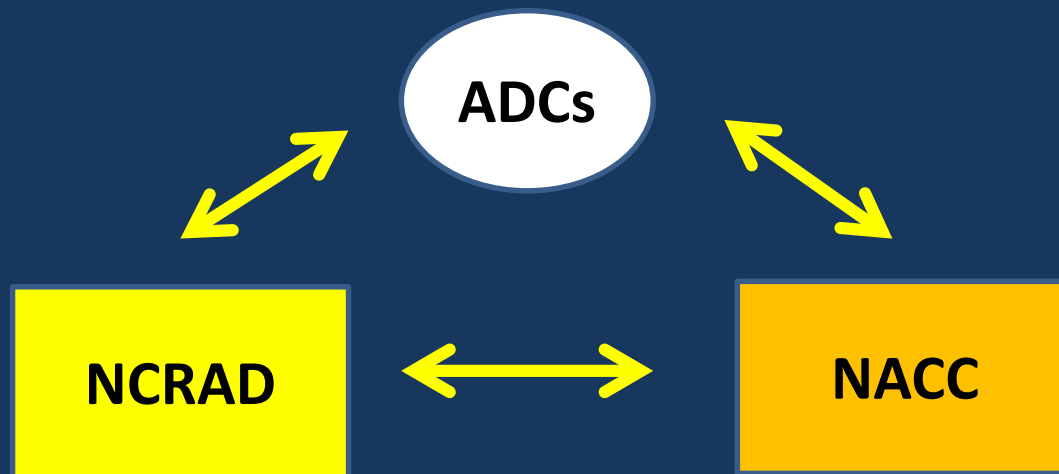
2015

Bank samples for 20+ studies

# NCRAD and NACC goal

For EVERYONE seen at an ADC,  
store uniform phenotypic data  
and a DNA sample

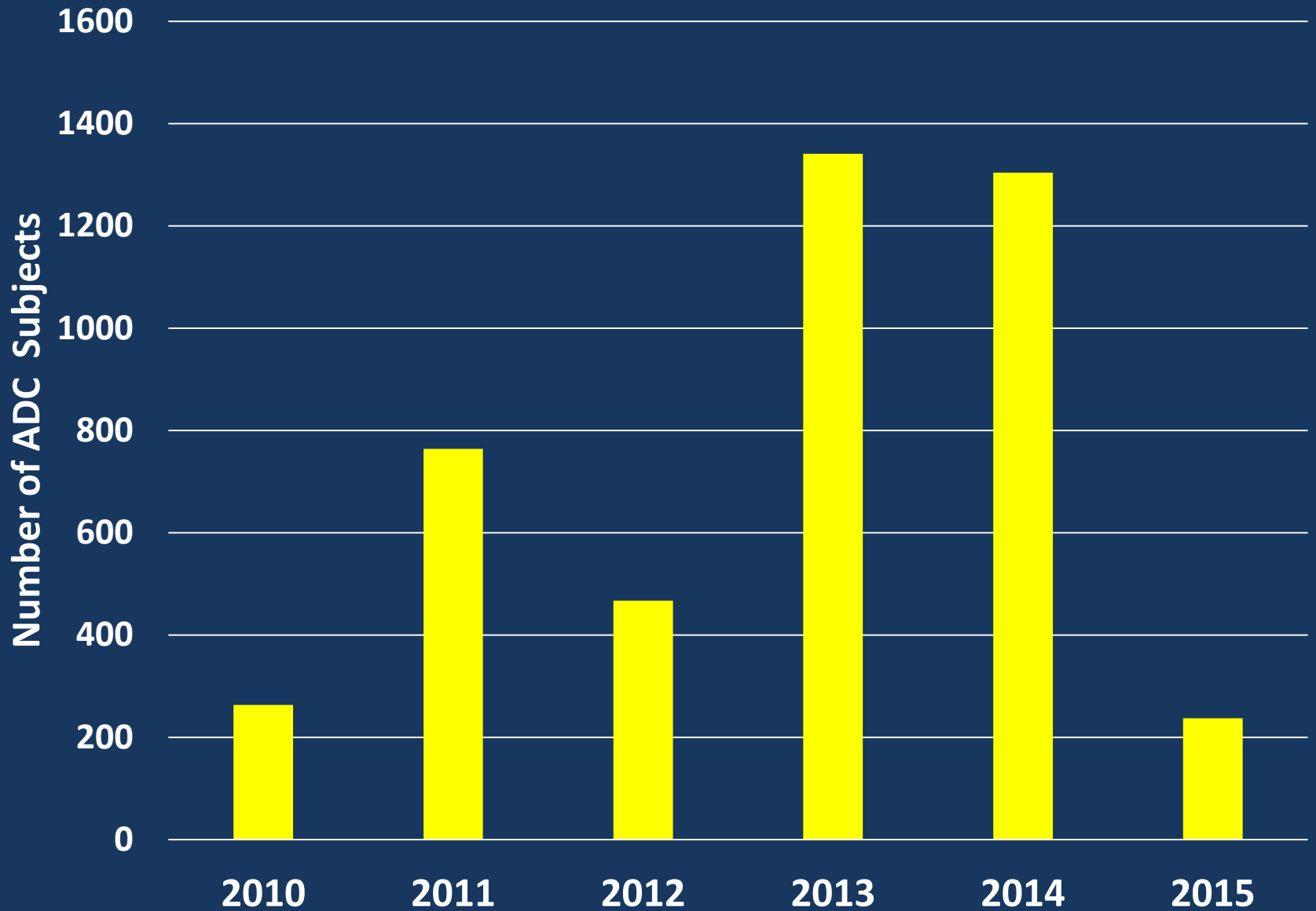
**Samples from 22,226 ADC subjects at NCRAD**



# ADC Blood Samples

- Major effort to encourage ADCs to send a blood sample for each subject seen at their ADC who has a UDS
- Received blood samples for 4,375 subjects
  - 3,675 new individuals
  - Some overlap with other samples that have been previously sent (DNA or buffy coat) and therefore aren't counted as a new unique sample on Phase 2 list

# ADC Blood Samples



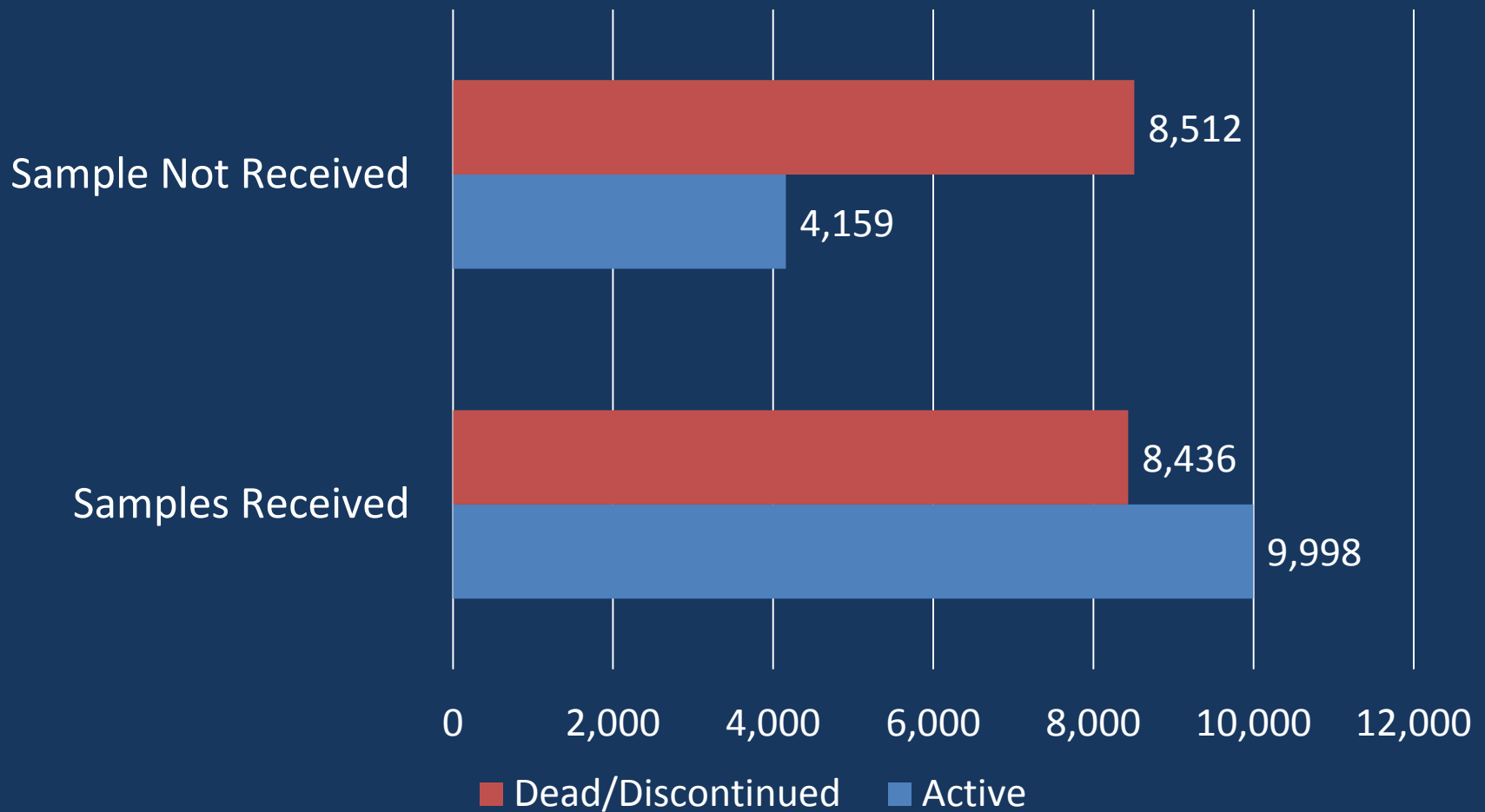
# Samples Received at NCRAD from ADCs

	Phase 1	Phase 2	Total
Brain Tissue	3,519	0	3,519
DNA	270	11,772	12,042
Buffy Coat	0	1,519	1,519
Blood	0	3,675	3,675
Internal Transfer	3	1,468	1,471
Total	3,792	18,434	<b>22,226</b>

**~4,000 new unique samples since last year  
(> 20% increase)**

# ADC Sample Status at NCRAD

## Subjects with a UDS (n=31,105)



# NCRAD Sample Distribution

	Since Inception
# of researchers	128
# of samples-DNA	176,841
# of samples-blood	811
# of samples-cell lines	1,917
# of samples-plasma	3,600
# of samples-serum	100
# of samples-PBMC	7

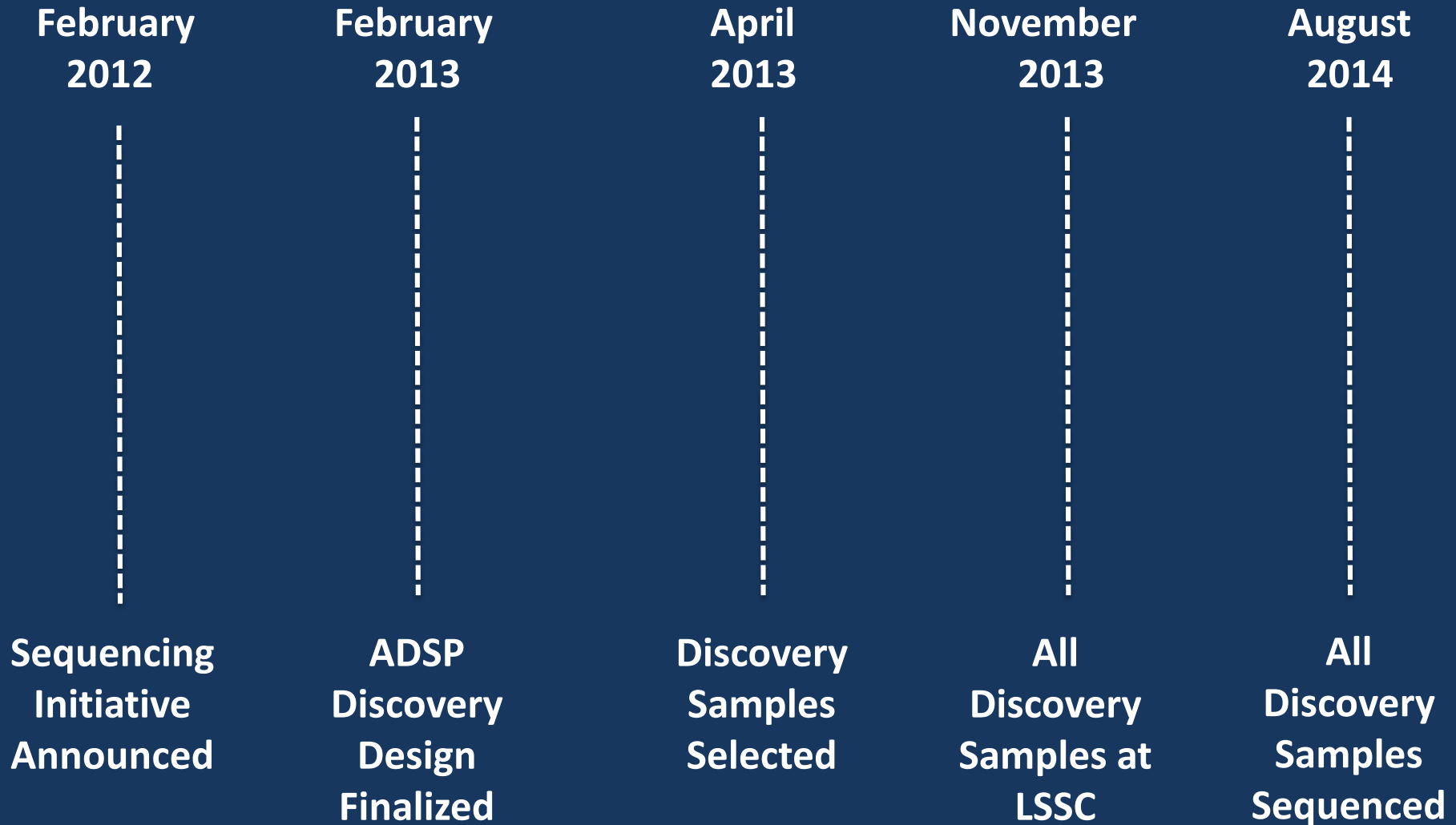
There have been 394 publications citing the use of NCRAD samples.  
95 publications in the past year, alone.



# NCRAD Calls with the ADCs

- Completed the annual calls with all ADCs
  - Reviewed sample contributions
  - Reviewed available data and how to obtain in
    - APOE, GWAS, WES
  - Reviewed GDS policy
  - Reviewed sample requests and grant numbers

# ADSP Discovery Sample Timeline



# Alzheimer Disease Sequencing Project (ADSP)

## Discovery Phase

Whole Genome  
Sequencing (WGS)  
578 individuals from 111 families

Whole Exome  
Sequencing (WES)  
10,939 individuals  
5,963 cases; 4,976 controls

## Replication Phase

Follow-up Sequencing

# ADSP Replication/Follow-up Designs

	Type	Rationale	Advantage	Disadvantage
1	Custom Targeted Sequencing	<ul style="list-style-type: none"> <li>Strong findings from WGS in nonexonic regions</li> <li>Promising regions poorly covered in WGS/WES</li> </ul>	<ul style="list-style-type: none"> <li>Follow-up non-exonic signals</li> <li>Deeper sequence coverage</li> </ul>	<ul style="list-style-type: none"> <li>Only small region studied</li> <li>Challenging to design</li> <li>Assumes strong prior hypothesis</li> </ul>
2	Whole exome sequencing	<ul style="list-style-type: none"> <li>Implemented if WGS and WES does not identify regions/variants to follow-up</li> </ul>	<ul style="list-style-type: none"> <li>Combine with Discovery WES to increase power</li> </ul>	<ul style="list-style-type: none"> <li>Does not cover non-exonic regions</li> <li>May not provide follow-up for WGS findings</li> </ul>
3	Hybrid - Target sequence & WES	<ul style="list-style-type: none"> <li>Promising findings from both WES and WGS</li> </ul>	<ul style="list-style-type: none"> <li>New WES replicate Discovery WES</li> <li>Provide follow-up for WGS</li> </ul>	<ul style="list-style-type: none"> <li>Reduced sample size for both studies</li> <li>Lower power to replicate/follow-up findings</li> </ul>

# ADSP Replication/Follow-up Designs

	Targeted Sequencing	WES	Targeted Sequencing (N)	WES (N)
<b>1</b>	Yes	No	35,000 (17,500 cases; 17,500 controls)	No
<b>2</b>	No	Yes	No	14,000 (7,000 cases; 7,000 controls)
<b>3</b>	Yes	Yes	5,750 (2,875 cases; 2,875 controls)	11,500 (5,750 cases; 5,750 controls)

# Replication/Follow-up Timeline

January  
2015

Analysis of ADSP  
Discovery Sample

Potential studies  
obtain IRB  
certification &  
Institutional  
Signature

December  
2015

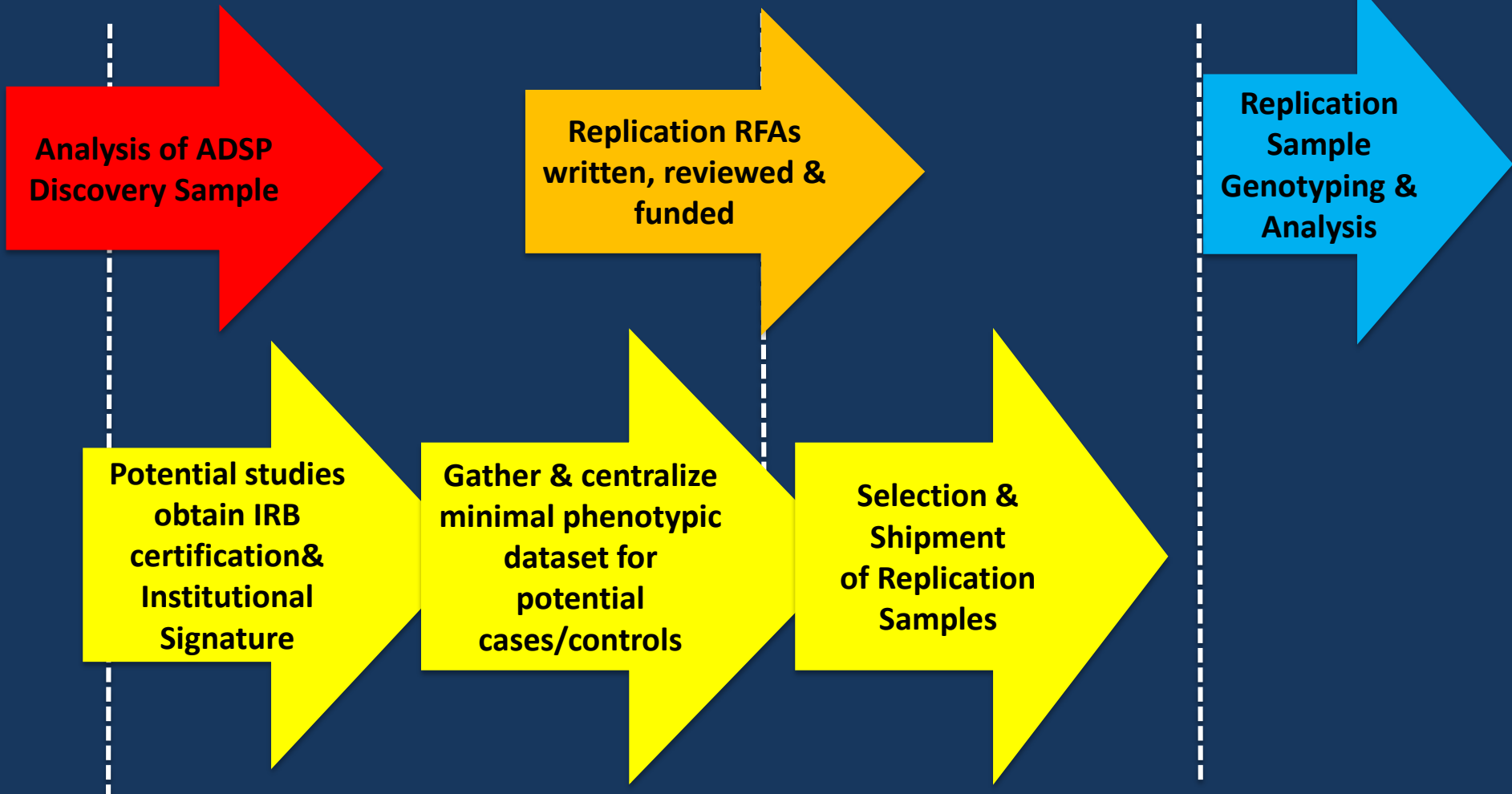
Replication RFAs  
written, reviewed &  
funded

Gather & centralize  
minimal phenotypic  
dataset for  
potential  
cases/controls

Selection &  
Shipment  
of Replication  
Samples

April  
2016

Replication  
Sample  
Genotyping &  
Analysis



# What is Needed NOW?

- All studies/centers that may participate in the Replication/Follow-Up must obtain approvals
  - New Genomics Data Sharing (GDS) Policy is in place
- GDS Requirements
  - IRB approval
    - Genomics language
    - Consent group assignment
  - Institutional Certificate
  - Copy of Informed Consent Document

# NCRAD/Indiana University Expansion

- Over the past few years.....
  - Expanded the scope of samples collected
  - Expanded our role in many studies to provide more study coordination and training
  - Expanded to other disorders



# Sample Types at NCRAD

- DNA (genomic, brain, LCL)
- RNA (PAXgene™ blood tubes)
- Plasma
- Serum
- CSF
- Brain Tissue
- Lymphoblastoid Cell Lines (LCLs)
- Peripheral Blood Mononuclear Cells (PBMCs)

# NCRAD Role in Other Studies

- Previously, simply received samples for ongoing studies
  - LOAD, ADNI, ADGC, DIAN, GIFT
- Now, providing study sample coordination
  - Generate specimen processing manuals and videos
  - Provide training to site coordinators for sample collection and processing
  - Provide on demand kits through website portal
  - Regular site and study specific reports

# AD Focused Studies

Study	Sample Types Received	# Sampled Subjects
Genetic Epidemiology of Alzheimer's Disease in African Americans (AA Genetics Study) (R01AG028786)	<ul style="list-style-type: none"> <li>Cell lines and DNA</li> </ul>	1688
African American GWAS Initiative	<ul style="list-style-type: none"> <li>Transferred DNA</li> </ul>	2,444
Alzheimer's Disease Genetics Consortium (ADGC) (U01AG032984)	<ul style="list-style-type: none"> <li>DNA (Brain tissue, buffy coat, blood)</li> <li>PBMCs</li> <li>Transferred DNA aliquots and saliva</li> </ul>	21,824
Dominantly Inherited Alzheimer Network (DIAN Study) (U01AG032438)	<ul style="list-style-type: none"> <li>Cell lines and DNA</li> </ul>	387
Genetic Consortium for Late Onset Alzheimer's Disease (LOAD Family Study) (U24AG026395 and R01AG041797)	<ul style="list-style-type: none"> <li>Cell lines and DNA</li> <li>DNA (Brain tissue and blood)</li> </ul>	6,761
NCRAD Family Study	<ul style="list-style-type: none"> <li>Cell lines and DNA</li> <li>DNA (Brain tissue and blood)</li> <li>PBMCs</li> </ul>	3,230
University of Kentucky ADC (UK-ADC) (P30AG028383)	<ul style="list-style-type: none"> <li>Cell lines and DNA</li> <li>DNA (blood)</li> </ul>	353
Washington University ADRC (WU-ADRC) (P50AG005681)	<ul style="list-style-type: none"> <li>Cell lines and DNA</li> <li>DNA (blood)</li> </ul>	827

# More AD Focused Studies

Study	Sample Types Received	# Sampled Subjects
Alzheimer's Disease Patient Registry (ACT) (U01 AG 06781)	<ul style="list-style-type: none"><li>• Transferred DNA</li></ul>	3,188
Indianapolis-Ibadan Dementia Project (R01AG009956)	<ul style="list-style-type: none"><li>• Cell lines and DNA;</li><li>• DNA (Blood)</li><li>• Transferred DNA and plasma aliquots</li></ul>	1,446
Hardy-Myers GWAS Study	<ul style="list-style-type: none"><li>• Transferred DNA and WGA DNA aliquots</li></ul>	765
Ginkgo Evaluation of Memory Study (GEMS); (5U01AT000162)	<ul style="list-style-type: none"><li>• Transferred DNA, plasma and serum aliquots</li></ul>	3,069

# ADNI Studies

Study	Sample Types Received	# Sampled Subjects
Alzheimer's Disease Neuroimaging Study (ADNI) (U01AG024904)	<ul style="list-style-type: none"> <li>• Yellow tops for cell lines and DNA</li> <li>• Transferred DNA aliquots</li> </ul>	821
Amyloid Imaging VMCI and Analysis for ADNI (ADNI-GO)(U01AG024904) And Alzheimer's Disease Neuroimaging Study (ADNI-2) (U01AG024904)	<ul style="list-style-type: none"> <li>• Yellow tops for cell lines and DNA;</li> <li>• Purple tops and buffy coats for genomic DNA</li> <li>• PAXgene tubes for RNA</li> </ul>	1,485
Effects of traumatic brain injury and post-traumatic stress disorder on Alzheimer's disease (AD) in Veterans with mild cognitive impairment (MCI) using the Alzheimer's Disease Neuroimaging Initiative (ADNI-DoD) (W81XWH-12-2-0012)	<ul style="list-style-type: none"> <li>• Yellow tops for cell lines and DNA;</li> <li>• Purple tops and buffy coats for genomic DNA</li> <li>• PAXgene tubes for RNA</li> </ul>	119
ADNI Depression	<ul style="list-style-type: none"> <li>• Yellow tops for cell lines and DNA;</li> <li>• Purple tops and buffy coats for genomic DNA and plasma</li> <li>• PAXgene tubes for RNA</li> <li>• Red tops for serum</li> <li>• Purple tops for telomere assays</li> </ul>	1

# FTD Studies

Study	Sample Types Received	# Sampled Subjects
Four Repeat Tauopathy Neuroimaging Initiative (4RTNI) (1R01AG32306-01)	<ul style="list-style-type: none"> <li>• Cell lines and DNA</li> </ul>	75
Identification of Genetic Risk Factors for AD and FTD (GIFT) (R01AG026938)	<ul style="list-style-type: none"> <li>• Cell lines and DNA</li> <li>• DNA (blood)</li> </ul>	1,471
The Frontotemporal Lobar Degeneration Neuroimaging Initiative (NIFD) (R01AG32306)	<ul style="list-style-type: none"> <li>• Cell lines and DNA</li> </ul>	151
Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) (U54NS092089)	<ul style="list-style-type: none"> <li>• CSF aliquots</li> <li>• Plasma aliquots</li> <li>• Buffy coat</li> </ul>	Just starting
Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS) (U01AG045390)	<ul style="list-style-type: none"> <li>• Buffy coat</li> <li>• PBMCs</li> <li>• Plasma aliquots</li> <li>• Serum aliquots</li> <li>• PAXgene tubes for RNA</li> <li>• CSF aliquots</li> </ul>	3

# NCRAD and Dementia Research

- NCRAD banks samples for the ADCs
- NCRAD provides banking services to dementia-related studies
- NCRAD can provide input during the study design/grant writing period

# Acknowledgements

- NCRAD Staff
  - Kelley Faber
  - Ashley Vctor
  - Kelly Horner
  - Drew Mitchell
  - Colleen Mitchell
  - Chris Hobbick
- Alzheimer's Disease Centers
- Studies contributing samples to NCRAD
- NACC
- NIAGADS
- ADGC
- NIA
- NCRAD Executive Committee
  - Deborah Blacker (Chair)
  - Steve DeKosky
  - Bernie Devlin
  - Alison Goate
  - David Holtzman
  - Bud Kukull
  - Richard Mayeux
  - Rosa Rademakers
  - Gerard Schellenberg
  - Julie Schneider
- Replication Working Group
  - Richard Mayeux
  - Sudha Seshadri



**Questions?**