

# HRS –Biomarkers and Genetics

Eileen Crimmins, **Jessica Faul**, Ken Langa, Bharat Thyagarajan & David Weir

HRS International Network Meeting

August 2023

# Venous Blood Collection in the HRS

- Verbal consent at the end of the core survey (Tel, FTF and Web)
- Blood draw contracted to national phlebotomy contractor (Hooper Homes, ExamOne)
  - Scheduled and conducted separate in-home visit for blood collection
  - Attempt as soon as possible after the core interview
  - Results from 28 assays returned to respondents within 2 weeks of collection
- Project collected venous blood from all panel HRS respondents in 2016
  - 79% consented and 83% who consented completed (N=9,934)
- 2018 – re-ask of the 2016 respondents who did not consent and first ask of the new cohort enrolled in 2016
  - N=3,089 (completed)
- Collection again in 2022 – sample is a follow-up on the 2016 sample, first draw on prior non-consenters
  - Current consent is 74.9%, some effects on broken appointments and supply availability due to the pandemic
- **Steady state plan is one draw per respondent per 6 year cycle**

# VBS Assays

Panel Sample N= 9,934	Innovative Sample
<b>N=4,104</b>	
<p><b>Comprehensive Metabolic Panel</b></p> <p><b>Lipid Panel</b></p> <p><b>Complete Blood Count (CBC)</b></p> <p><b>Ferritin (FRTN)</b></p> <p><b>IGF-1</b></p> <p><b>DHEA-S</b></p> <p><b>Cystatin C</b></p> <p><b>Vitamin D (25 Hydroxy)</b></p> <p><b>High sensitivity CRP (hsCRP)</b></p> <p><b>Cytokines (IL-6, IL-10, IL-1RA, sTNFR-I, TGF- <math>\beta</math>1 (activated form))</b></p> <p><b>Flow cytometry (cryopreserved cells)</b></p> <p><b>CMV seroprevalence</b></p> <p><b>B-type natriuretic peptide (NT-proBNP)</b></p>	
<ol style="list-style-type: none"> <li>1) <b>Traditional biochemical /harmonized marker</b></li> <li>2) <b>Immune system and inflammation marker</b></li> <li>3) <b>Innovative aging marker</b></li> </ol>	<p><b>DNA Methylation</b></p> <p><b>Homocysteine</b></p> <p><b>Telomere length</b></p> <p><b>RNA-seq</b></p> <p><b>mtDNA copy number</b></p> <p><b>Clusterin</b></p> <p><b>BDNF</b></p>

# DNA Methylation

- **DNA methylation** is one of several epigenetic mechanisms that cells use to control gene expression
- **N=4,018 (innovative subsample from 2016)**
- Several tools are coming online now to use methylation data in exciting new ways such as to estimate cell distribution, biological age, ancestry, etc.
- Interesting potential longitudinally
- QC'd beta matrix data uploaded to the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS) – 19 GB
- Full iDAT files will also be released via NIAGADS (500 GB)
- 13 Epigenetic clocks – already released from HRS
- Longitudinal DNA methylation at Time 2 being collected (2022)

# RNAseq

- Another approach to **Gene Expression**
- Research on smaller and younger samples shows strong effects of social, behavioral, economic, psychological factors on gene expression
- Population variability is not well known (e.g. race/ethnic differences)
  - Our sample will be valuable and unique in demonstrating variability in gene expression
- RNA sequencing assays (single end 50 bp reads ~90 million reads/sample)
- **N=3,749 (innovative subsample from 2016, overlap with DNAm)**
- Characterized ~50,000 transcripts, identified by Ensembl IDs
- Transcript abundance matrix (not identifiable) is being prepared as a “HRS Sensitive Health” product
- Compressed fastq files will be uploaded to NIAGADS

# HCAP Pilot Assays of Neurodegeneration

- HRS conducted a pilot to test promising biomarkers of neurodegeneration.  
Priorities:
  - (1) highly reliable and replicable in blood (plasma/serum);
  - (2) have validated correlations with AD/ADRD neuropathology from cerebrospinal fluid (CSF) or autopsy measures;
  - (3) are found in higher concentrations in people with cognitive impairment and AD/ADRD;
- Final list based on consultation with dementia experts at the NIA Intramural Research Program
- Using samples from the 2016 collection we assayed:
  - **A $\beta$ 40/A $\beta$ 40 ratio**
  - **Phosphorylated Tau Protein 181 (pTau181)**
  - **Neurofilament Light Chain (NfL)**
  - **Glial Fibrillary Acidic Protein (GFAP)**
  - **Olink Proteomics Neurology Panel**
- **N=4,469 respondents** (overlaps up with innovative sample – DNAm, RNA)
- Data forthcoming from HRS website



# HCAP Pilot – Predicting Incident Dementia and Mortality

Multinomial logistic regressions of Dementia/Death status in 2018, n=3923

	Dementia Onset in 2018 (OR)	Death in 2 years (OR)
zNfL	1.27**	1.38***
zGFAP	1.17	0.96
zAB42/40*100	1.01	0.91
zpTau181	1.01	0.80**

Multinomial logistic regressions of Dementia/Death status in 2020, n=3911

	Dementia Onset in 2020 (OR)	Death in 4 years (OR)
zNfL	1.56***	1.58***
zGFAP	1.06	0.97
zAB42/40*100	1.10	0.74**
zpTau181	0.90	1.14**

Age and gender controlled, \*\*\*p<.001, \*\*p<.01, \*p<.05

# HRS Heavy Metals ADRD Exposome Supplement

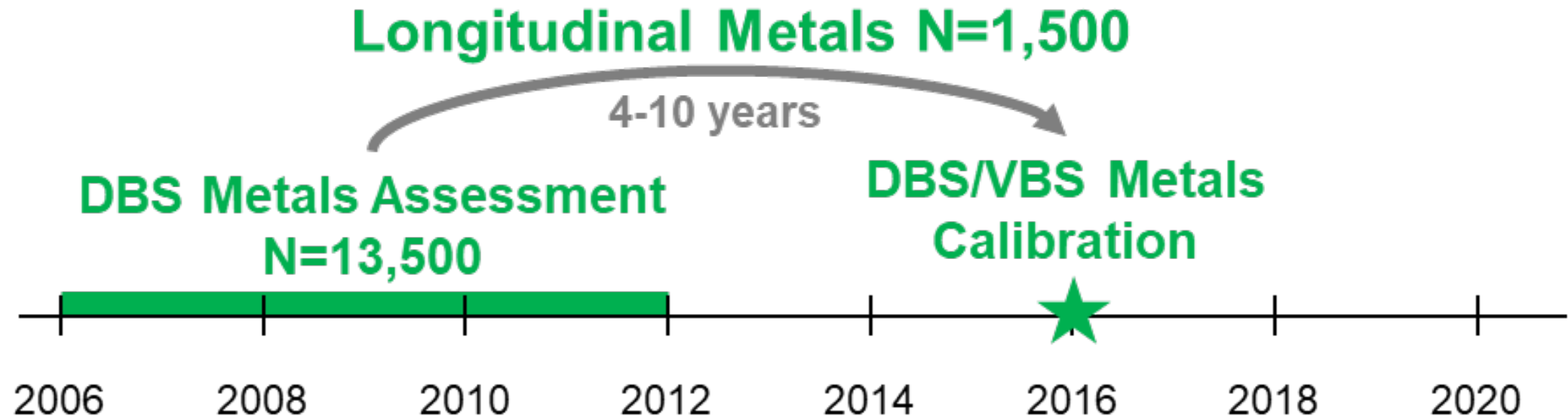


- Environmental exposures like **heavy metals** are of interest as contextual factors contributing to Alzheimer's disease and related dementias due to known neurotoxic effects and ability to cross the blood-brain-barrier
- Environmental hazards are **prevalent and exposure levels often co-vary spatially with socioeconomic status and race/ethnicity**

- Heavy metals (**lead, cadmium, mercury and arsenic**) measured in capillary DBS using energy-dispersive X-ray fluorescence (EDXRF)
  - Non-destructive approach
- **N=15,000**
- HRS will be one of the largest, representative and racially diverse datasets of individual-level heavy metals concentrations linkable to cognitive outcomes, social conditions, and health variables



# HRS Metals Measurement



**Prospective follow-up for AD/ADRD incidence**

*Existing* data follow-up: minimum 8 years, maximum 14 years

# HRS Genotype Data

**2006–2008**

**Version 1 - 12,500+ samples (dbGaP)**

- Posting includes measured SNPs and imputations using 1000 Genomes reference panel (22 million SNPs)

**2006–2012**

**Version 3 - 19,000+ samples (NIAGADS)**

- Additional expansion of minority sample
- Includes imputation to Haplotype Reference Consortium

**Version 2 - 15,600+ samples (dbGaP)**

- 1000 Genomes imputation (22 million SNPs)
- KING-robust Relationship Matrix

**2006–2010**

**Version 4 – 22,000+ samples  
forthcoming NIAGADS**

Includes (near) complete coverage of the VBS 2016 sample

**2006–2016**

# Polygenic Score (PGS) Data

- Public data files released by HRS
- PGS 4<sup>th</sup> release (Feb 2021) – 2006-2012 samples
  - Over 50 different scores on a variety of behaviors and traits
- Additional files released as user contributions (SSGAC consortium, including the [SSGAC Polygenic Index \(PGI\) Repository](#))
- PGSs are released for both the European ancestry and African ancestry groups, separately
  - Ancestry-specific Principal Components 1-10 are included (masked)
- PGS 5<sup>th</sup> release planned for Fall 2023
  - Will include newer AD scores and scores for Hispanic participants (n=2,381)

# APOE and Serotonin Transporter Alleles



N=19,000 (same Rs with genotyping)



APOE4 Genotyping (2 SNPs)

Taqman assays to test for the two SNPs



5'-HTTLPR L/S Genotyping

The repeat-length polymorphism (long or short genotype) within the promoter region of 5-HTTLPR



Performed by Johns Hopkins University (CIDR)



HRS Data Product and posted on NIAGADS

# Venous Blood Collection in the HRS – Renewal Approach

- Aims:
  - Proposed collection includes the markers from 2016 that have proven to be important predictors of cognition, aging phenotypes, and mortality
  - Cognitive / neurological assays
  - Biomarkers that help explain inequalities
  - Relate to contextual data
  - COVID-related long-term health
- Play to the strengths of the HRS:
  - Longitudinal collection
  - Nationally representative sample with oversamples of underrepresented groups
  - Well-characterized for ADRD and aging phenotypes

2024 on

Proposed Standard Panel

Expanded Viral Screening

Important markers of aging / TAME

Comprehensive Metabolic Panel

Lipid Panel

Complete Blood Count (CBC)

Ferritin (FRTN)

IGF-1

DHEA-S

Cystatin C

Vitamin D (25 Hydroxy)

HbA1c

High sensitivity CRP (hsCRP)

Cytokines (IL-6, IL-10, IL-1RA, sTNFR-I, TGF-  $\beta$ 1 (activated form))

Flow cytometry (cryopreserved cells)

→ CMV seroprevalence / CMV DNA

→ HSV1, HSV2, EBV, COVID

B-type natriuretic peptide (NT-proBNP)

→ GDF-15

→ IGFBP1

→ SuPAR

→ CXCL9

→ DNA Methylation

Neurodegenerative Markers ←

Metals ←

Important markers related to cognition

# Establishing a Public Bio Repository of Aging

- Intentionally set aside 0.5mL of serum and 0.5mL of plasma, as well as up to 10 micrograms (10ug) of venous blood DNA to make available for outside researchers
- Researchers will be able to apply for access to these samples – own funding required
- Will help fill the discovery research space between identification of a biomarker and uptake at HRS-type scope

**THANK YOU**

<https://hrs.isr.umich.edu>