Alzheimer's Disease Genetics Consortium (ADGC)

University of Pennsylvania School of Medicine

Goals

- Identify genetic variants that increase risk for AD
- Identify genetic variants that affect AD endophenotypes
  (Aβ load, tangle load, psychosis, biomarker levels, etc.)

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Bring together AD datasetsfor *meta*-analysis and combined analysis

Solve the genetics of Alzheimer's disease

Mechanism

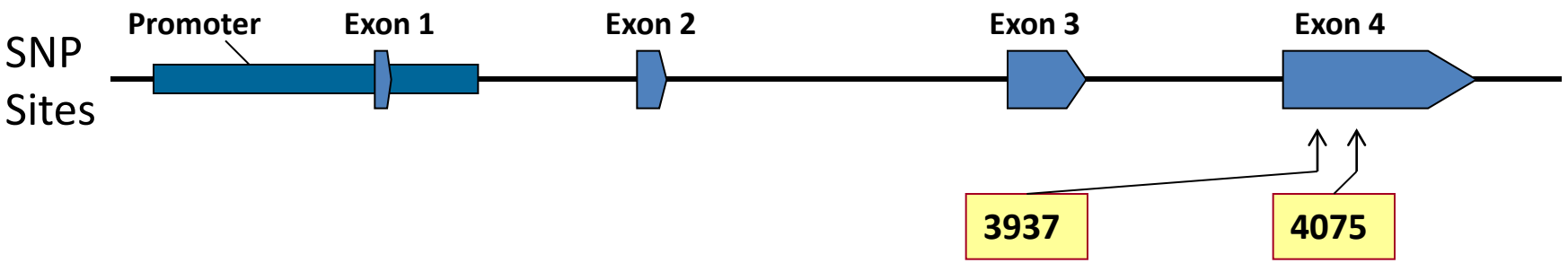
- Use existing AD case/control populations, data, DNA
- Genotype samples using high-density SNP platforms
- Analyze for genome-wide association
- *Meta*-analysis/combined analysis with other AD studies
- *Meta*-analysis with other neurodegenerative disease studies

Funding - NIA

- April 2009: UO1 is funded

  August 2009: initial genotyping

ApoE



Controls	AD		3937	4075
0.135	0.355	ε4	C (Arg)	C (Arg)
0.765	0.607	ε3	T (Cys)	C (Arg)
0.10	0.038	ε2	T (Cys)	T (Cys)

Genome-wide Association Studies (GWAS)

- ApoE – association for one gene
- GWAS – test all (most) genes simultaneously

  Genotype 600,000 sites in cases and controls

  Test each for association with AD
- Correct for multiple comparisons

  Need p value $< 5 \times 10^{-7}$
- Need large samples to detect small-effect genes

ADGC Projects – years one and two

1. Meta-analysis existing studies:
   - Reiman-TGEN*
   - Framingham*
   - University of Miami/Vanderbilt*
   - ADNI*
   - Jacksonville Mayo*
   - LOAD study (RichardMayeux)

2. ADC autopsy cases
   - ADGC: 2,000 AD cases
   - ADGC: 2,000 controls
     (supplement with UDS controls)

3. Samples with CSF biomarker data

Washington University:	431
University of Washington:	> 500
ADNI:	491*
University of Pennsylvania:	283

* Not funded by the ADGC but data is/will be available

ADGC Projects – years two - five

4. Prospective cohorts (European Ancestry)

Cohort	PI	n	≥ 3 evals.	incident dementia	incident MCI
CHAP	Evans	2,300	1,500	210	270
WHICAP	Mayeux	904	586	59	105
MAP	Bennett	1,050	950	150	250
WHISCA	Resnick	2,275	2,000	85	170
ACT*	Larson	4,000			
ADPR*	Kukull			~300	

* Not funded by the ADGC but data is/will be available

ADGC Organization

Administration – UPenn team

Gerard D. Schellenberg, PI
Li-San Wang, bioinformatics/statistical analysis/database
Laura Cantwell, project manager
Otto Valderes, computer programmer
Caitlin Goodman, administrative assistant
Mi Ryung Han, research assistant

Laura Cantwell
lcant@mail.med.upenn.edu
gerardsc@mail.med.upenn.edu

ADGC Organization

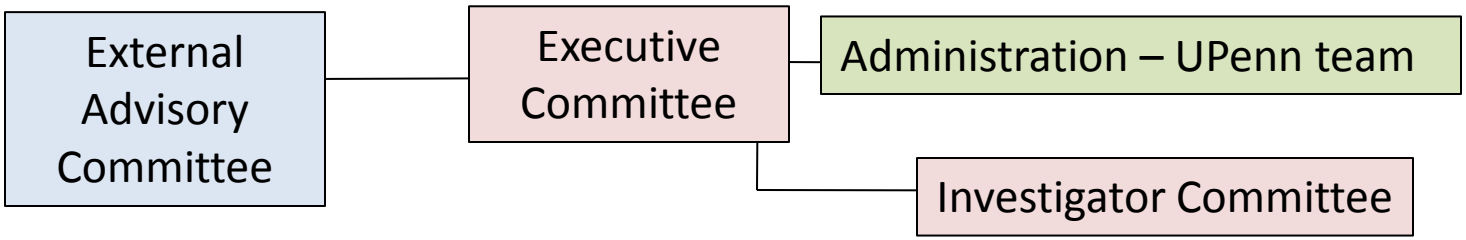
Membership
- PI/co-PI on UO1
- Contribute data/samples

Executive Committee

Administration – UPenn team

Gerard D. Schellenberg	PI	Chair	University of Pennsylvania
Li-San Wang	co-PI	Database	University of Pennsylvania
David Bennett	co-PI	Cohort studies	Rush University Medical Center
Deborah Blacker	co-PI	Familial AD	Massachusetts General
Richard Mayeux	co-PI	Familial AD	Columbia University
Lindsay Farrer	co-PI	Analysis group	Boston University
Margaret Pericak-Vance	co-PI	Analysis group	University of Miami
Tatiana Foroud	co-PI	NCRAD	Indiana University
Alison Goate	co-PI	Biomarkers	Washington University
Andy Saykin	co-PI	Biomarkers	Indiana University
Walter Kukull	co-PI	NACC	University of Washington
Thomas Montine	co-PI	Neuropathology	University of Washington
Eric Reiman	co-PI	Neuropathology	Banner Alzheimer's Institute
John Morris	co-PI	Clinical samples	Washington University
Debbie Tsuang	co-PI	Clinical samples	University of Washington
Hakon Hakonarson	co-PI	Genotyping	Children's Hospital of Philadelphia
Nilifer Tanner	member	Data contributor	Jacksonville Mayo
Marilyn Miller	Ex-officio	National Institute on Aging	National Institutes of Health
Tony Phelps	Ex-officio	National Institute on Aging	National Institutes of Health

ADGC Organization

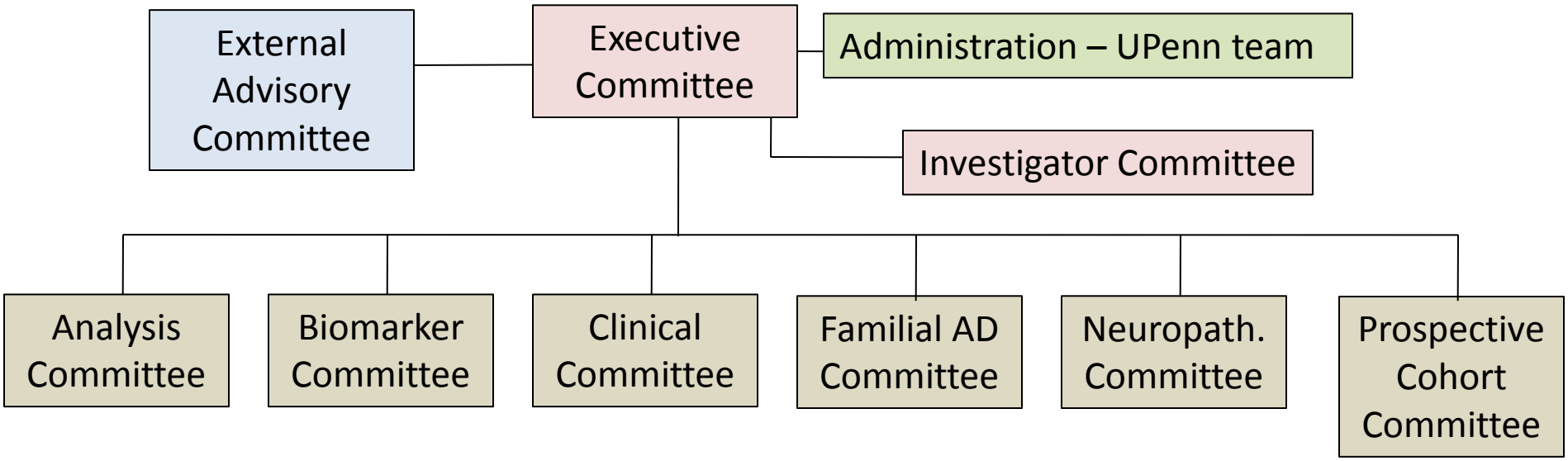


Name	Director	ADC/ADRC
Gerard D. Schellenberg/Li-San Wang	John Trojanowski	University of Pennsylvania, Philadelphia, PA
David Bennett/Dennis Evans	David Bennett	Rush University Medical Center, Chicago, IL
Deborah Blacker	Bradley T. Hyman	Massachusetts General, Boston, MA
Lindsay Farrar	Neil W. Kowall	Boston University, Boston, MA
Kathleen Hall/Andy Saykin	Bernardino Ghetti	Indiana University, Indianapolis, IN
Richard Mayeux	Michael L. Shelanski	Columbia University, New York, NY
John C. Morris/Alison Goate	John C. Morris	Washington University, St Louis, MO
Margaret Pericak-Vance	Huntington Potter	Florida Alzheimer's Center
Ronald C. Peterson/Steve Younkin	Ronald C. Peterson	Mayo Clinic
Eric Reiman	Eric Reiman	Banner Alzheimer's Institute, Phoenix, AZ
Debbie Tsuang/Thomas Montine/Elaine Peskind	Murray Raskind	University of Washington, Seattle, WA
Kathleen A. Welsh-Bohmer	Kathleen A. Welsh-Bohmer	Duke University Medical Center
tbn	Allan I. Levey	Emory University
tbn	Donald L. Price	Johns Hopkins University
tbn	Mary Sano	Mount Sinai School of Medicine
tbn	Steven H. Ferris	New York University
tbn	Jerome A. Yesavage	Stanford University
tbn	M. Marsel Mesulam	Northwestern University Medical School
tbn	Jeffrey Kaye	Oregon Health and Science University
tbn	Daniel Marson	University of Alabama
tbn	Cornelia Beck	University of Arkansas for Medical Sciences
tbn	Charles DeCarli	University of San Diego
tbn	Carl Cotman	University of California, Irvine
tbn	Jeffrey L. Cummings	University of California, Los Angeles
tbn	Doug Galasko	University of California, San Diego
tbn	Bruce L. Miller	University of California, San Francisco
tbn	William R. Markesbery	University of Kentucky
tbn	Sid Gilman	University of Michigan
tbn	Oscar Lopez	University of Pittsburgh
tbn	I. Helena Chui	University of Southern California
tbn	Roger Rosenberg	University of Texas Southwestern

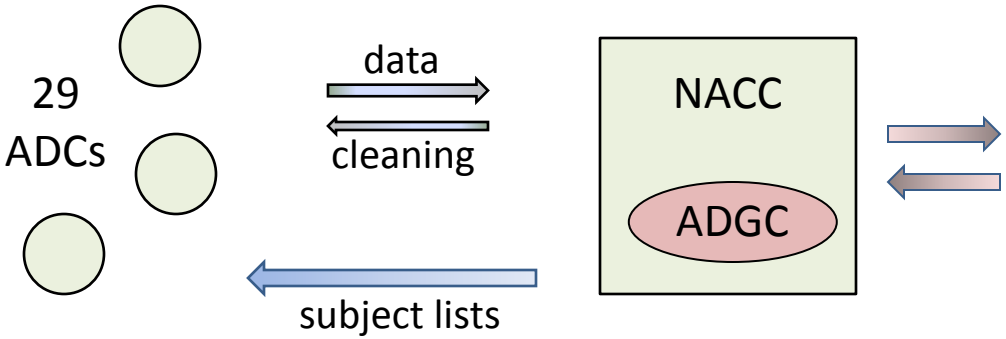
Investigator Committee

Walter Kukull	National Alzheimer's Coordinating Center
Hakon Hakonarson	Children's Hospital of Philadelphia
Tatiana Foroud	National Cell Repository for Alzheimer's Disease
Susan Resnick	NIA

ADGC Organization



Alzheimer's Disease Center Samples



Phase 2

Selection of samples for GWAS

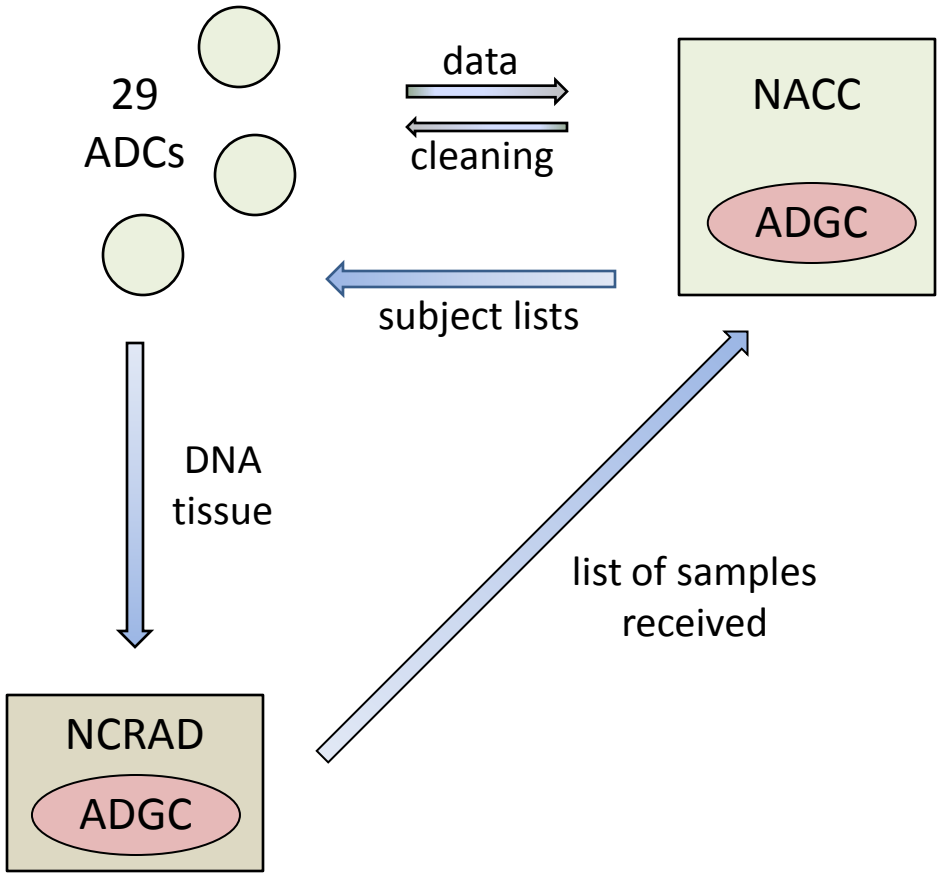
UDS Samples

Clinical committee

- John Morris — chair, co-PI
- Debbie Tsuang — co-PI
- Thomas Bird
- Helena Chui
- Jeffrey Cummings
- Charlie DeCarli
- Steven Ferris
- Douglas Galasko
- Neil Graff-Radford
- Richard Mayeux
- Elaine Peskind
- John Ringman
- Sandra Weintraub

- Walter Kukull — NACC
- Gerard Schellenberg — ADGC

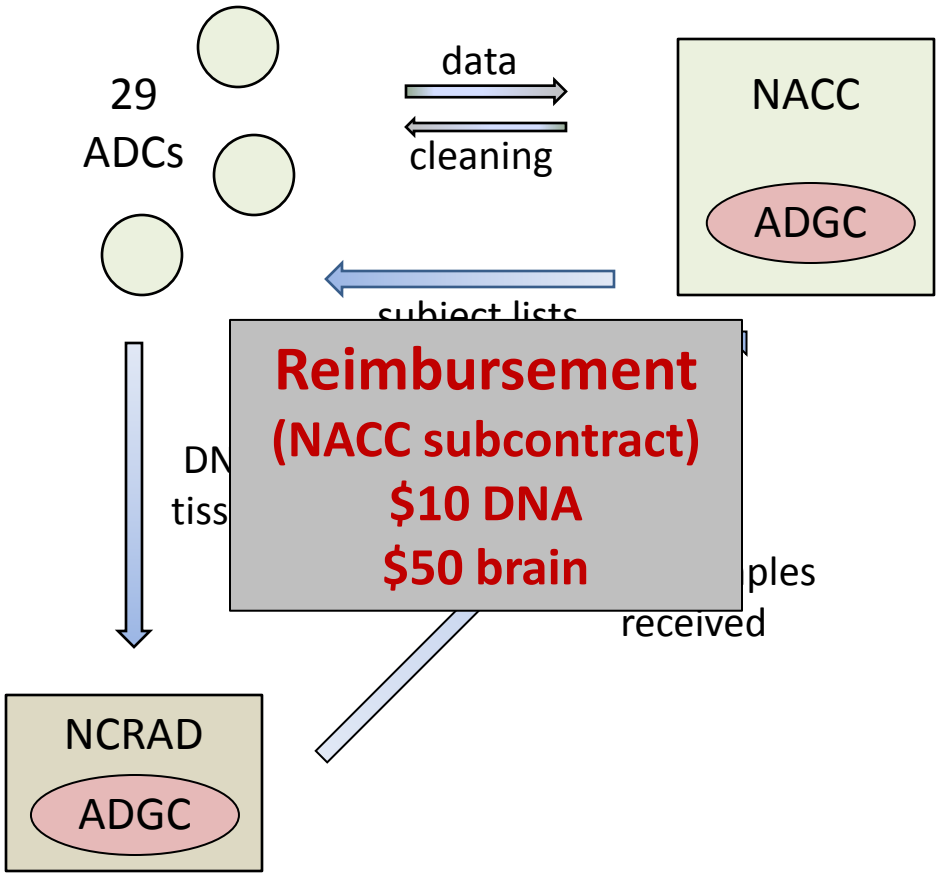
Alzheimer's Disease Center Samples



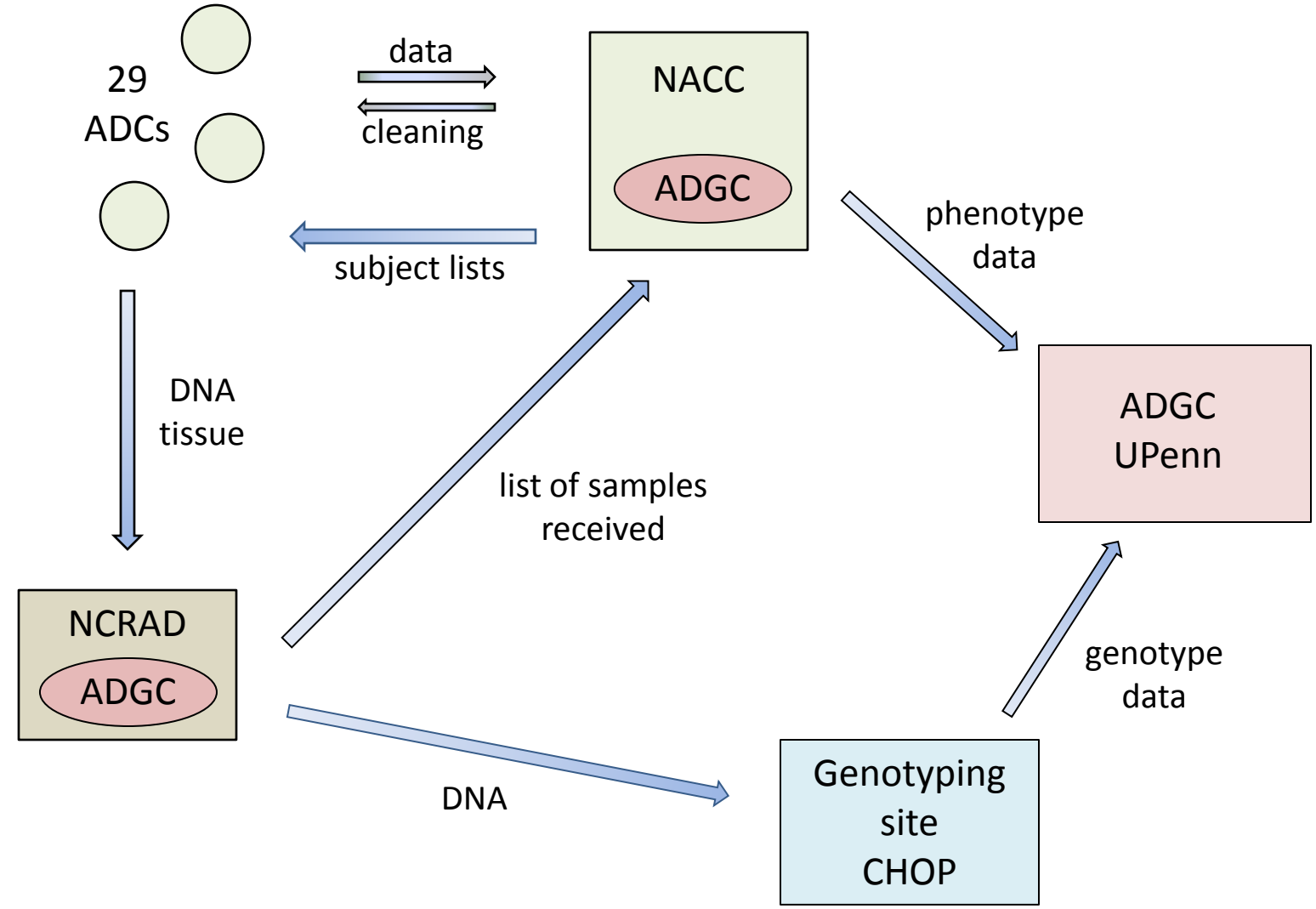
GWAS Phase I Summary Report - Samples Received at NCRAD 28SEP09

		Total GWAS IDs on List	Overlap with Other GWAS Studies	Total Samples Received	DNA Received	Brain Sample Received	AD Cases Received	Controls Received	Samples Depleted, Unavailable, or Ineligible
U Penn									
	ADC IDs	155	50	39	0	39	38	1	0
	Total	155	50	39	0	39	38	1	0
U Pitt									
	ADC IDs	292	186	209	0	209	207	2	0
	Total	292	186	209	0	209	207	2	0
U S C									
	ADC IDs	262	4	261	0	261	242	19	0
	Total	262	4	261	0	261	242	19	0
U Tex SW									
	ADC IDs	104	11	87	0	87	82	5	1
	Total	104	11	87	0	87	82	5	1
U Wash									
	ADC IDs	170	5	116	59	57	110	6	0
	Total	170	5	116	59	57	110	6	0
Wash U									
	ADC IDs	136	0	44	0	44	41	3	1
	Total	136	0	44	0	44	41	3	1
Total									
	ADC IDs	4513	720	3303	161	3142	2952	351	206
	Aff IDs	214	44	198	18	180	166	32	5
TOTAL		4727	764	3501	179	3322	3118	383	211

Alzheimer's Disease Center Samples



Alzheimer's Disease Center Samples



- Reiman – TGEN
- Younkin
- **Framingham**
- ADNI
- **Welcome Trust control data (1958 cohort)**
- **University of Miami/Vanderbilt**

otype
ata

ADGC
UPenn

genotype
data

- clean genotype data
- impute genotypes
- merge genotype/phenotype data

- assemble analysis package
  1. cleaned data
  2. original data
  3. Beadstudio package for CNVs

University of Miami
analysis group

Margaret Pericak-Vance

Boston University
analysis group

Lindsey Farrer

Special analysis
groups (SAGs)
others

Phase 1

	Sample type	NACC IDs	Overlap Other GWAS projects	Total Samples received	DNA received	Brain Samples Received	AD cases	Controls	Samples depleted, unavailable, ineligible
September, 2007	ADC samples	4,513	0	0	0	0	0	0	0
	Affiliated Samples	214	0	0	0	0	0	0	0
	Total	4,727	0	0	0	0	0	0	0
September, 2009	ADC samples	4,513	720	3,303	161	3,142	2,952	351	206
	Affiliated Samples	214	44	198	18	180	166	32	5
	Total	4,727	764	3,501	179	3,322	3,118	383	211

3,501 samples

Genotyping

- 660Quad Illumina
- 2,100 autopsy cases
- 862 controls (~200 from autopsied subjects)
- 462 subjects with CSF biomarker data

Goals

1. Replicate recent GWAS findings
   (ApoJ, etc)

   - ADGC samples
   - Miami/Vanderbilt data (Pericak-Vance/Haines)
   - Framingham data
   - Boston University data (Farrar)
   - Mt. Sinai data (Buxbaum)
   - LOAD data/Hispanic cohort - Columbia (Mayeux)
   - ~5,000 cases/5,000 controls

Next 2 weeks

Goals

1. Replicate recent GWAS findings

2. New GWAS

   - ADGC (3,000 cases/3,000 controls)
   - Miami/Vanderbilt data (Pericak-Vance/Haines)
   - Framingham data
   - Boston University data (Farrar)
   - Mt. Sinai data (Buxbaum)
   - LOAD data - Columbia (Mayeux)
   - ~5,000 cases/5,000 controls

January, 2010

Phase 2

ARRA GO grant
9/30/2009 – 9/30/2011

Collect and Analyze UDS samples

	Sample type	NACC IDs	Overlap Other GWAS projects	Total DNA received	Demented	Normal	MCI	Impaired Not MCI
September, 2009	UDS samples	17,270	3	2,301	954	729	511	107

Expect 1,744 in October

Alzheimer's Disease Genetic Consortium

Penn
University of Pennsylvania

Fall 2009

Special points of interest:

- View the new ADGC website
- Genotyping complete for over 2000 ADGC Phase 1 DNA
- New AD GWAS reports published online at Nature Genetics

Consortium for GWAS

The NIA recently awarded a 5-year, $19.5 million grant to the Alzheimer's Disease Genetics Consortium (ADGC) to conduct a genome-wide association study (GWAS) to identify the remaining genes associated with an increased risk of developing late-onset Alzheimer's disease (AD). Dr. Gerard D. Schellenberg of the University of Pennsylvania School of Medicine will lead the study.

GWAS requires a large number of samples to be studied to detect significant differences in genetic associations between people who have AD and those who do not. The ADGC is a collaborative effort of AD geneticists who are collecting more than 10,000 cases and 10,000 controls for such a study. In this study, investigators will look for genes that may influence the age of AD onset, rate of progression, and AD-related biomarkers. They will also be able to look for genes associated with age-related cognitive decline.

Identifying the remaining risk-factor genes will provide insight into new pathways that result in late-onset AD, a first step in the development of drugs to combat development of AD. It will also help identify people at high risk of developing late-onset AD, who would be prime candidates for prevention therapies and clinical trials.

- Press Release, *Spotlight on Aging Research,* NIA May 2009

New ADGC Website

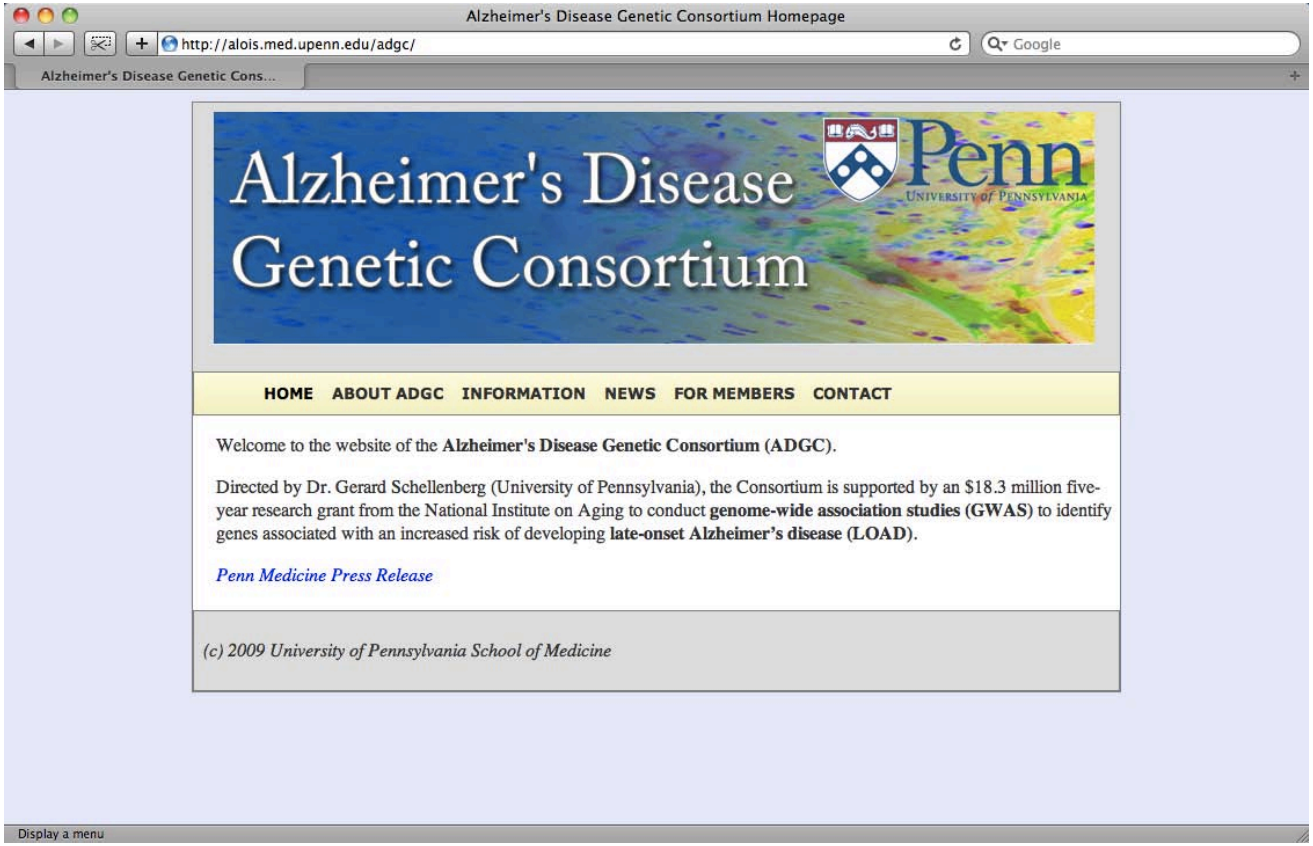
The ADGC website has been launched at:

http://alois.med.upenn.edu/adgc/
The site has information on the consortium, including members and committees, links to Alzheimer's disease (AD) information, and will eventually list consortium publications. This will also be your resource for guidelines to submit analysis proposals, description of datasets available, and rules of data use. We welcome comments and suggestions to continually improve the website.

<introductory note by Jerry>

GWAS Phase 1 Genotyping Initiated

ADGC Website



http://alois.med.upenn.edu/adgc/

The
End