



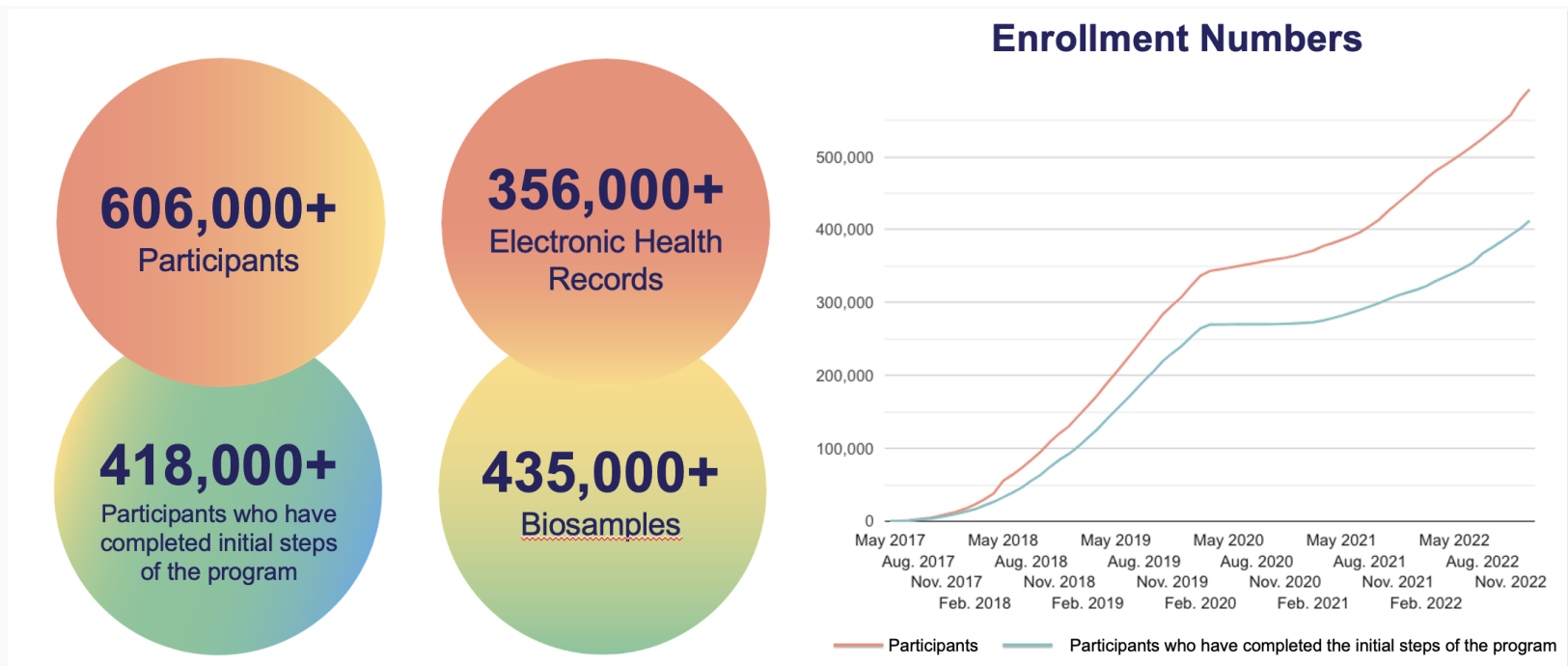
National Institute of Environmental Health Sciences
Your Environment. Your Health.

Cloud Computing for All of Us

Alison Motsinger-Reif, PhD

All of Us Cohort

- US-based cohort, goal to enroll over 1 million participants
 - Genetic data for all participants
- Focused on populations that are underrepresented in biomedical research (UBR)
 - >80% of participants fall into a UBR category



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Data Type		Participant Counts
Electronic Health Records	<u>Conditions</u>	227,740
	<u>Drug Exposures</u>	214,040
	<u>Labs/Measurements</u>	227,280
	<u>Procedures</u>	221,860
<u>Whole Genome Sequencing dataset</u>		98,560
<u>Physical Measurements</u>		331,300
<u>Fitbit Measurements</u>		12,880
<u>Social Determinants of Health Survey responses</u>		57,620
<u>Lifestyle Survey responses</u>		372,380

Computing in All of Us

Researcher Workbench

- Cloud-based platform where registered researchers can access Registered and Controlled Tier data
- Cannot download data → bring the compute to the data

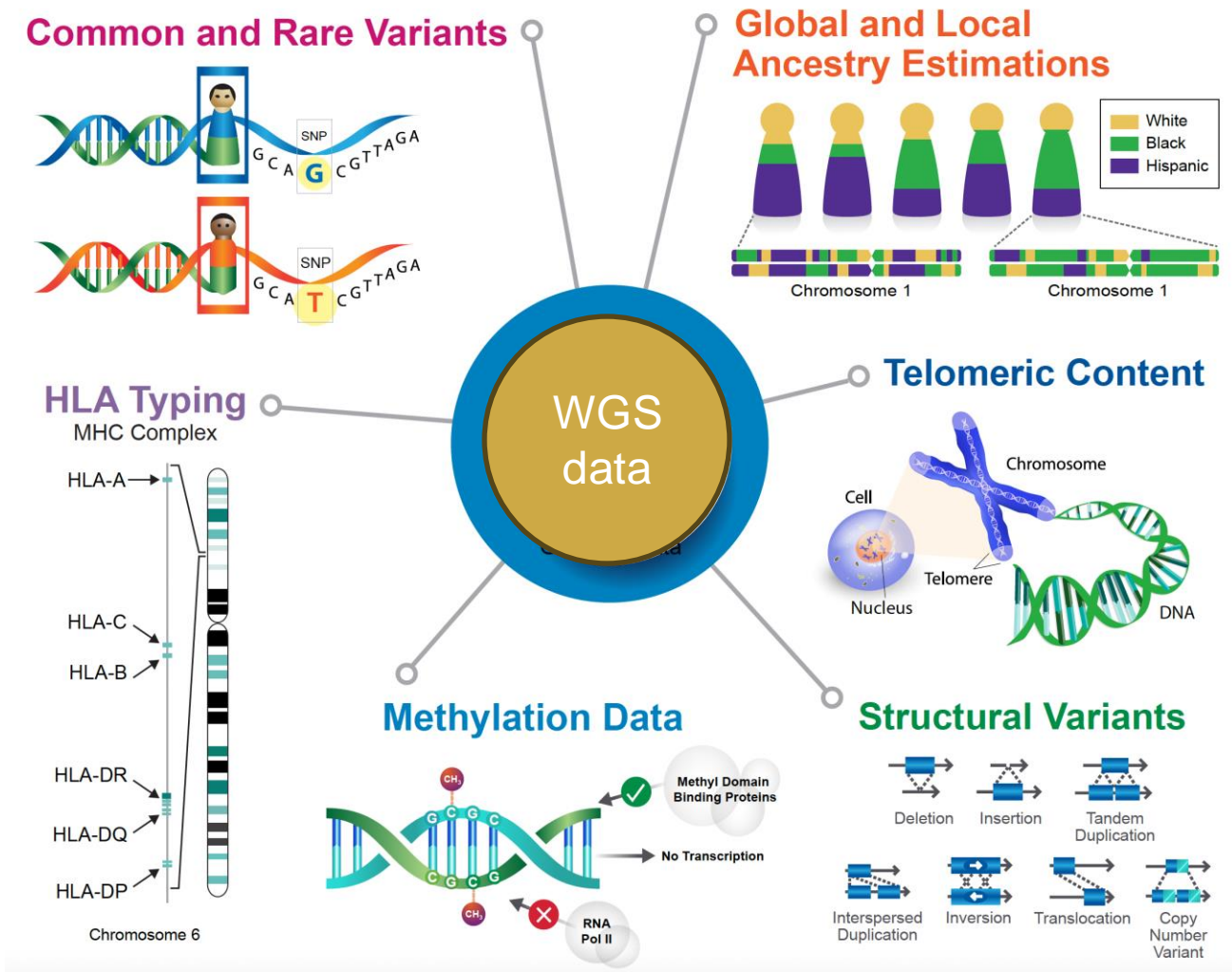
Workspaces

- Registered researchers use workspaces to access, store, and analyze data for specific research projects.

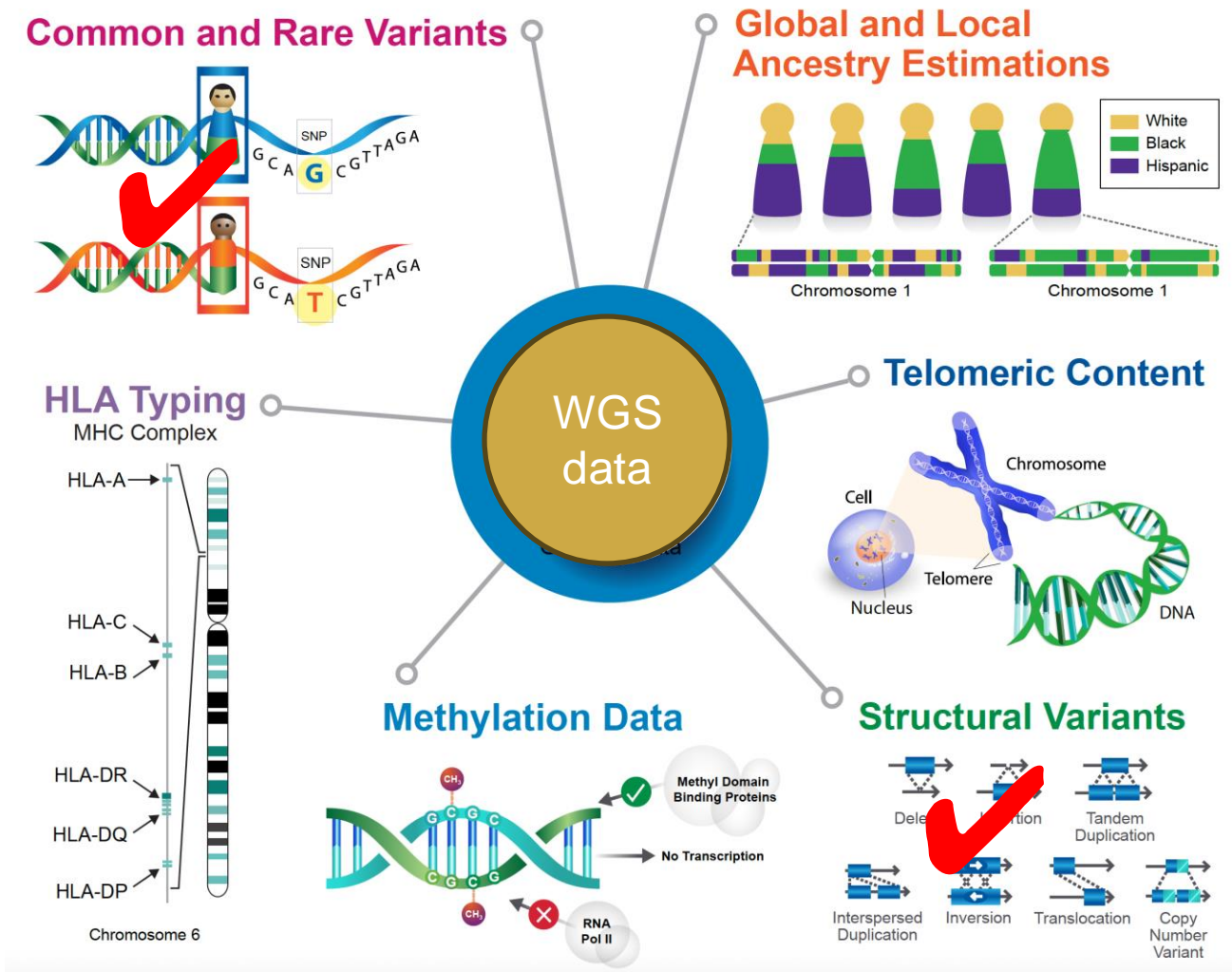
The screenshot shows the All of Us Researcher Workbench interface for a workspace titled "Major Depression Study". The interface is divided into several sections:

- Navigation:** A top navigation bar with tabs for "DATA", "ANALYSIS", and "ABOUT".
- Cohorts:** A section titled "Cohorts" with a sub-header "A cohort is a group of participants based on specific criteria." It features a diagram showing a group of "All of Us Participants" being filtered into "Your Cohort" (Participant ID 1, 2, 3).
- Datasets:** A section titled "Datasets" with a sub-header "A dataset is a table containing data about a Cohort that can be exported for analysis." It features a diagram showing "Your Cohort" (Participant ID 1, 2, 3) combined with "Data About Your Cohort" (Medication, Labs) to form "Your Dataset" (a table with columns for ID, Sheet, and Label).
- Help and Information:** A right-hand sidebar containing "Concept Sets" (describing information from medical records), "Datasets" (describing analysis-ready tables), and "Recent Data". A "Help Tips" button is visible in the top right corner of the sidebar.
- Footer:** A "Show:" dropdown menu with options for "Show All", "Cohorts", "Cohort Reviews", "Concept Sets", and "Datasets".

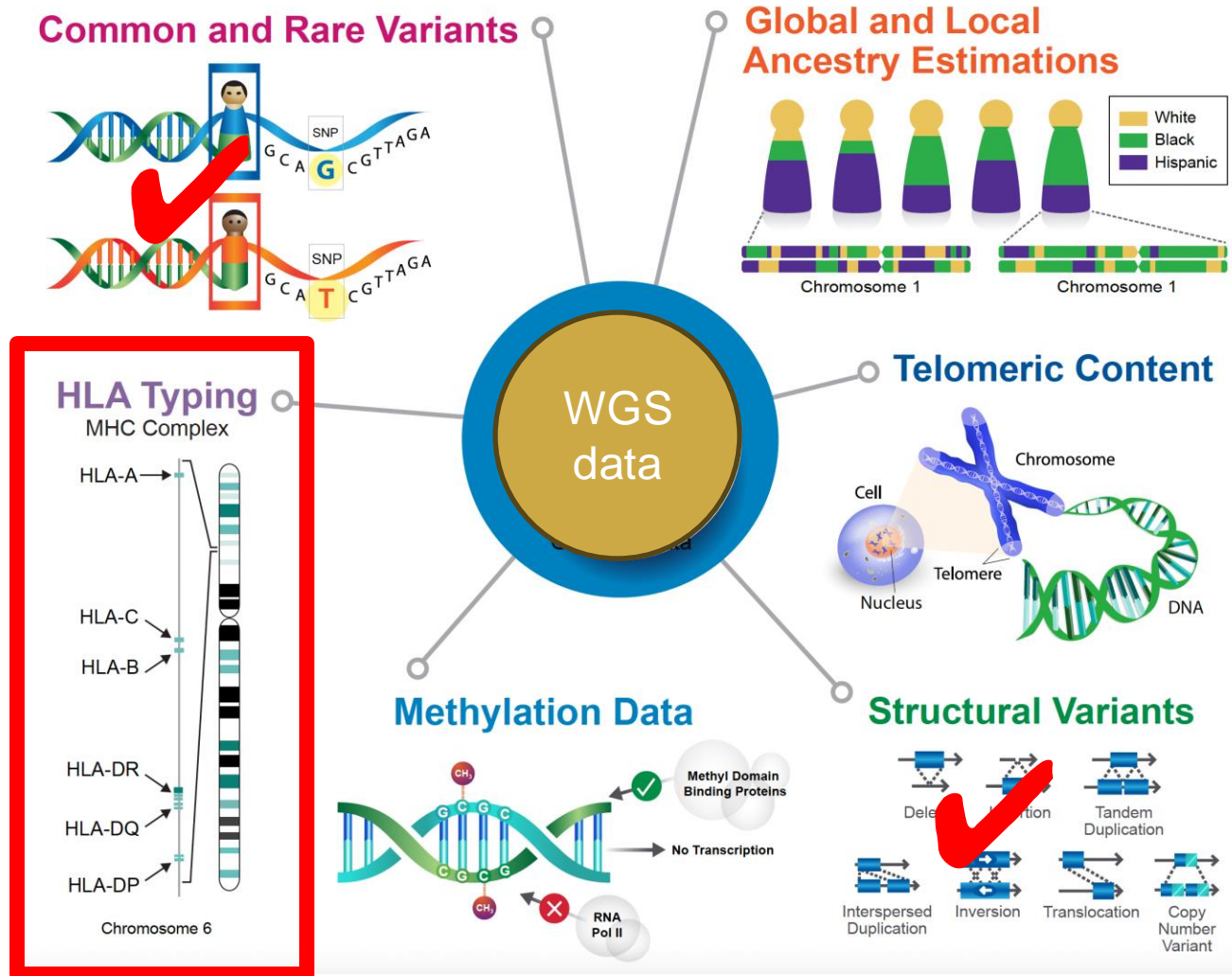
Types of Variants from Whole Genome Sequencing



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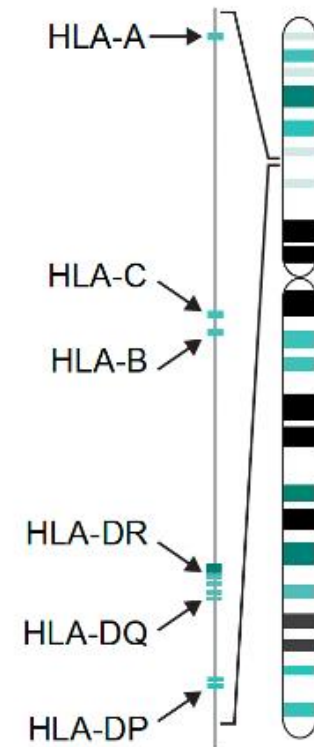


The importance of HLA

- HLA genes are crucial for the immune system.
- They help present foreign substances (antigens) to immune cells.
- HLA matching is vital for successful organ transplantation.
- Certain HLA variants are linked to autoimmune diseases.
- HLA genes affect susceptibility to infectious diseases.
- They influence how individuals respond to specific medications

HLA Typing

MHC Complex



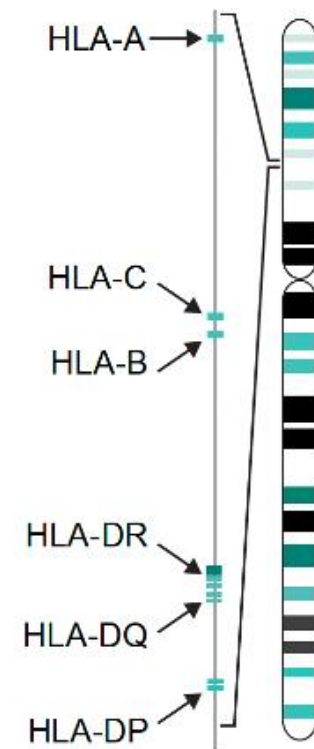
Chromosome 6

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Goal: Test for association of HLA genotypes and common, complex diseases

Workflow for Calling HLA variants

Assembly of HLA Alleles: Kourami

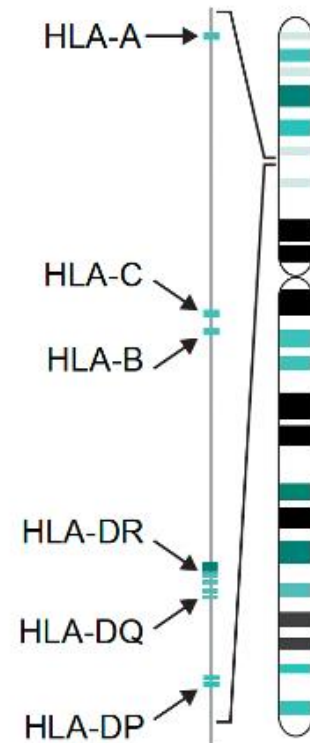
- Utilized Kourami for graph-guided assembly
- Generated four- and six-digit HLA alleles using WGS data
- Built reference panel from known HLA alleles in IPD-IMGT/HLA project database
- Assembled peptide-binding domain sequences for HLA genes
- Modified HLA graph for best paths with phasing information
- Filtered HLA alleles for clarity and accuracy

Amino Acid Position Inference: CookHLA and HATK

- Used CookHLA and HATK for HLA imputation
- Inferred amino acid residues
- Employed 1000 Genomes Project reference panels
- Conducted logistic regression for analysis

HLA Typing

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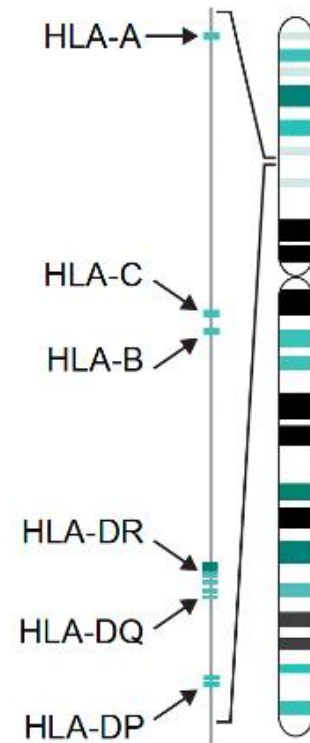
Chromosome 6

Variant Calling is Computationally Expensive

- **Data Volume:** Massive amounts of raw sequencing data, often in gigabytes or terabytes
- **Alignment:** Complex alignment of billions of short reads to a reference genome
- **Variant Detection:** Sophisticated algorithms needed for variant identification
- **Genome Complexity:** Highly complex genomes with repetitive regions and structural variants
- **Error Correction:** Correcting sequencing errors adds computational effort
- **Quality Control:** Ensuring data accuracy through extensive quality control steps
- **Population-Scale Studies:** Analyzing large-scale studies increases computational demands

HLA Typing

MHC Complex



Chromosome 6

Association Analysis

Linear and Logistic Regression:

- Linear regression used for continuous trait-genetic variant associations
- Logistic regression employed for binary trait-genetic variant associations
- Both methods handle confounding factors and population stratification
- Crucial for uncovering the genetic basis of complex diseases

Association Analysis

Challenges of Logistic Regression:

- Suitable for binary/categorical outcomes in machine learning and statistics
- Computationally complex, challenging for large datasets
- Requires more time and computing resources than linear regression
- Involves exponentials, divisions, and gradient calculations
- Linear regression is typically faster and more computationally efficient

Association Analysis

- Developed a fast regression (FastReg) algorithm
 - an iterative Fisher's scoring matrix that dramatically reduces need for the computing resources
 - For example, for 5,000 individuals and 10 million variants, Plink (the most commonly used GWAS software) requires approximately 12 minutes and 80 workers to conduct logistic GWAS.
 - Our FastReg algorithm can conduct the same analysis in less than half the time using a pre-formed indexable data structure (HDF5)
 - Is flexible for data types and model matrices outside genetic data use cases.

Project Goals

- Perform variant calling for the HLA regions for All of Us participants
 - Testing timing now
 - Goal 10K participants
- Use FastReg to conduct association analyses with HLA variants and ~1600 common complex diseases
- Support and distribute FastReg

Project Team

- Dr. David Fargo, Director of Environmental Science Cyberinfrastructure
- Greg Stamper, Computer Systems Analyst
- Matt Jordan, NIEHS Information Systems Security Officer
- Dr. Adam Burkholder, Computer Systems Analyst
- Dr. John House, Staff Scientist, BCBB
- Dr. Matthew Wheeler, Staff Scientist, BCBB

Questions

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