

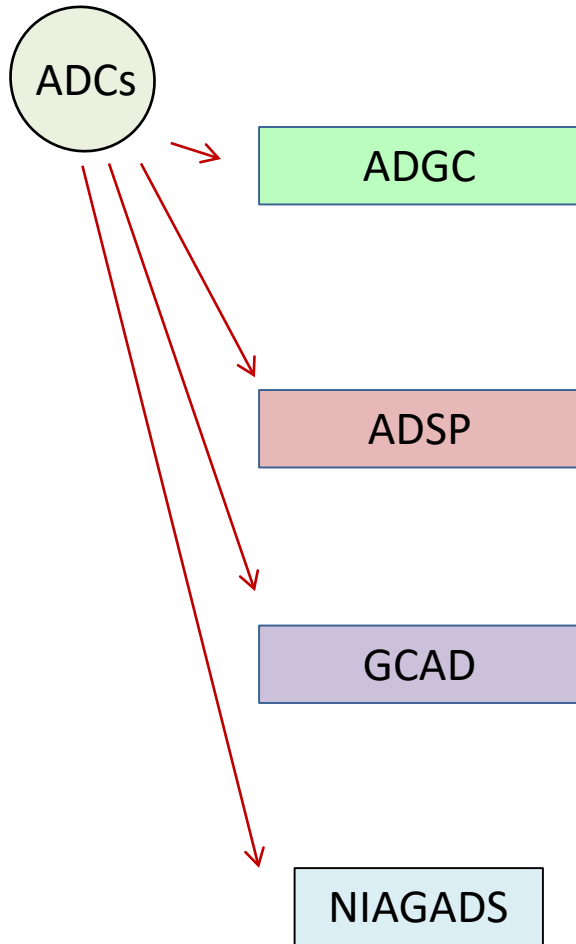
Overview: Alzheimer's Disease Genetics Projects

No conflicts



**Perelman School of Medicine
University of Pennsylvania**

Overview



Alzheimer's Disease Genetics Consortium

- Assemble/genotype/analyze cohorts for GWAS
- Sequence analysis – African Americans
- Support ADSP sequencing projects.

Alzheimer's Disease Sequencing Project

- Generate DNA sequence data
- Analyze sequence data

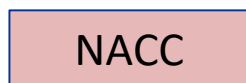
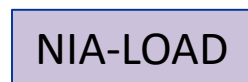
Genomic Center for Alzheimer's Disease

- Assemble all ADSP and augmentation sequence data
- Generate harmonized variant call sets for all data
- Coordinate analysis of all data

NIA Genetics of Alzheimer's Disease Storage site

- Collect/distribute AD genetic and phenotype data
- Manage data flow for the ADSP and GCAD

Partners



Alzheimer's Disease Centers

- AD cases and controls
- Standardized phenotype data
- Autopsy data

NIA-Late-onset Alzheimer's Disease

- Multiplex AD families
- Standardized phenotype data
- Autopsy data

National Alzheimer Coordinating Center

- Collect/distribute all ADC data
- Manage phenotype definitions

National Cell Repository for Alzheimer disease

- Collect tissue/DNA from ADCs and other studies
- Distribute samples to investigators **AND** sequence sites

Alzheimer's Disease Genetics Consortium

ADGC

- **Cohort expansion**
- **MCI**
- **Early-onset**
- **Exome sequencing**
- **Phenotype harmonization**

Meta-analysis of genetic association with diagnosed Alzheimer's disease identifies novel risk loci and implicates Abeta, Tau, immunity and lipid processing

[Kunkle BW](#) et al., submitted

Introduction

Late-onset Alzheimer's disease (LOAD, onset age > 60 years) is the most prevalent dementia in the elderly¹, and risk is partially driven by genetics². Many of the loci responsible for this genetic risk were identified by genome-wide association studies (GWAS)³⁻⁸. To identify additional LOAD risk loci, we performed the largest GWAS to date (89,769 individuals), analyzing both common and rare variants. We confirm 20 previous LOAD risk loci and identify four new genome-wide loci (*IQCK*, *ACE*, *ADAM10*, and *ADAMTS1*). Pathway analysis of these data implicates the immune system and lipid metabolism, and for the first time tau binding proteins and APP metabolism. These findings show that genetic variants affecting APP and A β processing are not only associated with early-onset autosomal dominant AD but also with LOAD. **Analysis of AD risk genes and pathways show enrichment for rare variants ($P = 1.32 \times 10^{-7}$) indicating that additional rare variants remain to be identified.**

Rare coding variants in *PLCG2*, *ABI3*, and *TREM2* implicate microglial-mediated innate immunity in Alzheimer's disease

Cases - 37,022; Controls - 48,402 Controls; Total = 85,133

Gene	P-value	OR	MAF cases	MAF controls
TREM2	5.4×10^{-24}	2.46	0.004	0.002
TREM2	1.6×10^{-14}	1.67	0.014	0.008
PLCG2	5.4×10^{-10}	0.68	0.006	0.009
ABI3	4.6×10^{-10}	1.43	0.011	0.008

$1/\text{OR} = 1.47$

ADC Subjects with GWAS

Race	Cases		Controls	
	All	(autopsy)	All	(autopsy)
Non-Hispanic white	7,641	3,833	5,339	316
Hispanic	346	66	224	3
African American	630	145	840	11
Asian	103	9	158	0
All	8,720	4,053	6,561	330

ADCs/NACC/NCRAD and NIA-LOAD are the largest single source of data for genetic studies

Cohorts

ACT	Crane/Larson
ADC	many
ADNI	Weiner
BIOCARD	Albers
CHAP	Bennet/Evans
EAS	Lipton
EFIGA	Mayeux
GSK	St George-Hyslop
MAYO	Peterson
MESA	Rich
MIRAGE	Farrer/Green
NBB	Riemenschneider
NIA-LOAD	Foroud/Mayeux
OHSU	Kramer
PFIZER	Whelan
RMAYO	Younkin
ROSMAP	Bennet

TARCC	Barber
TGEN	Reiman
UKS	Riemenschneider
UPITT	Kamboh
WASHU	Cruchaga/Goate
WHICAP	Mayeux
UMVUMSSM	Pericak-Vance/Haines /Buxbaum

	Caucasians	
	Cases	Controls
ADCs	7,641	5,339
Non-ADC cohorts	10,445	12,079
Total:	18,086	17,418

WHICAP2
NIA-LOAD2
MESA
MHAS
REGARDS

Early-Onset AD (<65 years)

	Non-Hispanic Whites	Hispanic	African Americans	Asian	Total
Age group	Case/cont. (autopsy)	Case/cont. (autopsy)	Case/cont. (autopsy)	Case/cont. (autopsy)	Case/cont. (autopsy)
<40	9/4(0)	0/0(0)	0/0(0)	0/0(0)	9/4(0)
40-44	19/2(1)	0/0(0)	0/0(0)	0/0(0)	19/2(1)
45-49	91/4(10)	0/0(0)	0/0(0)	0/0/(0)	91/4/(10)
50-54	273/4(67)	1/1(1)	1/0(0)	0/0(0)	275/5(68)
55-59	378/13 (136)	4/6(0)	2/1(2)	0/0(0)	384/20(138)
60-64	570/431(158)	41/16(4)	58/65(7)	9/26(1)	678/538(170)
Total	1340/458(372)	46/23(5)	61/66(9)	9/26(1)	1456/573(387)

Endophenotype group

Chair: Richard Mayeux

Members: Sandra Barral
Deborah Blacker
Will Bush
Paul Crane
Carlos Cruchaga
Mike Cuccaro
Charles DeCarli
Myriam Fornage
Tim Hohman
Bud Kukull
Jesse Mez
Andy Saykin
Sudha Seshadri
Giuseppe Tosto

Goals

- Catalogue phenotype data from different cohorts.
- Harmonize endophenotype data from multiple cohorts for use in genetic and other studies.

<https://goo.gl/forms/9vVbNxw2DlrpXHym1>

Endophenotype Profile Questionnaire

Section 1 of 11- Please fill out the form to give us an idea about your study.

* Required

Cohort Name *

Your answer _____

PI and Co-Investigators *

Include name and email of Investigators.

Your answer _____

Additional Contacts

Include name and email of any additional people we can contact about your study.

Your answer _____

Approximate Number of Subjects in Cohort

Your answer _____

What type of data do you collect? *

Control

Case

Familial

Other: _____

Endophenotype Profile Questionnaire

* Required

Samples and Genetic Data Collected

Section 2 of 11

Are your samples consented for sharing? *

- Yes, and they are GDS certified.
- Yes, but they are NOT GDS certified.
- Working on GDS certification.
- No, my samples are not consented for sharing.

Do you have stored DNA? *

- Yes
- No

Do you have DNA collected longitudinally? *

- Yes
- No
- Does not apply.
- Other: _____

What other biosamples do you have? *

- Whole Blood
- Monocytes
- Serum
- Plasma
- RNA
- None
- Other: _____

Endophenotype Profile Questionnaire

* Required

Neuropsychological Tests

Select all that apply.

Neuropsychological Tests *

- Memory
- Executive Function
- Language
- Visuospatial
- Attention
- Clinical Dementia Rating Scale
- None
- Other: _____

Are the neuropsychological tests collected longitudinally? *

- Yes
- No
- Other: _____

Is the name and email of the contact person for neuropsychological tests provided at the beginning of the questionnaire? *

- Yes
- No

Proposed Projects

1. Cognitive performance

- Trajectories of cognitive decline
 - MCI to AD
 - Aging controls


2. CVD-MRI

- Role of cerebrovascular factors in AD
- Measurement of stroke and WMH volumes in AD

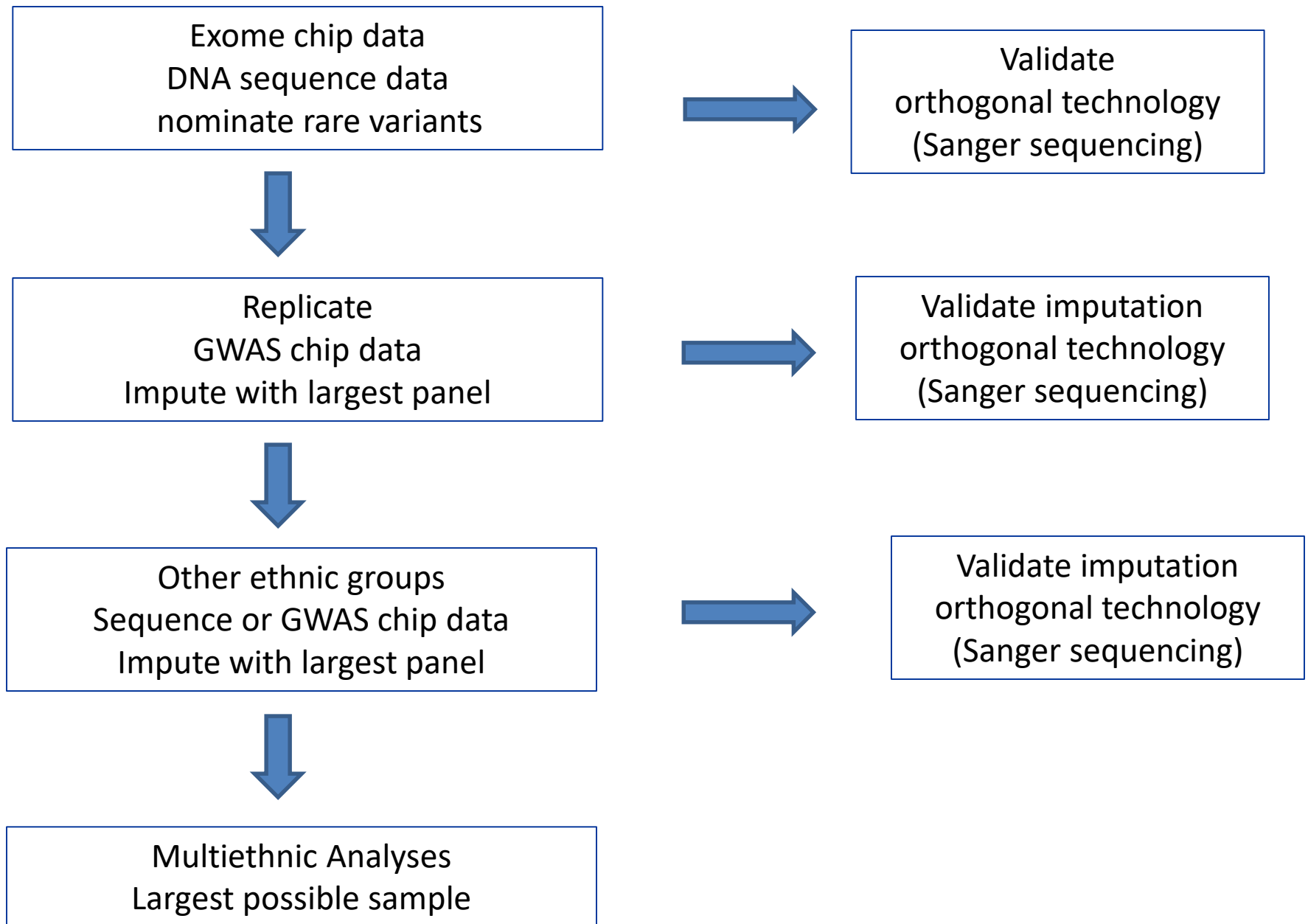
3. Non-genetic modifiers of risk

Collaborators welcome!

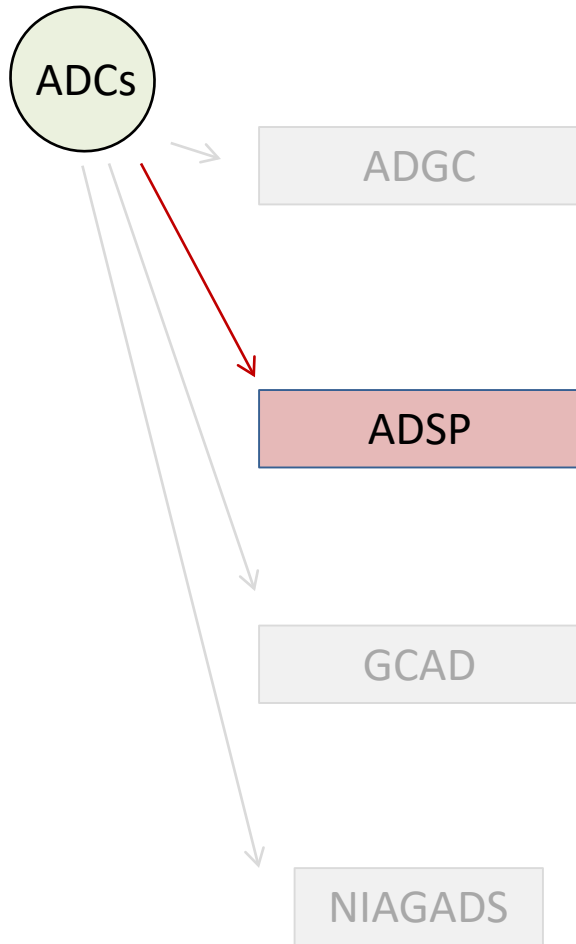
African American WES: by study

Study	Affected	Unaffected	Total
MIRAGE	105	125	230
Miami/Duke	180	309	489
North Carolina A&T	186	256	442
Case Western	44	60	104
 Alzheimer's Disease Centers	572	740	1,312
GenerAAtions	211	187	471
Rush	78	84	162
Total	1,376	1,761	3,210

sequencing completed, analysis in progress



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ADSP

completed

WGS: **1,000 Family-based**
3,000 multiethnic

ADC samples	
Caucasians	339 cases 366 controls
African Americans	248 cases 202 controls



WES **11,000 Caucasians + Caribbean Hispanics**

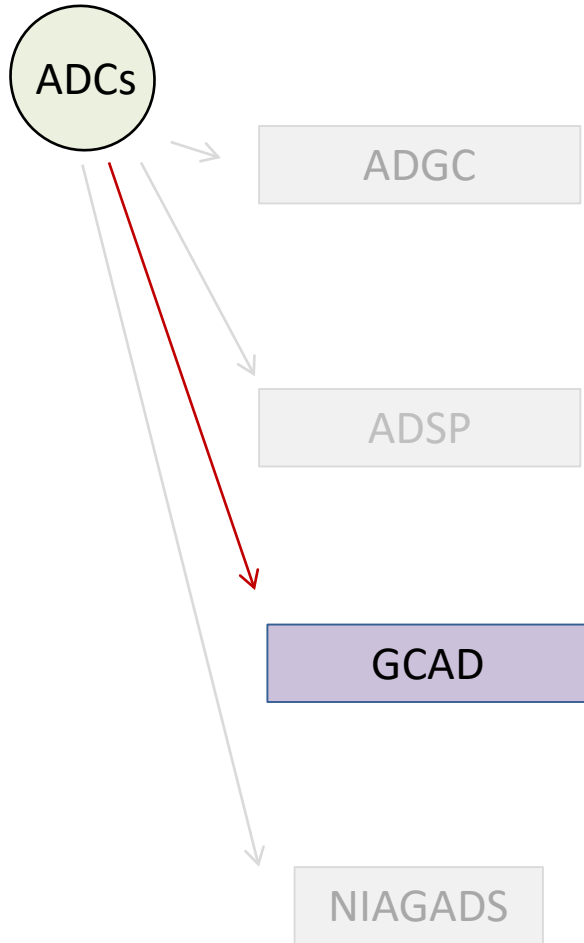
ADC samples	
Caucasians	2,386 cases 709 controls



WGS Sequencing in progress

ADC samples		
Caucasians	1,500 cases	1,500 controls
African American	569 Cases	791 controls

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Process all AD-relevant sequence data

- **All variants called in all data sets (gVCF)**
- ADSP QC protocol
- Merged data set with 2 callers
- WES and WGA data merged
- Analysis-ready file

- HG38
- GATK + ATLAS
- **Amazon cloud platform**

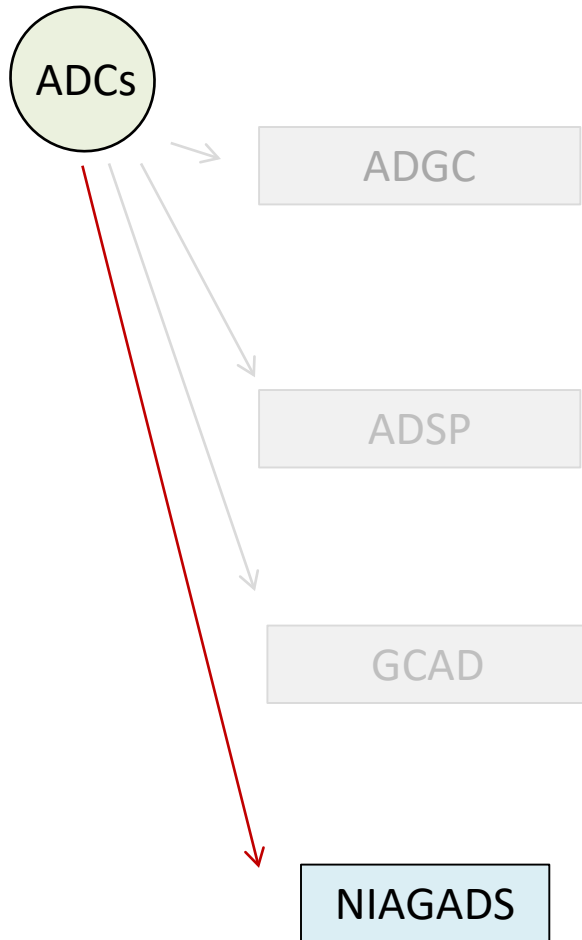
Current Status:

5,000 WGS samples called/processed

14,000 WES samples in process

2020: ~20,000 WGS (cases + controls)
~25,000 WES (cases + controls)
non-ADSP data ?

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NIAGADS

Qualified access data access: individual level data

On-line application process

- GWAS genotypes
- Sequence data: CRAMS (large)
variant call files (gVCF)
replace dbGaP

Roll-out
1-2 months

Visualization of variants: genome browser format
annotated variants

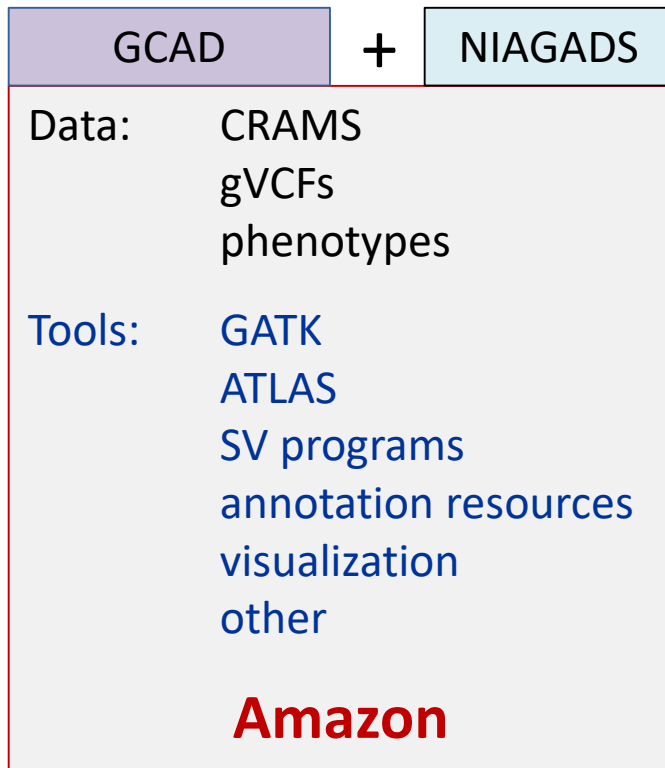
Resources for the non-expert (non-genetics) user

Alzheimer's Disease Discovery Commons

GCAD

+

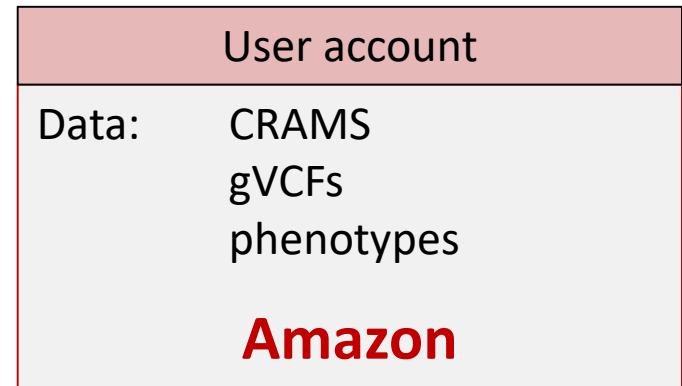
NIAGADS



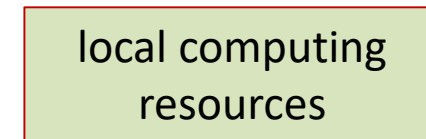
Qualified
access
user



Data
tools



Download
Optional



University of Pennsylvania

Li-San Wang
Adam Naj
Fanny Leong
Amanda Kuzma
Laura Cantwell

NIA

Marilyn Miller
Dallas Anderson

NIA/NIH
Alzheimer's Association

University of Miami

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Eden Martin
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Columbia University

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Sandra Barral
Christiane Rietz

Boston University

Lindsay Farrer
Gyungah Jun
Jaeyoon Chung

Case Western

Jonathan Haines
Will Bush

NACC

Walter "Bud" Kukull
Duane Beekly

NCRAD

Tatiana Foroud
Kelly Michelle Faber

The End