Title: NIAGADS: A Comprehensive National Data Repository for Alzheimer's Disease and Related Dementia Genetics and Genomics Research

Authors:

Amanda Kuzma[1]
Otto Valladares[1]
Emily Greenfest-Allen[1]
Heather Nicaretta[1]
Maureen Kirsch[1]
Youli Ren[1]
Zivadin Katanic[1]
Heather White[1]
Andrew Wilk[1]
Lauren Bass[1]
Jascha Brettschneider[1]
Luke Carter[1]
Jeffrey Cifello[1]
Wei-Hsuan Chuang[1]
Kaylyn Clark[1]
Prabhakaran Gangadharan[1]
Jacob Haut[1,2]
Pei-Chuan Ho[1]
Wenhwai Horng[1]
Taha Iqbal[1,2]
Yumi Jin[1]
Peter Keskinen[1]
Alexis Lerro Rose[1]
Michelle K Moon[1]
Joseph Manuel[1]
Liming Qu[1]
Flawless Robbins[1]
Naveensri Saravanan[1]
Jin Sha[1,2]
Sam Tate[1]
Yi Zhao[1]
Alzheimer's Disease Sequencing Project
Laura Cantwell[1]
Jake Gardner[1,3]
Shin-Yi Chou[1,4, 5]
Jung-Ying Tzeng [1,6, 7]
William Bush [8]
Adam Naj[1,2]
Pavel Kuksa[1]

Wan-Ping Lee[1]
Yuk Yee Leung[1]
Gerard Schellenberg[1]
Li-San Wang (Contact author)[1]

1. Department of Pathology and Laboratory Medicine, Penn Neurodegeneration Genomics Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States.
2. Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA.
3. Department of Computer and Information Science, University of Pennsylvania, Philadelphia, PA, USA.
4. Department of Economics, Lehigh University, Bethlehem, PA, United States.
5. National Bureau of Economic Research, Cambridge, MA, United States.
6. Bioinformatics Research Center, North Carolina State University, NC, USA.
7. Department of Statistics, North Carolina State University, NC, USA.
8. Cleveland Institute for Computational Biology, Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, Ohio, USA.

Contact author email: lswang@pennmedicine.upenn.edu

Abstract:

NIAGADS is the National Institute on Aging (NIA) designated national data repository for human genetics research on Alzheimer's Disease and related dementia (ADRD). NIAGADS maintains a high-quality data collection for ADRD genetic/genomic research and supports genetics data production and analysis. NIAGADS hosts whole genome and exome sequence data from the Alzheimer's Disease Sequencing Project (ADSP) and other genotype/phenotype data, encompassing 209,000 samples. NIAGADS shares these data with hundreds of research groups around the world via the Data Sharing Service, a FISMA moderate compliant cloud-based platform that fully supports the NIH Genome Data Sharing Policy. NIAGADS Open Access consists of multiple knowledge bases with genome-wide association summary statistics and rich annotations on the biological significance of genetic variants and genes across the human genome. NIAGADS stands as a keystone in promoting collaborations to advance the understanding and treatment of Alzheimer's disease.

Introduction

Human genetics signals and functional genomic data holds great promise for nominating candidate therapeutic targets in complex diseases. Much progress has been made in the genetics of Alzheimer's Disease (AD) since genome-wide association studies (GWAS) were introduced in the mid-2000s. Large collaborations such as the Alzheimer's Disease Genetics Consortium (ADGC)[1], International Alzheimer's Genomics Project (IGAP) and population surveys such as UK Biobank[2] increased sample size and statistical power. These studies[3-11] have reported multiple high confidence, reproducible findings, confirmed the causal role of immunity, and helped clarify genetic (dis)similarities with other AD related neurodegenerative disorders. We see the following trends and challenges in advancing Alzheimer's disease genetics: (1) Increasing sample size, especially for underrepresented populations, for sufficient statistical power in gene finding; (2) transitioning to rich phenotypes, biomarkers, and functional omics beyond case/control status; (3) developing novel statistical methods, analysis platforms and tools for rare variant discovery; (4) generating new approaches to translate genetic findings to mechanisms and pathways. Developing accurate, population-specific disease risk models will allow identification of high-risk individuals for trial recruitment and development of sensitive early diagnostics. To this end, researchers need a large, high-quality AD genetics data resource with rich phenotypes and functional genomic data.

NIAGADS is the National Institute on Aging (NIA) designated national data repository for AD and AD-related dementia (ADRD) human genetics research. Supported by a U24 cooperative agreement with the University of Pennsylvania since 2012, NIAGADS functions as a one-stop access portal for AD genetics, managing and sharing genetic data and findings with the research community. The funding coincided with the announcement of the Alzheimer's Disease Sequencing Project (ADSP), an NIA strategic initiative to analyze complete genomes of AD patients and cognitively normal controls from diverse populations to find novel genetic variants modulating AD risk. NIAGADS is the data coordinating center for ADSP. See Figure 1 for the timeline of NIAGADS and ADSP data growth.

NIAGADS has three major objectives: (1) Curate, update, and disseminate a high-quality data collection for genetic/genomic research of AD/ADRD; (2) Develop secure informatics infrastructure for data management, dissemination and use; (3) Support AD genetics data production and analysis activities. This article reports the available datasets, design principles, and IT infrastructure of NIAGADS as a valuable resource for the research of Alzheimer's disease and human genetics in general.

Results

Overview. NIAGADS provides two web-based platforms for users to explore and access its rich and complex data collection (Figure 2). Individual datasets are released via the NIAGADS Data Sharing Service (DSS) website. Sensitive datasets such as individual GWAS genotype data and ADSP whole genome sequences require a review process mandated by NIH and are

available by a Data Access Request (DAR) process that is compliant with NIH Genome Data Sharing (GDS) Policy. Datasets that are not sensitive can be downloaded directly via the DSS Open Access data portal. AD genetics knowledge and genomic annotation are available via NIAGADS Open Access, an integrated suite of genomics knowledge bases coupled with web interfaces for querying available data, viewing gene and variant reports, and allows much of the annotation data to be downloaded directly.

AD genetics datasets. As of June 2024, NIAGADS has 125 distinct datasets of various genomic data types for more than 209,000 samples (Figure 3). The primary data types hosted at NIAGADS are human genetic data from GWAS SNP arrays and imputations, and whole-exome/whole-genome sequencing data (WES/WGS). Both individual level data and summary statistics are available. Genetic data are connected with clinical phenotypes including Alzheimer's disease case/control diagnosis, age at onset/last visit/death, sex and population (based on cohort reports). Other data types include functional omics, fluid biomarkers, aggregated imaging data (such as volumetric data for brain regions of interest), and summary statistics. For a significant (and increasing) subset of these subjects, fully harmonized phenotype data, developed by the ADSP Phenotype Harmonization Consortium (PHC), are available through NIAGADS. Datasets are governed by more than 200 institutional certifications that provide informed consent research use limitations determined by the Institutional Review Boards (IRBs) governing these studies. Figure 3b shows the location of cohorts that contribute to NIAGADS data collection. These datasets are used widely by the research community around the world. As of June 2024, NIAGADS supported more than 500 unique data requests from qualified investigators and is officially acknowledged in over 330 articles (Figure 3a).

The largest data in NIAGADS in terms of data size are whole genome and whole exome sequence data as well as derived data (e.g. structural variant calls) and associated phenotypic data from the ADSP. These data are produced by participating cohorts, infrastructure grants, and workgroups. Currently NIAGADS works with 73 cohorts in ADSP and will add more cohorts into ADSP in future releases.

NIAGADS offers a comprehensive collection of genomic data types for Alzheimer's Disease and Related Dementias (ADRD) research. The majority of data in NIAGADS are relevant to human genetics/genomics research, with datatypes such as summary statistics, GWAS SNP array data (with imputation using very large reference panels), exome chips, WGS/WES data, and associated clinical phenotype data. For some of the cohorts managed by NIAGADS, NIAGADS also hosts omics data such as RNA-Seq, proteomics, methylation, and metabolomics data. See Figure 3c for a breakdown of data stored in NIAGADS as of July 2024.

ADSP data. NIAGADS started sharing ADSP sequence data with the research community in 2018. ADSP continues to generate WGS data from cohorts selected by the National Institute on Aging. New genomic data are passed to the Genome Center for Alzheimer's Disease (GCAD) to generate compressed read alignment files (in the CRAM format) and individual genotype calls (in the genomic VCF or gVCF format) which are then released in batches after sample level quality control is completed. In addition, ADSP releases fully harmonized genetic data as

cumulative joint genotype calls (project-level VCF files) by GCAD for every observed variant across all previously released and new genomes. Between these major releases, ADSP also releases additional information including in-depth quality control results, population structure principal component estimates, variant annotations, and structural variant calls. As of June 2024, ADSP has released four major freezes (R1: 4,789 genomes; R2: 20,503 exomes; R3: additional 12,116 genomes and joint genotype calls of 16,905 genomes; R4: additional 19,456 genomes and joint genotype calls of 36,361 genomes – see Figures 1b and 4) across 13 versions. All genome sequences have been processed using a GATK-based processing pipeline[12] against the human genome reference 38 genome build. All exome sequences have been processed using the same pipeline that accounts for differences in capture region designs from 10 different exome capture kits [13] to retain as many variants as possible. R2 WES data includes 8.2 million autosomal variants, and R4 WGS data includes more than 438 million variants. Starting with R4, ADSP has more genomes from underrepresented non-European groups than genomes from European participants. ADSP is currently working on the next R5 release (fall 2024) which will bring the total number of genomes to more than 60,000 from 57 different cohorts.

ADGC GWAS data. NIAGADS releases GWAS SNP array data submitted by the ADGC. ADGC assembles AD cohorts, collects GWAS SNP array data, and performs data harmonization, quality control, and imputation using the latest reference panels (TOPMed-r2 panel consisting of 97,256 genomes and 308 million variants across diverse populations). ADGC also genotypes DNA from subjects recruited by more than 30 NIA Alzheimer's Disease Research Centers (ADRCs)[14] as part of the National Alzheimer's Coordinating Center (NACC)[15] data collection. In Spring 2024, NIAGADS released 15 batches of the NACC sample genotyping array datasets generated by ADGC (Table 1). The dataset consists of 29,694 subjects with TOPMed-r2 imputed genotype data. All data have been mapped to the human reference genome 38 and sample ID mappings to ADSP genomes are included so researchers can link across the two datasets.

Other human genetics datasets. NIAGADS houses many other datasets such as Health and Retirement Study (HRS) GWAS and Knight ADRC collection datasets (Table 1), and data derived from NIAGADS datasets such as genome-wide summary statistics submitted by investigators from published studies. Users can access datasets with special research use limitations (e.g. sensitive population or required by the original informed consent) by submitting data access requests. NIAGADS also has data for participants with other types of dementias like Parkinson's disease (PD), frontotemporal dementia (FTD), Lewy body dementia (LBD), and progressive supranuclear palsy (PSP) (Figure 2). Of note, NIAGADS hosts whole genome sequences of 1,992 samples with PSP as part of the ADSP release.

NIAGADS Data Sharing Service (DSS). Most of the datasets housed within NIAGADS require users to submit a data access request (DAR) as there are special research use limitations as required by the original informed consent. Whenever possible, NIAGADS makes summary statistics without such limitations available for direct download or through the NIAGADS Open Access resources. NIAGADS DSS is a qualified access data sharing platform following relevant

NIH and federal policies. Much of the platform design and organization is based on the dbGaP website to ensure policy compliance and familiarity to the research community. NIAGADS DSS is compliant with FISMA Moderate risk level requirements[16] built on the Amazon Web Services[17] (AWS) cloud platform. DSS relies on the NIH eRA grant management system to validate user identities.

NIAGADS supports the NIH Genomic Data Sharing (GDS) policy[18]. All cohorts submit a completed Institutional Certification approved by the cohort's institutional Review Board (IRB). The IRB reviews the original consent forms and determines the research use limitations using the GDS framework, including permission to use the data for research outside AD/ADRD and permissibility for use by for-profit organizations. If the cohort has multiple versions of informed consent, the cohort needs to specify which research use limitation applies to each participant in the consent form. Per GDS policy, certain cohorts may specify research use limitations for genomic summary results (e.g. populations of special status such as tribal nations in the United States) and will require the requestor submit a formal data request.

The cloud-based DDS platform consists of three components. The *File Repository* includes a web-based data portal front end that allows users to browse and filter all files in each dataset and links to the file objects on the Simple Storage Service (S3) buckets on the Amazon Web Service. The *DSS website* contains detailed information about submitting and managing Data Access Requests (DARs), a catalog of all datasets and detailed metadata such as cohorts, acknowledgements and grant numbers, Digital Object Identifiers (DOIs), sample size, file manifests (with MD5 checksum) and version/release history. The DSS website lists all approved DARs with succinct research use summaries and has a tool that generates the acknowledgement statement from a list of dataset accession numbers.

The *Data Access Request Management (DARM)* system is the core of the DSS platform that manages user and file access permissions. Users log into DARM using their NIH eRA login credential to submit new DARs and manage existing requests. The DAR submission interface is similar to the dbGaP system with additional features developed based on user feedback such as a DAR administrator role, which allows the requesting investigator to designate a preparer to enter request information before submission by the investigator. The DARM system also implements many features to support the Data Access Committee. The NIA ADSP Data Access Committee (NADAC) consist of NIH program officers who are federal employees. The DARM system allows NADAC members to review all requested materials, vote to approve for each requested dataset by each research use limitation level based on the research use statement and requesting institution. Review outcomes include approving a DAR, requesting additional information or correction, or rejecting the DAR. All approved DARs are required to submit annual renewal requests with progress reports (e.g. summary of findings and publications) to retain access. See Figure 5 for the DAR review process.

NIAGADS Open Access. NIAGADS hosts many non-sensitive analysis summaries and genome annotations that do not require a special request and review process. The NIAGADS Open Access (Figure 6) platform facilitates access to these datasets via direct file download

from the Open Access data portal on the DSS website (or through AWS) and other resources and services: AD GenomicsDB[19], ADVP[20], FILER[21] and VariXam.

The NIAGADS Alzheimer's Genomics Database (AD GenomicsDB) is a public knowledge base for the integration of AD genetic findings, genomic annotations, analysis summaries, and ADSP variant information. As the core of the NIAGADS Open Access framework, the AD GenomicsDB is powered by the PostgreSQL relational database engine, optimized for large-scale queries and scalable data integration. All records are assigned unique stable IDs for cross-version compatibility and harmonized for compatibility with ADSP data, ENSEMBL[22] , dbSNP[23], and other genomic databases.

The AD GenomicsDB hosts a wide range of information of biological significance associated with variants, genes, and genomic intervals. More than 438 million annotated single-nucleotide polymorphisms (SNPs) and insertions/deletions (indel) from the ADSP R4 data freeze are available with key information such as observed alleles, population frequency (from gnomAD[24], 1000Genomes 30x[25], and the NIH ALFA project[26], GWAS findings (from GWAS Catalog[27], ADVP, and more than 60 genome-wide GWAS summary statistics in NIAGADS), co-located genes, effect on the coding sequence or predicted functional impact, loss of function, and CADD deleteriousness scores (using the ADSP Annotation Pipeline). AD GenomicsDB assigns unique variant identifiers by chromosomal coordinates and allelic variants, ensuring accurate mapping of risk-association statistics. Gene models are linked to various identifies such as ENSEMBL IDs and NCBI Gene IDs and linked with key information from external databases including pathways (e.g. KEGG[28] and Reactome[29]), functional annotations (e.g. Gene Ontology[30]), protein information (UniProt[31]) and clinical significance (OMIM[32]).

The AD GenomicsDB website is built using the VEuPathDB Web Development Kit[33] to allow for a responsive interface and gene and variant report pages customized for AD human genetics research. Variant report pages provide context views of the genomic region such as linkage disequilibrium (LocusZoom[34]). Finally, researchers can generate genome browser views using the AD GenomicsDB genome browser. Powered by IGV.js[35], users can view various annotations in the given genomic region, add their own tracks, and interact with the data records to gain insights into genetic associations and functional activities and their interactions.

The AD Variant Portal (ADVP) provides a curated collection of statistically significant genetic associations for AD and related dementia in the research literature. The first version of ADVP, released in 2021, includes almost 7,000 genome-wide significant genetic associations from 125 ADGC publications. These signals come from 1,800 distinct variants in more than 900 loci and are associated with disease risk, expression quantitative traits, age at onset, biomarkers, neuropathology, and other relevant outcomes. All records are harmonized for variant rsIDs, allele coding, and genome coordinates (human reference genome builds hg37 and hg38) to ensure compatibility with ADSP data and analysis results. ADVP also captures relevant metadata including study population (cohort-reported), sample size, imputation panel, and publication. Users can search these records by publication title, gene name, and variant IDs, visualize the distributions of records on the human genome ideogram using the ADVP variant

viewer, or follow URL links to access additional information in the AD GenomicsDB or PubMed database. The next version of ADVP will add 10,000 more association records from >450 new articles.

The Functional genomics repository (FILER) was designed to address the challenge of making large queries across different public sources of functional genomic annotations stored as "tracks" per genome browser jargon. Each track consists of between thousands and millions of genomic intervals with functional significance, including tissue-specific regulatory elements, transcription factor binding activity, chromatin states, genetic regulation (eQTL, sQTL), and chromatin conformation. Currently FILER has more than 70,000 tracks and more than 17 billion records for both hg37 and hg38 builds. The data come from more than 20 data sources such as ENCODE[36], GTEx[37], FANTOM5[38], and NIH Roadmap Epigenomics[39], and cover over 1,100 distinct tissue/cell types. FILER provides metadata such as tissue or cell type and experimental assay that are harmonized using ontology standards. Researchers can freely download all tracks in FILER or access individual records via its website. FILER provides a scalable query interface that can cross-compare all tracks and records against a user-provided list of genomic intervals and return all overlaps. This allows users to quickly identify functional significance and tissue context for genomic regions of interest, and generate large data feature matrices to be used in association tests, machine learning and artificial intelligence.

VariXam is a quick access viewer for assessing the quality of genetic variant calls in ADSP whole exome and whole genome data. Developed using a React framework for the frontend and PostgreSQL for the backend, VariXam facilitates efficient querying by gene names, coordinates, genomic regions, or variant rsIDs. The database encompasses all four major ADSP freezes, ensuring comprehensive data coverage for genetic variant analysis.

FAIR compliance and community engagement. Introduced in 2016, the FAIR principles (Findable, Accessible, Interoperable, Reproducible)[40] have become the ubiquitous guidelines for data repositories and knowledge bases. NIAGADS follows the FAIR principles when designing websites and databases, data sharing infrastructure, data curation workflows, and procedures for engaging and supporting researchers (Table 2). NIAGADS implements common standards in genetics and genomics, widely accepted best practices and software tools for processing genomic data, and community support. Beginning in 2023, NIAGADS now assigns Digital Object Identifiers[41] (DOI) to each dataset, facilitated by NIH's membership in the international DataCite consortium[42]. DOIs are persistent identifiers and will enhance FAIR compliance.

To complement these FAIR features, NIAGADS has an active community outreach and engagement program. In 2023 NIAGADS held 3 online office hours and developed video tutorials for GenomicsDB, and hosted booths at major conferences such as Alzheimer's Association International Conference (AAIC), American Society for Human Genetics (ASHG), and Society for Neuroscience (SfN). NIAGADS has a user support web page with detailed documentation and frequently asked questions (FAQs), and a ticketing system for user requests. NIAGADS maintains news posts on the ADSP website with latest findings, data releases, and investigator profiles. NIAGADS has been releasing 3 joint NCRAD/NIAGADS

newsletters each year. In May 2024, NIAGADS started releasing monthly newsletters. Table 2 summarizes how NIAGADS implements FAIR compliance.

Data production, curation and partnership. Modern GWAS designs (SNP array or whole genome sequencing) often require many cohorts to obtain very large sample sizes to reach better statistical power. Thus, production and assembling of data for these projects require substantial planning and coordination beyond simply receiving data from contributing cohorts. As the data coordinating center for ADSP, NIAGADS achieves these goals through meticulous planning and close interactions with major contributors, producers, and stakeholders. NIAGADS implements a single data flow path (Figure 7) for receiving, processing and sharing data. All data coming into ADSP are sent to NIAGADS so data transfer agreements can be set up to ensure all subsequent data flows and sharing are compliant with the original informed consent. NIAGADS executes ADSP data production by routing raw and intermediate data to designated data processors with domain expertise and capacities and receiving processed data products. The single data flow path design ensures consistency, legitimacy, transparency, and reduces human errors.

The ADSP data production process begins when a new cohort joins the program. NIAGADS registers the cohort, collects research use limitations using the GDS Institution Certification form, and sets up data transfer agreements that authorizes NIAGADS to direct data to production partners and eventually share with qualified investigators through DSS. Currently NIAGADS works with 73 ADSP cohorts (and growing) from 31 countries across 6 continents governed by 21 different levels of research use limitations. These cohorts either provide completed whole genome sequence data in the form of raw sequencing reads or submit DNA to the National Centralized Repository for Alzheimer's Disease and Related Dementias[43] (NCRAD), an NIA-designated national biorepository operated by Indiana University. NCRAD performs quality control and plates the DNA for sequencing by one of the ADSP sequencing partners such as The American Genome Center (TAGC) at the Uniformed Services University of the Health Sciences (USUHS) or the John P. Hussman Institute for Human Genomics (HIHG) at the University of Miami School of Medicine. Raw sequencing data are returned to NIAGADS and then routed to the Genome Center for Alzheimer’s Disease (GCAD) for read mapping, variant calling, quality control, and documentation. Cohorts also submit phenotypes to NIAGADS, which relays to the Phenotype Harmonization Consortium[44] for phenotype harmonization. NIAGADS works with NIA program officers, GCAD, sequencing partners, the ADSP Follow-Up Study coordinating team, and PHC to plan release dates and the final list of cohorts for each major freeze.

The same coordinating process is used to coordinate structural variant calling for all ADSP WGS data (processed by GCAD and the ADSP structural variant workgroup), and the multi-omics quantitative trait linkage (XQTL) project in the ADSP Functional Genomics Consortium (processed by GCAD and the XQTL workgroup). In addition, NIAGADS supports other components of the ADSP project, including the AI/ML consortium (common benchmark datasets for AI and machine learning algorithms), the gene verification committee (ADSP website hosts a list of AD susceptibility loci and genes with high confidence), and the ADSP Executive

Committee/Cross-Consortium Communication Committee (ADSP website and project management support). NIAGADS also interoperates with other NIA infrastructure including the National Alzheimer's Coordinating Center (NACC - returning sequencing and GWAS data to individual ADRCs), NCRAD (sample and genetic data availability across the two repositories), AD Knowledge Portal (the Agora website[45] connects recommended therapeutic target genes to individual gene report pages in the AD GenomicsDB), and the AD NeuroImaging Initiative[46] (ADNI; federated data sharing request process via the Laboratory of NeuroImaging (LONI) at the University of Southern California).

Discussion

The design philosophy of NIAGADS is a natural consequence of the idiosyncrasies with studying Alzheimer's Disease genetics. Although Alzheimer's disease is a common ailment among seniors, recruiting large numbers of Alzheimer's disease patients for research remains difficult. Even if neuroimaging is not used, proper diagnosis is still expensive, time consuming and requires special expertise in neurology or neuropsychiatry that is rarely available at community level primary care. AD remains stigmatic, especially among underrepresented minorities. Retaining AD patients in longitudinal studies are challenging and burdensome on the patients and caregivers but essential for the slowly converting and progressing disease. The only way to obtain hundreds of thousands of participants for human genetics research is through collaborations with all available cohorts, most of which would only comprise several hundred participants, some enrolled decades ago. Data collection procedures and diagnostic approaches have changed over years as our understanding of the disease evolved. Careful planning and coordination for phenotype and genotype harmonization and consistent adjudication is essential, time-consuming, unavoidable, but adds great value to the research community.

The DSS qualified data access process provides legal protection for researchers. A complete implementation of the NIH Genome Data Sharing policy properly captures research use limitations specified in the original informed consent for every participant and ensures that their data will only be used within the scope and by organizations that were agreed upon when they were recruited in the study. The whole process as defined in the GDS policy is complex and resource intensive, although continuous work with the data access committee to streamline the process is ongoing. Note that a single request allows investigators to access all the data in ADSP comprising decades of investment by the US government and the cumulative accomplishments by thousands of researchers. Proper protection is necessary to retain the trust granted by the participants when they signed on to these cohorts.

As mentioned earlier, DSS relies on the NIH eRA to verify data requesters and their institutions. As research institutions around the world register their investigators and signing officials with the NIH eRA platform, NIAGADS can verify if the institution is eligible to access qualified access NIH data (e.g. dbGaP), if the investigator is currently employed by the institution and in good standing, and if the signing official has legal authority to represent the institution. An important

legal concept is that all data transfers are between institutions and not with the investigators directly, just like research grants are issued by the federal government to the investigator's institution, not to the investigator. This is required so data protection requirements can be legally enforced. The validation process is especially important when data requests come from commercial entities and/or institutions outside the United States.

Coordination and direct support by NIAGADS remain critical to the ADSP production process since it started in 2012. The richness and complexity of ADSP data means every analysis will have its own quality control challenges and study design considerations. Nonetheless, most researchers will want genotype calls and not the massive raw data or detailed quality information. For this reason, NIAGADS releases compact versions of joint calls, with detailed quality tags removed to reduce file size, and preview versions of genotype calls after sample quality checks are completed. ADSP is composed of harmonized genetic and phenotypic data from studies with very different designs and missions, making it is impossible to define a single definitive version that works for all analysis objectives. To this end, it is essential that the data come with proper documentation and critical metadata. Additionally, NIAGADS has developed quick guides and scripts for phenotype integration for users to better understand the rich dataset.

Currently in beta, the NIAGADS Open Access API aims, to increase the accessibility of data compiled in the AD genetics knowledge bases and encourage data reuse. This service conforms to the OpenAPI specification[47] to harmonize information across the Open Access resources and enable programmatic access and integration of these data and annotations into analysis pipelines. Calls to the API are simple and allow users to build queries based on feature types (e.g., gene, variant, or locus), feature identifier(s) and filter criteria (e.g., experimental design or bio-source), defining an intuitive, templated interface for programmatic access. The API calls for gene or variant records return functional annotations as well as genetic evidence for AD/ADRD-risk compiled across the AD GenomicsDB, VariXam, and ADVP knowledge bases. Queries can also be made against FILER or the GenomicsDB to retrieve functional annotations and risk-associated variants within a genomic span of interest across one or multiple datasets. The API supports both single-lookups and batch queries, with paginated results to improve query and response times.

NIAGADS continues to improve our service, strengthen interoperability with other resources, and enhance the data platform to align with user feedback and new data technologies and research trends. NIAGADS plans to roll out new data discovery features for DSS using Gen3[48]. Developed by the University of Chicago, Gen3 is a mature platform that has been adopted for several other large genomics projects such as the NCI Genomic Data Commons Data Portal[49]. NIAGADS also is developing a Data Submission Portal that provides guidance and automated validation for investigators to deposit new datasets or return analysis summaries and derived data based on NIAGADS datasets. NIAGADS is working with ADSP investigators to set up a cloud-based analysis enclave. The ADSP Cloud Analysis Commons will make data on DSS directly accessible to analysts on the Amazon cloud while maintaining FISMA Moderate

security, enabling investigators to collaborate more closely on the cloud and easily integrate ADSP data with other large genomics datasets.

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Alzheimer's Disease Sequencing Project (sa000001) data:

The Alzheimer's Disease Sequencing Project (ADSP) is comprised of two Alzheimer's Disease (AD) genetics consortia and three National Human Genome Research Institute (NHGRI) funded Large Scale Sequencing and Analysis Centers (LSAC). The two AD genetics consortia are the Alzheimer's Disease Genetics Consortium (ADGC) funded by NIA (U01 AG032984), and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) funded by NIA (R01 AG033193), the National Heart, Lung, and Blood Institute (NHLBI), other National Institute of Health (NIH) institutes and other foreign governmental and non-governmental organizations. The Discovery Phase analysis of sequence data is supported through UF1AG047133 (to Drs. Schellenberg, Farrer, Pericak-Vance, Mayeux, and Haines); U01AG049505 to Dr. Seshadri; U01AG049506 to Dr. Boerwinkle; U01AG049507 to Dr. Wijsman; and U01AG049508 to Dr. Goate and the Discovery Extension Phase analysis is supported through U01AG052411 to Dr. Goate, U01AG052410 to Dr. Pericak-Vance and U01 AG052409 to Drs. Seshadri and Fornage.

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The ADGC cohorts include: Adult Changes in Thought (ACT) (U01 AG006781, U19 AG066567), the Alzheimer's Disease Research Centers (ADRC) (P30 AG062429, P30 AG066468, P30 AG062421, P30 AG066509, P30 AG066514, P30 AG066530, P30 AG066507, P30 AG066444, P30 AG066518, P30 AG066512, P30 AG066462, P30 AG072979, P30 AG072972, P30 AG072976, P30 AG072975, P30 AG072978, P30 AG072977, P30 AG066519, P30 AG062677, P30 AG079280, P30 AG062422, P30 AG066511, P30 AG072946, P30 AG062715, P30 AG072973, P30 AG066506, P30 AG066508, P30 AG066515, P30 AG072947, P30 AG072931, P30 AG066546, P20 AG068024, P20 AG068053, P20 AG068077, P20 AG068082, P30 AG072958, P30 AG072959), the Chicago Health and Aging Project (CHAP) (R01 AG11101,

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The FUS cohorts include: the Alzheimer's Disease Research Centers (ADRC) (P30 AG062429, P30 AG066468, P30 AG062421, P30 AG066509, P30 AG066514, P30 AG066530, P30 AG066507, P30 AG066444, P30 AG066518, P30 AG066512, P30 AG066462, P30 AG072979, P30 AG072972, P30 AG072976, P30 AG072975, P30 AG072978, P30 AG072977, P30 AG066519, P30 AG062677, P30 AG079280, P30 AG062422, P30 AG066511, P30 AG072946, P30 AG062715, P30 AG072973, P30 AG066506, P30 AG066508, P30 AG066515, P30 AG072947, P30 AG072931, P30 AG066546, P20 AG068024, P20 AG068053, P20 AG068077, P20 AG068082, P30 AG072958, P30 AG072959), Alzheimer's Disease Neuroimaging Initiative (ADNI) (U19AG024904), Amish Protective Variant Study (RF1AG058066), Cache County Study (R01AG11380, R01AG031272, R01AG21136, RF1AG054052), Case Western Reserve University Brain Bank (CWRUBB) (P50AG008012), Case Western Reserve University Rapid Decline (CWRURD) (RF1AG058267, NU38CK000480), CubanAmerican Alzheimer's Disease Initiative (CuAADI) (3U01AG052410), Estudio Familiar de Influencia Genetica en Alzheimer (EFIGA) (5R37AG015473, RF1AG015473, R56AG051876), Genetic and Environmental Risk Factors for Alzheimer Disease Among African Americans Study (GenerAAtions) (2R01AG09029, R01AG025259, 2R01AG048927), Gwangju Alzheimer and Related Dementias Study (GARD) (U01AG062602), Hillblom Aging Network (2014-A-004-NET, R01AG032289, R01AG048234), Hussman Institute for Human Genomics Brain Bank (HIHGBB)

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secondary prevention trial in preclinical Alzheimer's disease, aiming to slow cognitive decline associated with brain amyloid accumulation in clinically normal older individuals. The A4 Study is funded by a public-private-philanthropic partnership, including funding from the National Institutes of Health-National Institute on Aging, Eli Lilly and Company, Alzheimer's Association, Accelerating Medicines Partnership, GHR Foundation, an anonymous foundation and additional private donors, with in-kind support from Avid and Cogstate. The companion observational Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) Study is funded by the Alzheimer's Association and GHR Foundation. The A4 and LEARN Studies are led by Dr. Reisa Sperling at Brigham and Women's Hospital, Harvard Medical School and Dr. Paul Aisen at the Alzheimer's Therapeutic Research Institute (ATRI), University of Southern California. The A4 and LEARN Studies are coordinated by ATRI at the University of Southern California, and the data are made available through the Laboratory for Neuro Imaging at the University of Southern California. The participants screening for the A4 Study provided permission to share their de-identified data in order to advance the quest to find a successful treatment for Alzheimer's disease. We would like to acknowledge the dedication of all the participants, the site personnel, and all of the partnership team members who continue to make the A4 and LEARN Studies possible. The complete A4 Study Team list is available on: a4study.org/a4-study-team.; the Adult Changes in Thought study (ACT), U01 AG006781, U19 AG066567; Alzheimer’s Disease Neuroimaging Initiative (ADNI): Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.;Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.;Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California; Estudio Familiar de Influencia Genetica en Alzheimer (EFIGA): 5R37AG015473, RF1AG015473, R56AG051876; Memory & Aging Project at Knight Alzheimer’s Disease Research Center (MAP at Knight ADRC): The Memory and Aging Project at the Knight-ADRC (Knight-ADRC). This work was supported by the National Institutes of Health (NIH) grants R01AG064614, R01AG044546, RF1AG053303, RF1AG058501, U01AG058922 and R01AG064877 to Carlos Cruchaga. The recruitment and clinical characterization of research participants at Washington University was supported by NIH grants P30AG066444,

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Alzheimer's Disease Neuroimaging Initiative (sa000002) data:

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Alzheimer's Disease Genetics Consortium (sa000003) data:

ADGC_AA_WES (snd10003) data:

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ADGC-TARCC-WGS (snd10030) data:

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Progressive Supranuclear Palsy Study (sa000010) data:

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Accelerating Medicines Partnership-Alzheimer's Disease (AMP-AD) (sa000011) data:

Mayo RNAseq Study- Study data were provided by the following sources: The Mayo Clinic Alzheimer's Disease Genetic Studies, led by Dr. Nilufer Ertekin-Taner and Dr. Steven G. Younkin, Mayo Clinic, Jacksonville, FL using samples from the Mayo Clinic Study of Aging, the Mayo Clinic Alzheimer's Disease Research Center, and the Mayo Clinic Brain Bank. Data collection was supported through funding by NIA grants P50 AG016574, R01 AG032990, U01 AG046139, R01 AG018023, U01 AG006576, U01 AG006786, R01 AG025711, R01 AG017216, R01 AG003949, NINDS grant R01 NS080820, CurePSP Foundation, and support from Mayo Foundation. Study data includes samples collected through the Sun Health Research Institute Brain and Body Donation Program of Sun City, Arizona. The Brain and Body Donation Program is supported by the National Institute of Neurological Disorders and Stroke (U24 NS072026 National Brain and Tissue Resource for Parkinson's Disease and Related Disorders), the National Institute on Aging (P30 AG19610 Arizona Alzheimer's Disease Core Center), the Arizona Department of Health Services (contract 211002, Arizona Alzheimer's Research

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Mount Sinai Brain Bank (MSBB)- This work was supported by the grants R01AG046170, RF1AG054014, RF1AG057440 and R01AG057907 from the NIH/National Institute on Aging (NIA). R01AG046170 is a component of the AMP-AD Target Discovery and Preclinical Validation Project. Brain tissue collection and characterization was supported by NIH HHSN271201300031C.

University of Pittsburgh- Kamboh (sa000012) data:

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NACC Genentech Study (sa000013) data:

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Samples from the National Cell Repository for Alzheimer’s Disease (NCRAD), which receives government support under a cooperative agreement grant (U24 AG21886) awarded by the National Institute on Aging (NIA), were used in this study. We thank contributors who collected

samples used in this study, as well as patients and their families, whose help and participation made this work possible.

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Cache County Study (sa000014) data:

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NIH, CurePSP and Tau Consortium PSP WGS (sa000015) data:

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CurePSP and Tau Consortium PSP WGS (sa000016) data:

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The Diagnostic Assessment of Dementia for the Longitudinal Aging Study of India (LASI-DAD) (sa000019) data:

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Dissecting the Genomic Etiology of non-Mendelian Early-Onset Alzheimer Disease (EOAD) and Related Phenotypes (sa000023) data:

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Figures and Tables

Figure 1. (a) NIAGADS and ADSP Timeline. (b) ADSP Data Growth by Releases.

Figure 2. Layout of the NIAGADS platforms. NIAGADS shares controlled-access human genetics/genomics data and open-access genomic knowledge through an integrated system of interoperable data access platforms. The dual approaches facilitate broad data sharing while ensuring compliance with ethical and privacy standards.

Figure 3. NIAGADS at a glance. (a) NIAGADS by the numbers. (b) A global map of cohorts contributing to the NIAGADS data collection. (b) The NIAGADS Data Collection breakdown by data types.

Figure 4. ADSP Release 4 whole genome sequence data by cohort-reported population.

Figure 5. Overview of the Data Access Request (DAR) submission and review process in the NIAGADS Data Sharing Service (DSS). Users start by browsing the meta data for available datasets and access documentation for submitting or applying for datasets. 1. Using an eRA commons ID, users log into the DSS platform where they can submit look at the applications or datasets they have available to them. 2. In the DARM, users can submit, revise, renew, or close data applications. 3. Approving officials can review user applications for applicability for each consent level of each dataset users applied for, which informs what files users can see in the files portal. 4. Users are notified their application is approved. 5. In the Files Portal, users can see files they have access to based on their approve application. 6. Users transfer or download the files from AWS.

Figure 6. NIAGADS Open Access Knowledge Bases and API architecture. See Online Methods for technical details.

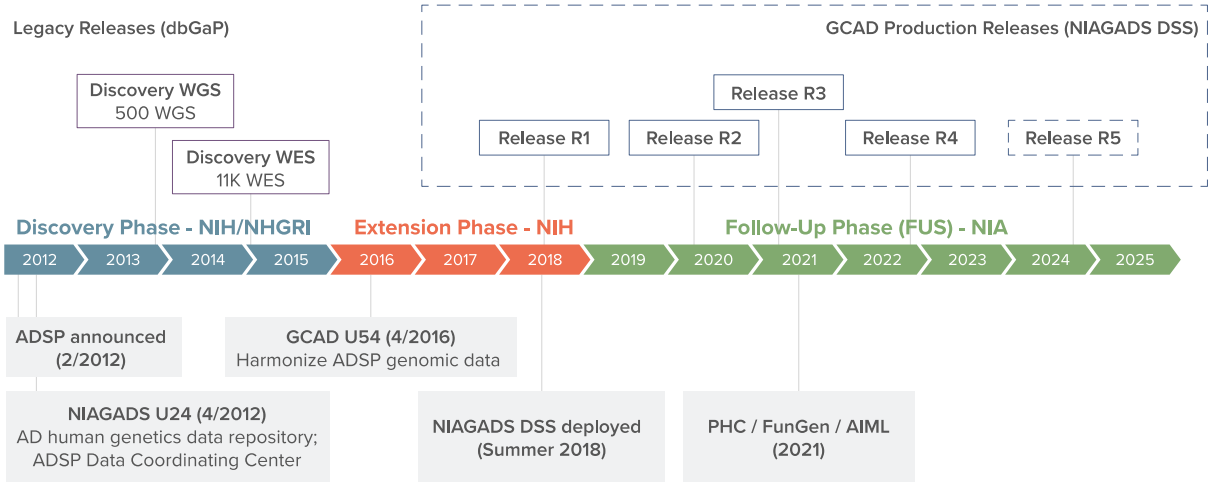
Figure 7. Flow diagram of the ADSP data production process. A unified data flow allows NIAGADS to manage and move files during the process and track the progress of all data processing and sharing activities, while ensuring compliance with NIH Genomic Data Sharing (GDS) policy. A straightforward and centralized coordination process is easy to understand and facilitates communication with all contributors. Data are dispatched to designated domain experts by data types.

Table 1. Featured datasets: ADSP, ADGC, HRS genomics data, and Knight ADRC Genetics Collection.

Table 2. NIAGADS features in support of the FAIR principle (Findable, Accessible, Interoperable, Reproducible).

Figure 1

A.



B.

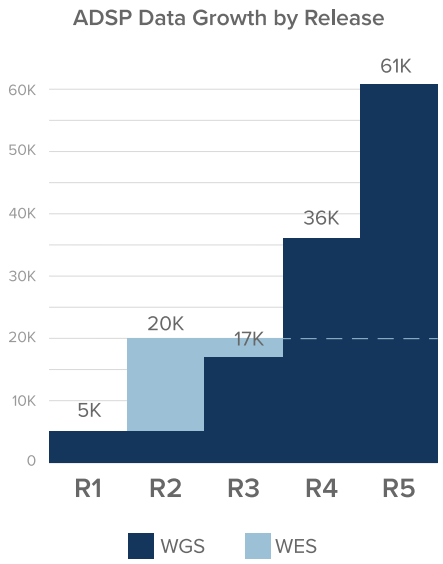
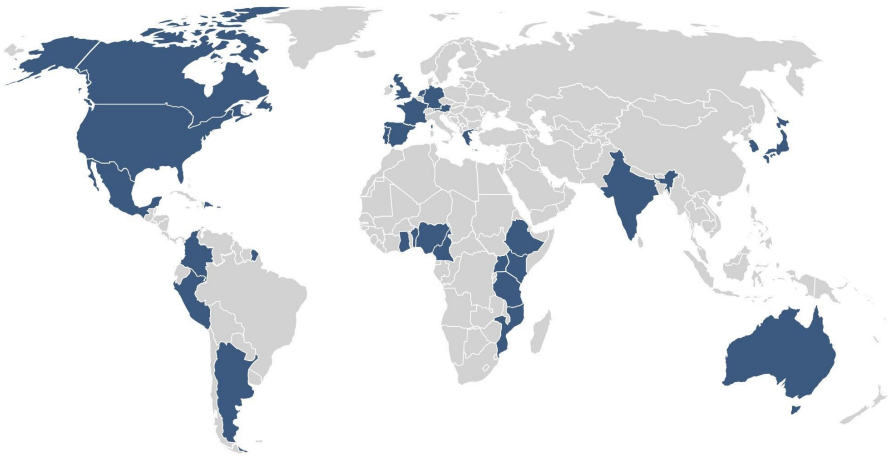


Figure 2

Figure 3

A.

B.



C.

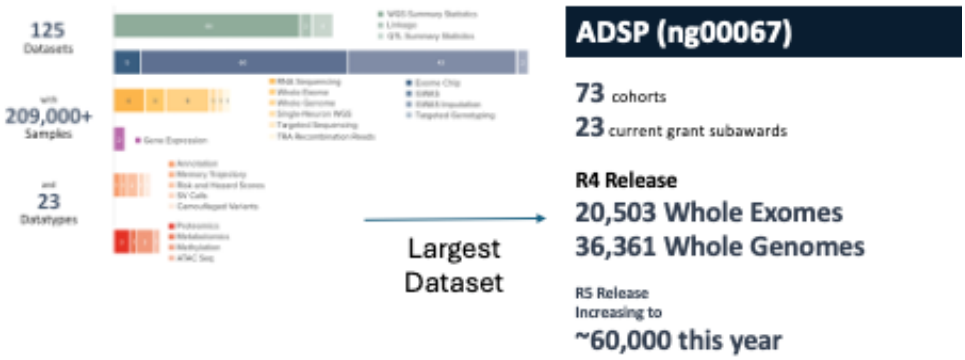


Figure 4

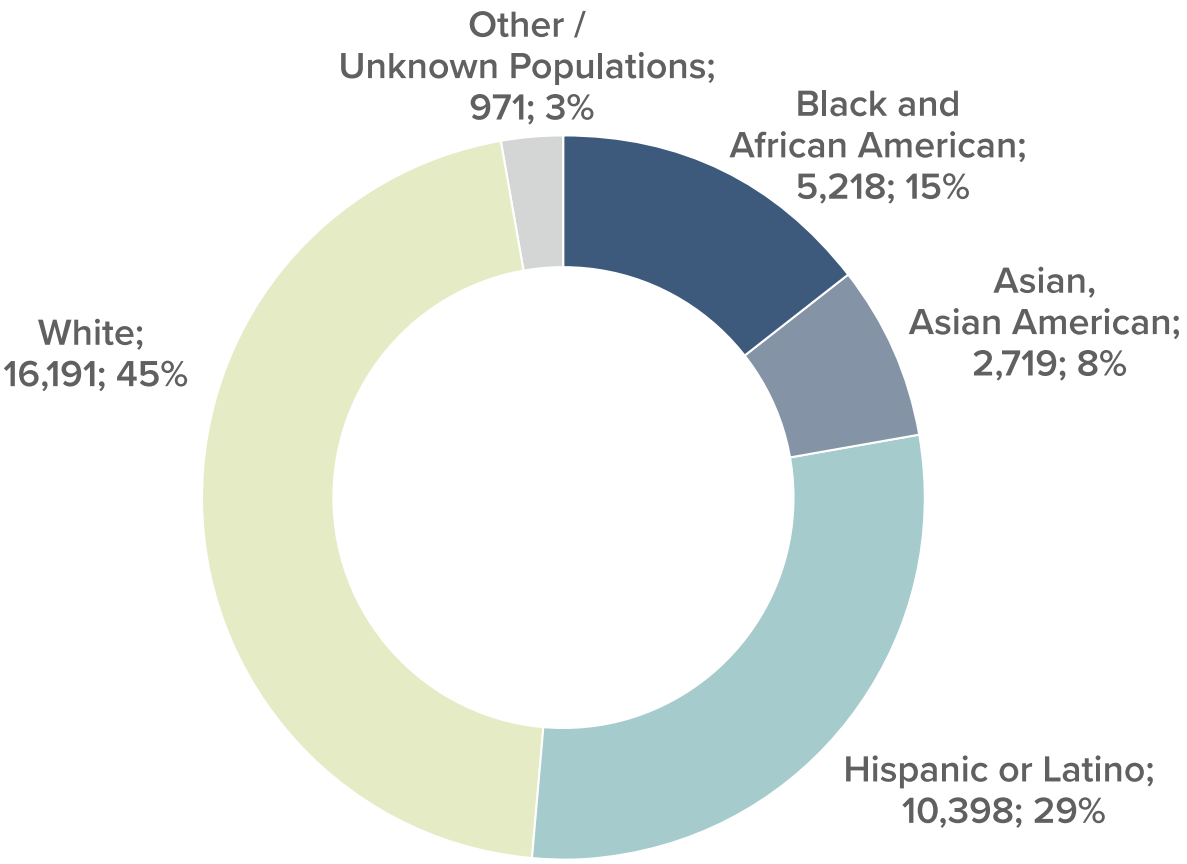


Figure 5

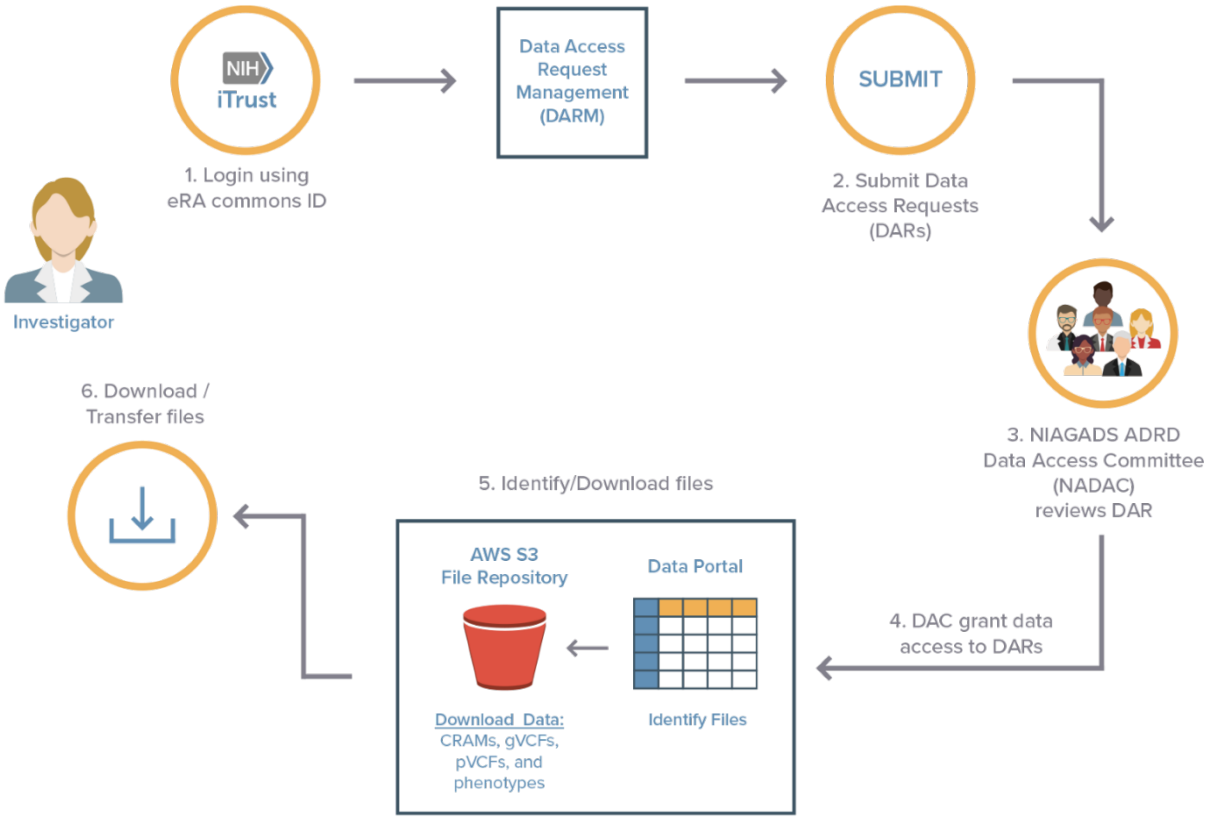


Figure 6

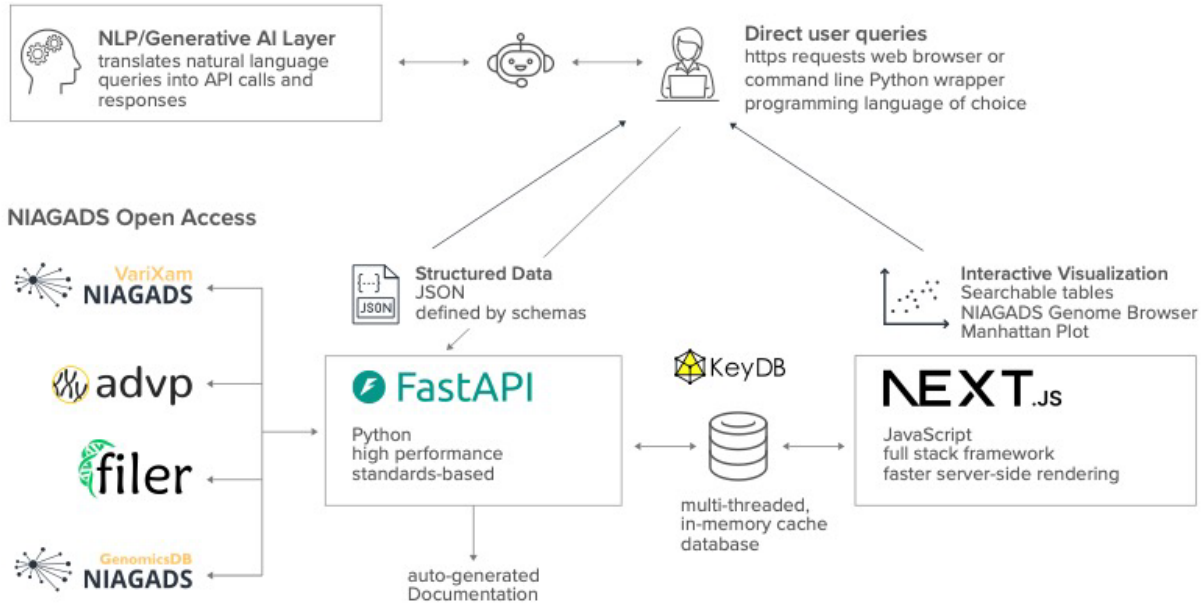


Figure 7

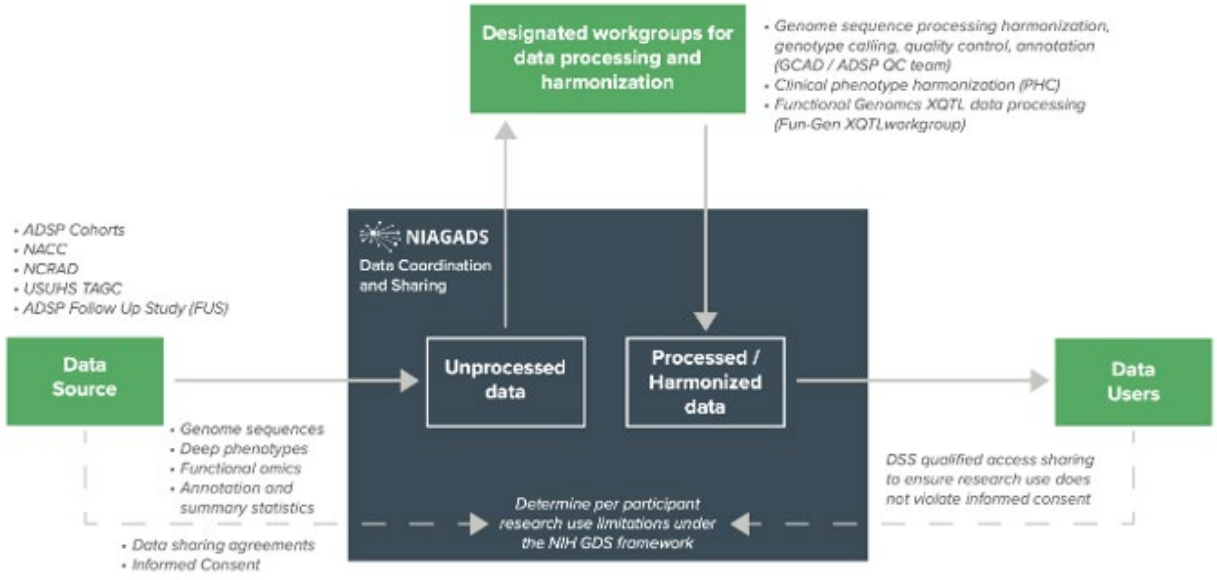


Table 1.

	adsp Alzheimer's Disease Sequencing Project	ADGC Alzheimer's Disease Genetics Consortium Collection	HRS Health and Retirement Study	Knight ADRC Knight Alzheimer Disease Research Center Collection
Data Types	Whole genome sequencing (WGS) Whole exome sequencing (WES) Structural Variant Calls Harmonized phenotypes from the ADSP Phenotype Harmonization Consortium Annotation files	Genotyping array data from the Alzheimer's Disease Research Centers (ADRCs) Harmonized phenotypes from the ADSP Phenotype Harmonization Consortium	Genotyping array data DNA Methylation APOE and Serotonin Transporter Alleles	Proteomics Single Cell RNAseq Metabolomics Methylation Genotyping array data WGS in NG00067
Accession Numbers	NG00067	NG00022 NG00023 NG00024 NG00068 NG00069 NG00070 NG00071 NG00136 NG00137 NG00138 NG00139 NG00140 NG00149 NG00150 NG00151	NG00119 NG00132 NG00153	NG00128 NG00102 NG00108 NG00113 NG00114 NG00127 NG00130 NG00131

Table 2.

Initiatives	Findable	Accessible	Interoperable	Reusable
Gen3 Platform (In Beta)				
RAS Authentication (In Progress)				
Data Submission Portal (In Development)				
Datasets with Globally Unique Identifiers (DOI via DataCite)				
Outline Clear Usage of Data (Data Request Policies and Procedures)				
Outreach Initiatives (Newsletters, Office Hours, Video Tutorials, Booths)				
NIAGADS Knowledgebases (Alzheimer's Genomics Database, FILER, ADVP, VariXam)				
NIAGADS Open Access (Summary Statistics & Annotations)				
Searchable Metadata				
Using Open Frameworks (OpenAPI, OBO Foundry, JSON / JSON schemas, RDF/XML)				
Use Standard File Formats (Genetic/Genomic data & Annotations)				

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