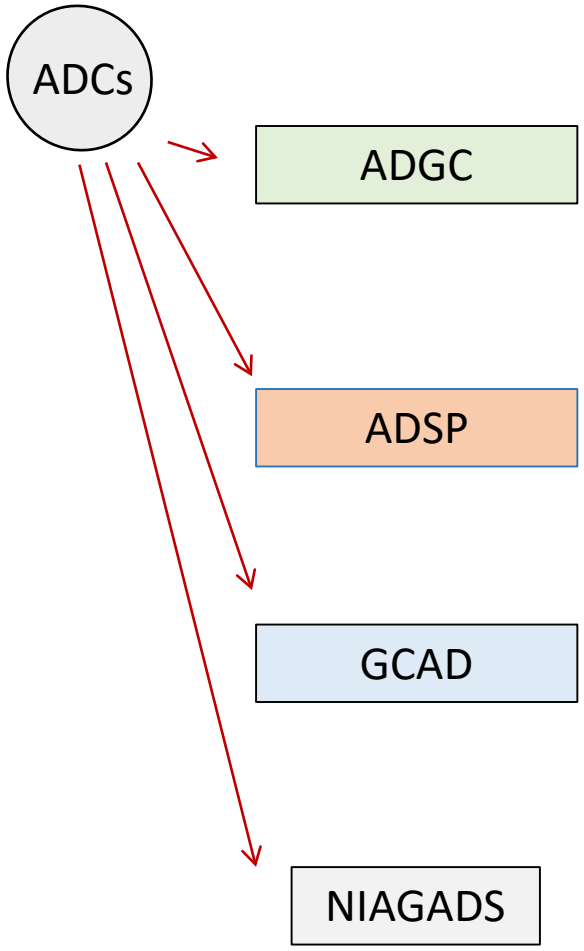
Update – Alzheimer's disease genetics



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

No disclosures

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

Kunkle, B.W., Grenier-Boley, B., Sims, R., Bis, J.C., Damotte, V., Naj, A.C., ……. Wang, L.-S., Ruiz, A., van Duijn, C.M., Holmans, P.A., Seshadri, S., Williams, J., Amouyel, P., Schellenberg, G.D., Lambert, J.C., Pericak-Vance, M.A

Risk for Late-onset Alzheimer's disease (LOAD), the most prevalent dementia in the elderly1, is partially driven by genetics. To identify LOAD risk loci, we performed the largest genome-wide association meta-analysis of clinically diagnosed LOAD to date (94,437 individuals), analyzing both common and rare variants. We confirm 20 previous LOAD risk loci and identify **five new genome-wide loci (IQCK, ACE, ADAM10, ADAMTS1 and WWOX)**. Fine-mapping of the human leukocyte antigen (HLA) region confirms the neurological and immune-mediated disease haplotype HLA-DR15 as a risk factor for LOAD. Pathway analysis implicates the immune system and lipid metabolism, and for the first time tau binding proteins and APP metabolism, showing that genetic variants affecting APP and Aβ 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 ($P=1.32x10^{-7}$) indicating that additional rare variants remain to be identified. Finally, we also identify important genetic correlations between LOAD and other traits including family history of dementia and education.**

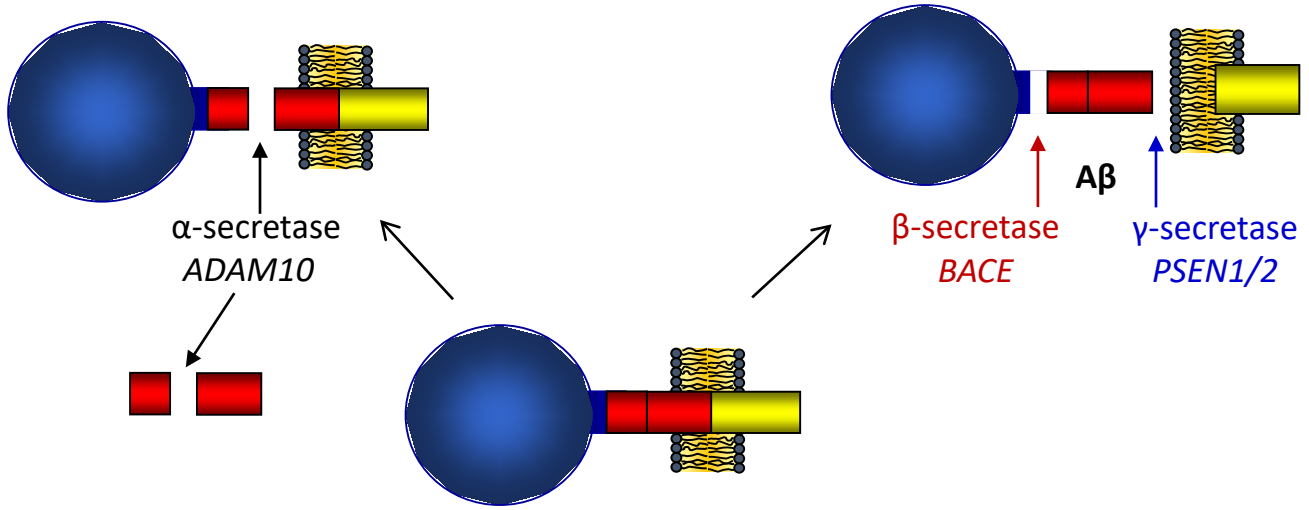
bioRxiv 294629; doi: https://doi.org/10.1101/294629

IGAP GWAS - 2018

Consortium	cases	controls
ADGC	15,456	16,142
CHARGE	2,240	13,474
EADI	5,288	7,770
GERAD	12,290	21,777
Totals	35,274	59,163
Grand total	94,437	

Chr.	Position	Closest gene	MAF	OR (95% CI)	Meta P
15	**59,045,774**	***ADAM10***	**0.295**	**0.93 (0.91-0.95)**	**6.8×10^{-9}**
16	**19,808,163**	***IQCK***	**0.180**	**0.92 (0.89-0.95)**	**2.4×10^{-8}**
17	**61,538,148**	***ACE***	**0.020**	**1.30 (1.19-1.42)**	**5.3×10^{-9}**
21	**28,156,856**	***ADAMTS1***	**0.308**	**0.93 (0.91-0.96)**	**2.6×10^{-8}**
16	**179,355,857**	***WWOX,MAF***	**0.116**	**1.16 (1.10-1.23)**	**3.7×10^{-8}**
6	**41,034,000**	***OARD1***	**0.030**	**1.32 (1.22-1.42)**	**2.1×10^{-13}**
6	**41,129,252**	***TREM2***	**0.008**	**2.08 (1.73-2.49)**	**2.7×10^{-15}**
10	11,720,308	*ECHDC3*	0.390	1.08 (1.06-1.11)	1.8×10^{-11}
17	56,409,089	*MIR142/TSPOAP1-AS1*	0.440	0.94 (0.91-0.96)	5.3×10^{-8}

APP

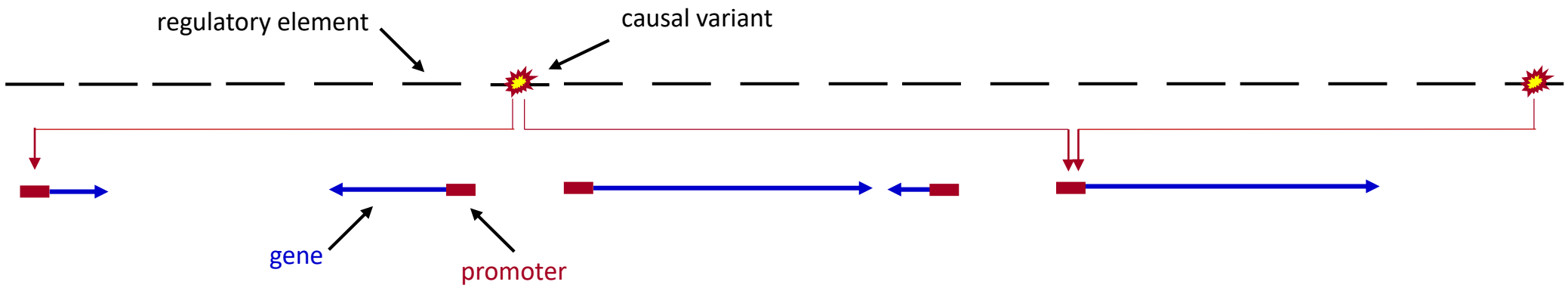


APP	amyloid precursor protein
PSEN1/2	presenilin 1 and 2
ADAM10	α-secretase
SORL1	intracellular APP transport
ADAMTS1	ADAM metallopeptidase with thrombospondin type 1 motif 1

close to *APP*

GWAS signals: 90-95% of causative variants are in non-promoter regulatory elements

eQTLs: only 50% affect the closest gene



Significant pathways (q-value≤0.05) from MAGMA pathway analysis for common SNV and rare SNV subsets.

Pathway	N genes in pathway in dataset	Common SNVs P*	Common SNVs-q q-value	Rare SNV P*	Rare SNVs q-value	Pathway description
GO:65005	20	1.45E-07*	9.53E-04	6.76E-02	8.42E-01	protein-lipid complex assembly
GO:1902003	10	4.56E-07*	1.49E-03	4.94E-02	8.42E-01	regulation of beta-amyloid formation
GO:32994	39	1.16E-06*	2.54E-03	1.78E-02	8.17E-01	protein-lipid complex
GO:1902991	12	3.54E-06*	5.80E-03	5.66E-02	8.42E-01	regulation of amyloid precursor protein catabolic process
GO:43691	17	5.55E-06*	6.75E-03	3.08E-02	8.17E-01	reverse cholesterol transport
GO:71825	35	6.18E-06*	6.75E-03	1.27E-01	8.42E-01	protein-lipid complex subunit organization
GO:34377	18	1.64E-05*	1.53E-02	1.82E-01	8.42E-01	plasma lipoprotein particle assembly
GO:48156	10	3.19E-05*	2.61E-02	7.77E-01	8.54E-01	tau protein binding
GO:2253	382	6.32E-05*	4.60E-02	2.09E-01	8.42E-01	activation of immune response

Sub-threshold loci are enriched for rare-variants

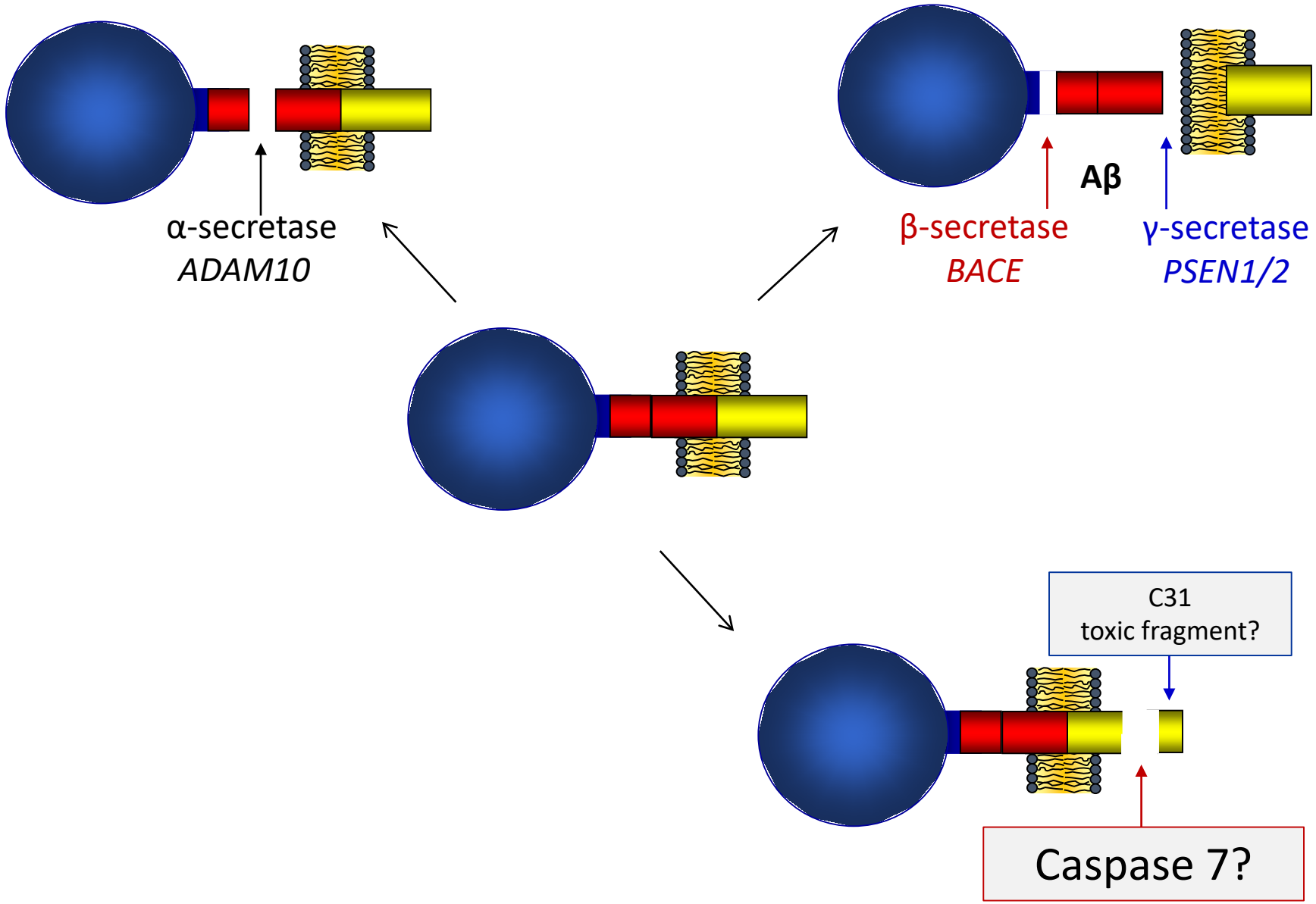
ADSP analyses

Bis JC, Jian X, Kunkle BW, Chen Y, ……..Wang, L.-S., Schellenberg GD, Seshadri S, Naj AC, Fornage M, Farrer LA. **Whole exome sequencing study identifies novel rare and common Alzheimer's-associated variants involved in immune response and transcriptional regulation.** Mol Psychiatry. 2018 Aug 14. doi: 10.1038/s41380-018-0112-7. [Epub ahead of print]. PMID:30108311

Gene/Locus	Chromosome
ZNF655	7
ISYNA1	19
AARD	8
AC099552.4	7
ANXA5	4
C4ORF17	4
CD1E	1
PLEC	8
PTPRC	1
STAG3	7
TBC1D32	6
CASP7	10
C1ORF173	3
IGHG3	14
IGHJ6	14
NSF	17

ADSP Case-control group

APP


α-secretase
ADAM10
β-secretase
BACE
Aβ
γ-secretase
PSEN1/2
C31
toxic fragment?
Caspase 7?

Is late-onset AD the same as early-onset autosomal dominant AD?

- *APOE* genotypes influence onset age in both late-onset AD and early-onset autosomal dominant AD (*PSEN1* and *PSEN2* mutation families)
- Icelandic mutations that reduces Aβ levels is protective against late-onset AD
- *ADAM10* is a late-onset AD gene – degrades Aβ amyloid
- Pathways for regulation of beta-amyloid formation and *APP* processing are enriched in late-onset risk loci

Samples with array data

Ethnic group	AD	MCI	NC	Total
Non-Hispanic white	16,229	2,333	17,010	35,572
African American	2,845	418	5,271	8,143
Caribbean Hispanics	3,859	-	6,365	10,224
Non-Caribbean Hispanics	351	194	216	761
Asian	2,337	90	3,273	5,700
Totals	25,621	3,035	32,135	57,756

Mexico/Mexican Americans:	MHAS 10/66 cohort, TARCC, MESA
Asians:	Chosen University KLoSA

Non-Hispanics white:	A4 REGARDS MESA ADES GAPMP - Georgia
African Americans:	REGARDS RAPID
India:	DAD-LASI Center for Brain Research

Sequence data

Study	sequence	Cases	Controls
ADSP: Case-control (non-Hispanic white)	WES	5,711	4,634
ADSP: Case-control (Caribbean Hispanics)	WES	160	171
ADGC: case-control (African American)	WES	1,140	1,517
ADSP: families (non-Hispanic whites)	WGS	225	160
ADSP: families (Caribbean Hispanics)	WGS	315	275
ADSP: families (African American)	WGS	16	10
ADSP: Case-control (African Americans)	WGS	2,882	4,126
ADSP: case-control (Caribbean Hispanics)	WGS	2,888	2,475
ADSP: case-control (non-Hispanic whites)	WGS	3,239	2,249
Totals	WGA +WES	16,575	16,617
Totals	WGA only	9,564	10,295

Release 1

NIAGADS: 1st release: ~5,000 whole genome sequences
hg38
Called using common pipeline
ADSP QC protocol
pVCF, gVCF, CRAMS
joint-called – all variants called at all sites

multiplex family data
- 132 families
- 990 subjects

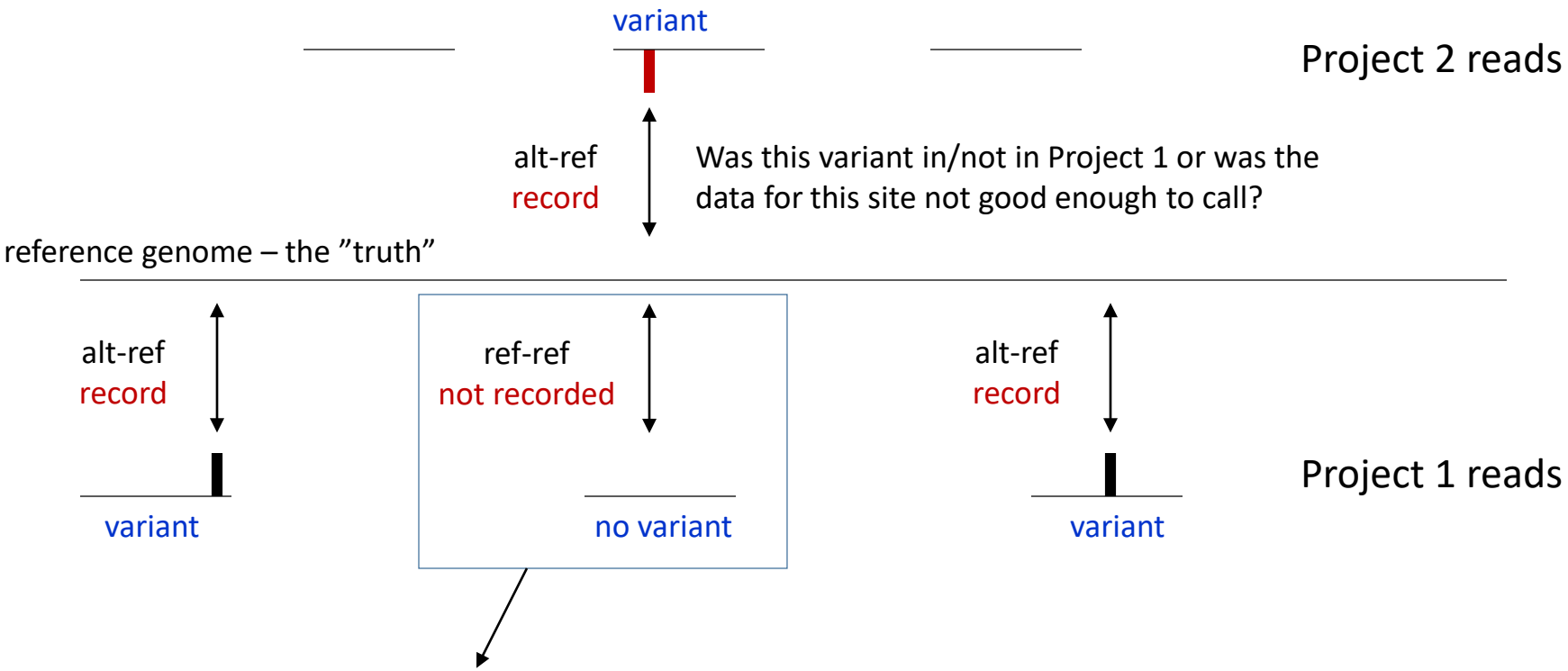
ADNI: ~200 controls, 400 MCI, 200 AD,

case-control: African American, 500 AD, 500 control
Caribbean Hispanics, 500 AD, 500 control
non-Hispanic white, 500 AD cases, 500 controls

Release 2 – winter 2019

Case-control - whole exome sequencing:

- ~20,000 subjects
- 5,000 unrelated cases: 4,220 from the ADGC
  2,430 from ADC's
- 5,000 elderly normal controls: 3,240 from the ADGC
  840 from the ADC's
- 1,000 cases from multiplex families – one/family



Solution:

- store ref-ref calls
- compress to reduce file size
- use gVCF format

All variants called at all sites for all data sets

Data Sharing - NIAGADS

- I want it all
- I want it now
- I want it delivered

Today!

Data sharing principles:

1. Respect consent agreement: → what the subject says the data/sample can and cannot be used for
   → 25 use categories from consent forms

Data use categories

• Disease-Specific (Aging/Dementia, IRB) (DS-AGEDEM-IRB)	IRB approval required aging and dementia
• Disease-Specific (Alzheimer Disease, IRB) (DS-ALZ-IRB)	IRB approval required Alzheimer's disease
• Disease-specific (neurodegenerative) (DS-ND)	neurodegenerative disease
• Health/Medical/Biomedical (IRB-PUB) (HMB-IRB-PUB)	IRB approval required health/medical/biomedical required to release data
• General Research Use (GRU)	general use

- **20 more categories**

Commercial/non-commercial use

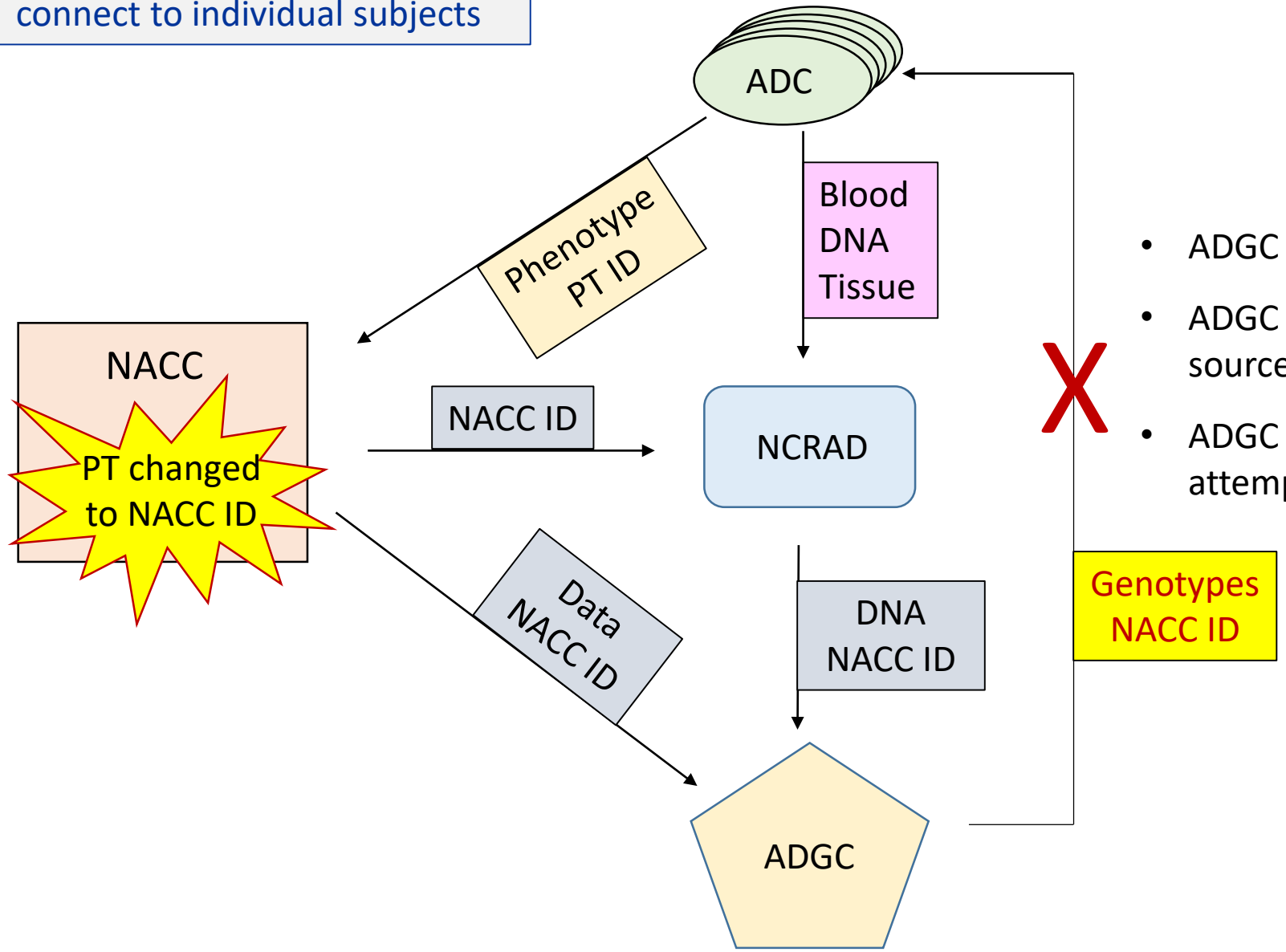
Data sharing principles:

1. Respect consent agreement: → what the subject says the data/sample can and cannot be used for
   - → 25 use categories from consent forms

2. Respect promise investigator makes to subject: → we will use your data for disease research
   - → Make data access easy

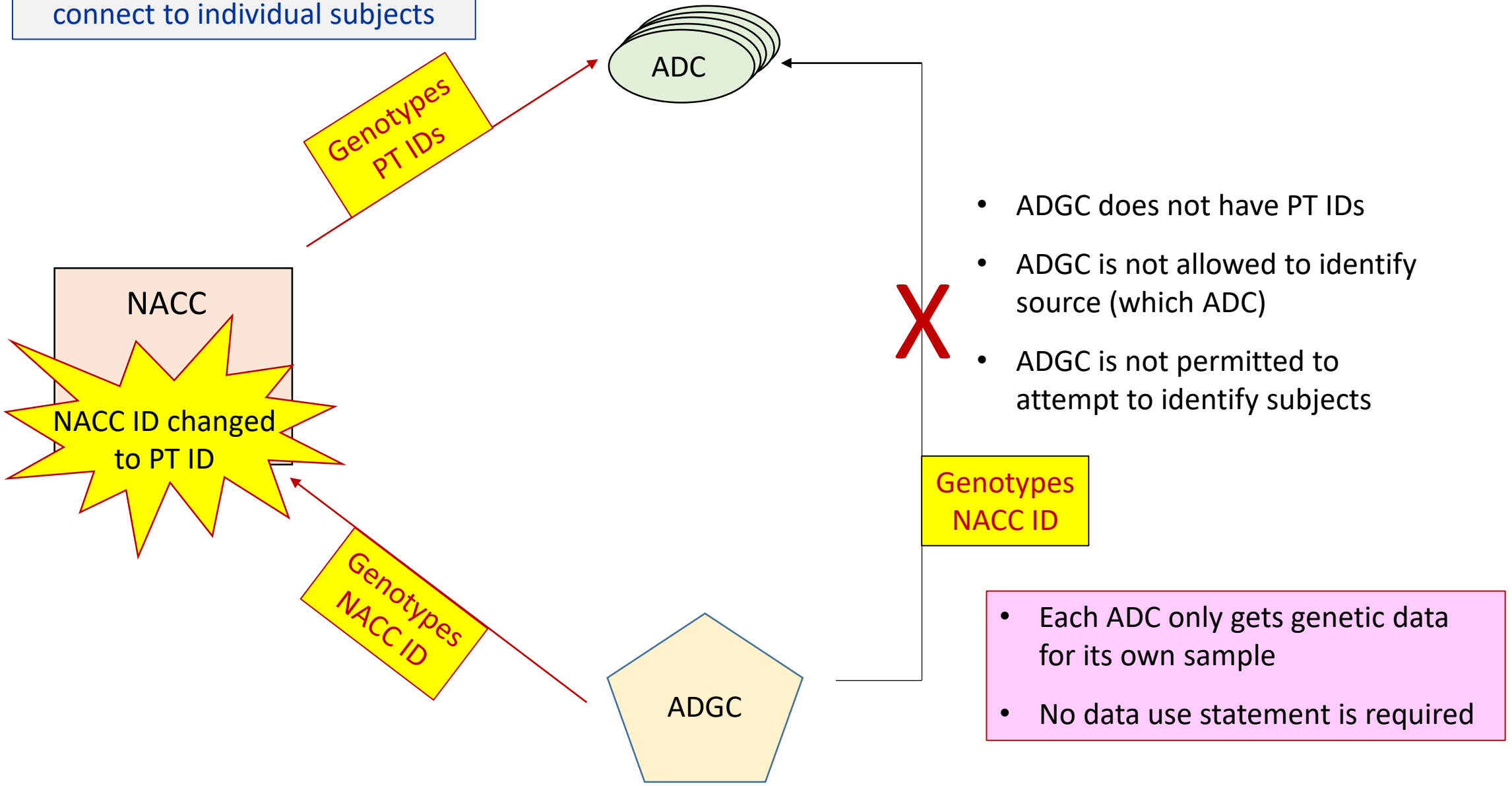
3. Protect public trust in medical research: → Keep data secure
   - → take “reasonable” steps to prevent inappropriate use and distribution

GWAS data return to ADCs: connect to individual subjects



- ADGC does not have PT IDs
- ADGC is not allowed to identify source (which ADC)
- ADGC is not permitted to attempt to identify subjects

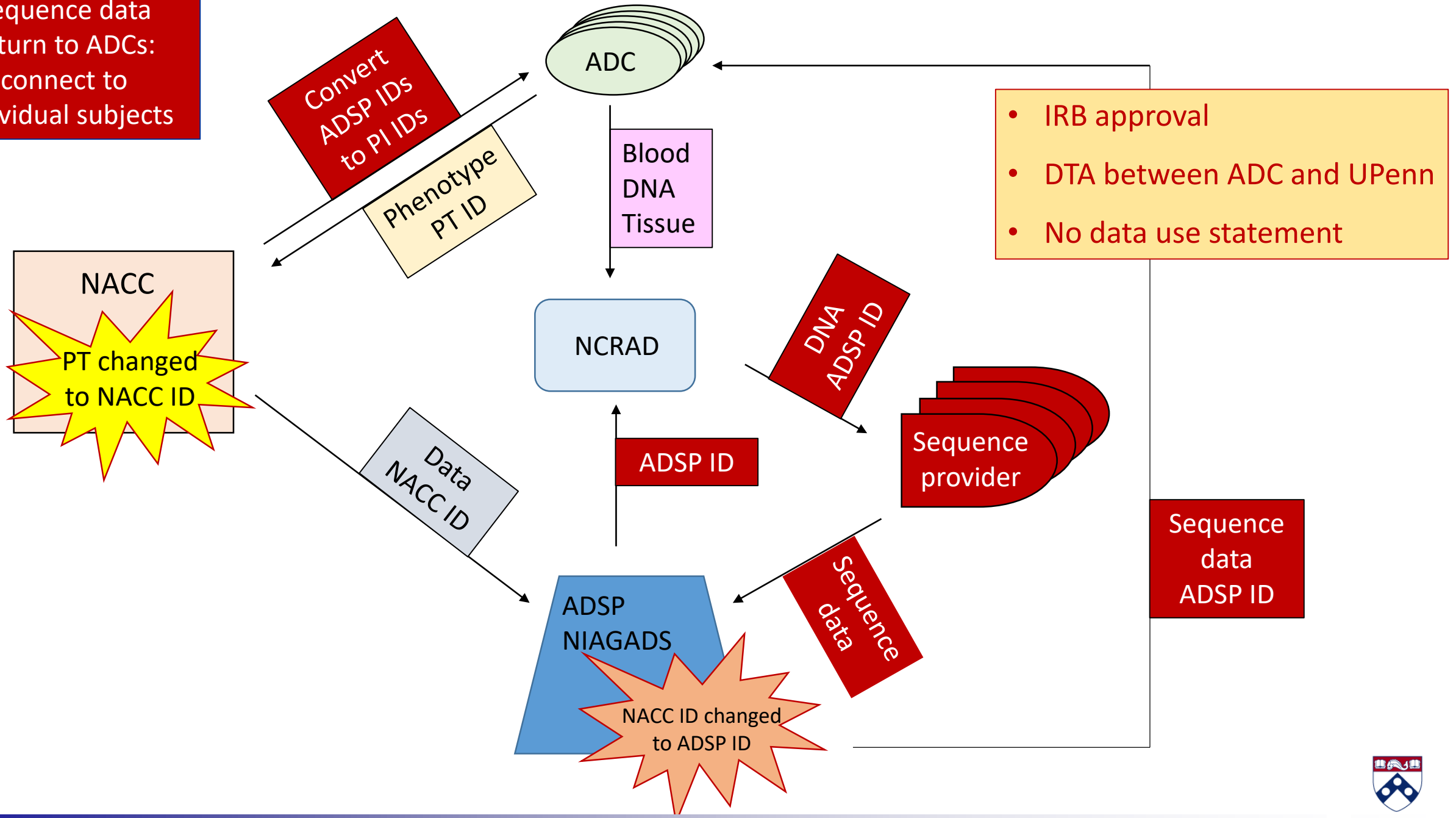
GWAS data return to ADCs: connect to individual subjects



- ADGC does not have PT IDs
- ADGC is not allowed to identify source (which ADC)
- ADGC is not permitted to attempt to identify subjects

- Each ADC only gets genetic data for its own sample
- No data use statement is required

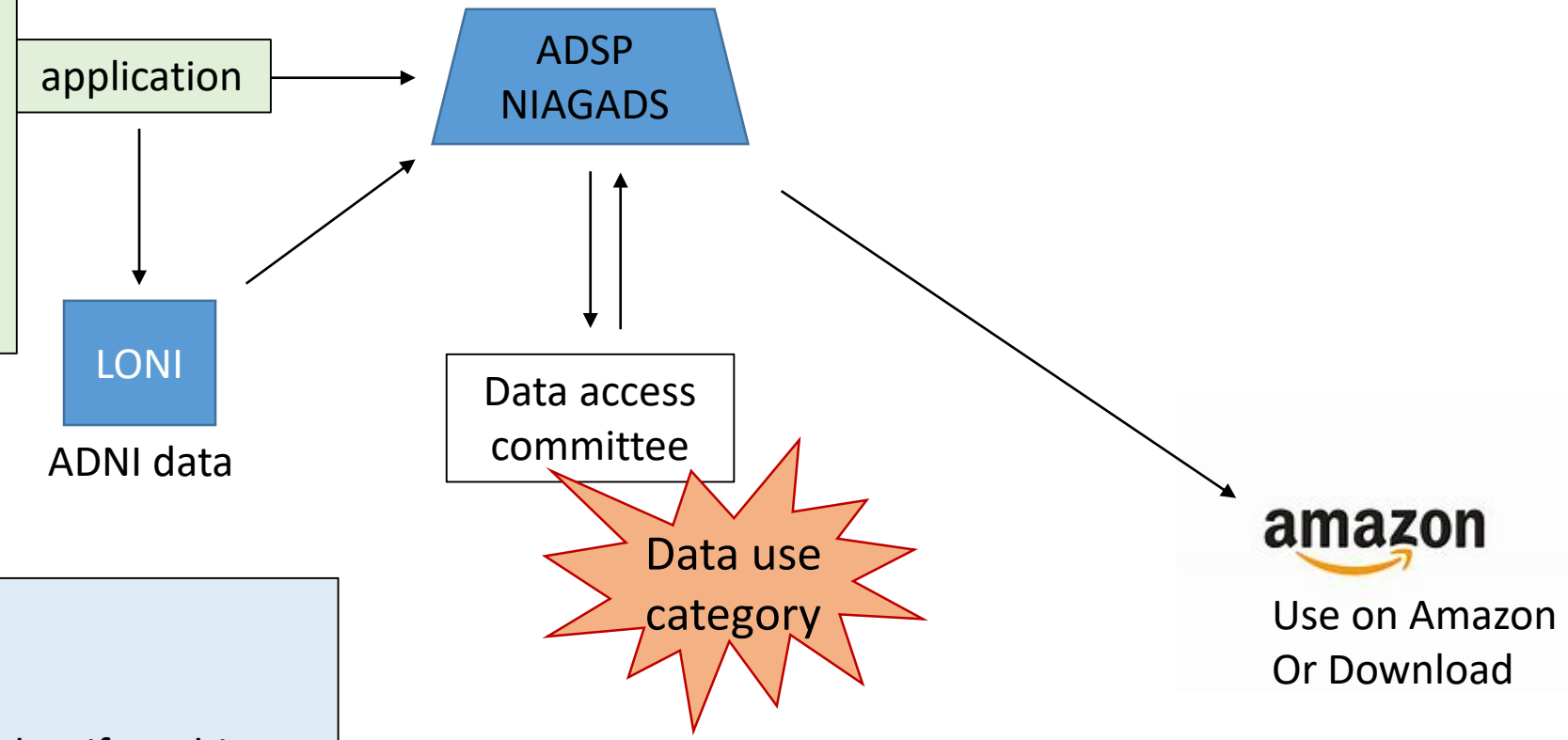
Sequence data return to ADCs: connect to individual subjects



- IRB approval
- DTA between ADC and UPenn
- No data use statement

So you want it all?

- Data use statement
- Data transfer agreement
- IRB approval
- IRB Protocol
- Secondary data return plan
- NIA genetic data sharing plan
- NIAGADS distribution agreement



- No secondary sharing
  (unless linked applications)
- Cannot attempt to identify/re-identify subjects

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Jaeyoon Chung

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NCRAD

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Kelly Michelle Faber

The End