HRS | HEALTH AND RETIREMENT STUDY
A Longitudinal Study of Health, Retirement, and Aging
Sponsored by the National Institute on Aging

Health and Retirement Study: Biological Markers PAA Biomarker Meeting March 30, 2016

David Weir, PI

Jessica Faul, Co-Investigator

Institute for Social Research

HRS

- Began collecting dried blood spots and salivary DNA in 2006
- Half-sample rotation: half assigned to biomarkers starting in 2006, half in 2008
- New cohort added in 2010 was also split across the half-sample
- Goal was to build a longitudinal biomarker resource
- And a genetic repository

HRS DBS Collection by wave

		Number of samples by wave				
Sample	First eligible	2006	2008	2010	2012	2014
Panel	2006	6735		5709		5133
	2008		6329		4958	
New cohort	2010			2073		2373
	2012				2285	

HRS

HRS DBS Collection: Longitudinal patterns

		Number of waves gave DBS		
Sample	First eligible	1	2	3
Panel	2006	2,196	2,295	3,597*
	2008	2,735	4,276	*[2016]*
New cohort	2010	1,204	1,621	
	2012	2,285	*[2016]*	

* Data not yet released

HRS

By the time this grant cycle ends in 2017

- Expect ~20,000 people to have given at least one DBS sample
- Expect ~7,000 old panel cases with three consecutive waves of DBS
- Expect ~3,000 new cohort cases with two consecutive waves of DBS

HRS

Assays

- 2006-14
  - HbA1c, CRP, cystatin-C, total and HDL cholesterol
- 2016
  - Same plus IL-6
- We await this network's validation of the UW IL-6 assay, but we will also be able to validate in our own sample

HRS

PLAN FOR HRS 2016
VENOUS BLOOD COLLECTION

Key partners:

Hooper Holmes (phlebotomy)

University of Minnesota (lab)

HRS | HEALTH AND RETIREMENT STUDY

Advantages of whole blood over DBS

- Assay reliability
- Range of analytes
- Storage

HRS

Motivation in HRS

1. Improve biological assessment of health/disease status
2. Continue search for the elusive biological pathways connecting social experience to health
3. Explore experimental markers of aging

1. Clinical markers

- Much broader set of standard markers that can be reported to respondents to encourage participation
- Markers that harmonize to ELSA and other studies
- Major organ system functioning
- (Alzheimer's)

HRS

2. Pathways

- Gene expression
- Modifications at cellular level, and specific to cell type
- Focus on the immune system, which is significantly managed in blood
- Markers of inflammation and immune function
- Cryopreserve cells for future analysis
- RNA (paxgene)

HRS

3. Experimental markers

- DNA methylation
- Telomere length
- mtDNA copy number

HRS

Overview of plan for blood collection and processing

- Consent must be obtained at time of HRS 2016 interview
- Contact info for consented respondents will be sent to Hooper Holmes, a contract phlebotomy service selected by competitive bid
- Attempt blood draw within 4 weeks of core interview
- Fasting will be recommended and preferred but not required
  - Most of our immediate assays do not require fasting but it will enhance potential of stored samples
- We project 9850 collections (proxy and NH excluded)
- Prepare samples in field and ship overnight to lab
  - Centrifuge
  - Cold / room temp shipping

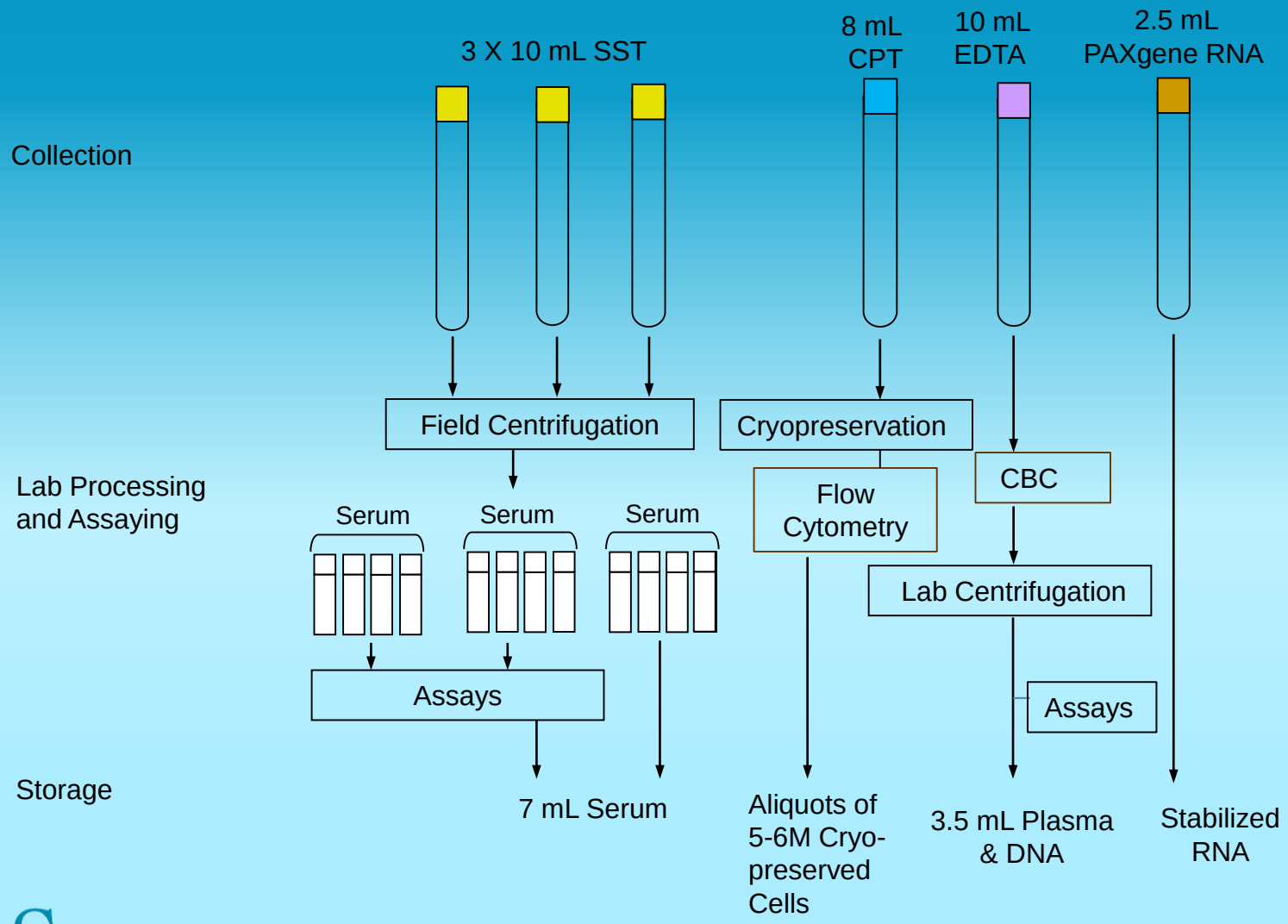
Overview of plan for processing at the lab

- Minnesota to receive samples within 24-48 hours
- Perform assays that must be done immediately
- Freeze serum and plasma
- Cryopreserve white blood cells
- Over course of 2016/17 perform our selected assays on frozen samples
- Retain remaining material (about half) in repository for future use

HRS

HRS Venous Blood Collection

(50.5 mL Venous Blood in six tubes)



HRS

Revised Sample/Assay Plan

Panel Sample	Innovative Sample
N=7850	N=2000
Metabolic Panel Lipid Panel CBC High sensitivity CRP (hsCRP) Ferritin (FRTN) IGF-1, DHEA-S Cystatin C Vitamin D (25 Hydroxy) Cytokine panel Flow cytometry (cryopreserved cells) CMV seroprevalence B-type natriuretic peptide (NT-proBNP) mtDNA copy number	
	DNA Methylation Homocysteine Telomere length P16

- 1) Traditional biochemical /harmonized marker
- 2) Immune system and inflammation marker
- 3) Innovative aging marker

HRS

Enabling Genetic-based Social Science Research Using HRS

- Over 130 approved research projects at dbGaP
- Mostly bio-medical, narrowly focused
- Full genetic database: large,unwieldy, restricted data
- We are working on data products that will be easier to use in social science
- And not a risk for respondent identification

Beyond Candidate Genes

- Complex health outcomes or behaviors of interest to the research community are often highly polygenic, or reflect the aggregate effect of many different genes (Visscher, Hill, & Wray 2008)
    - Individuals fall somewhere on a continuum of genetic risk that reflects small contributions from many genetic loci (Gibson 2012)
    - Genetic loci influencing the etiology of complex phenotypes have low penetrance—i.e. one single gene does not produce a symptom or trait at a detectable level (ibid)
- Use of single genetic variants or candidate genes may not capture the dynamic nature of more complex phenotypes
- Providing even a few direct genotypes is a confidentiality risk

Polygenic Risk Score (PRS)

- Using the published effect sizes from a GWAS, researchers can construct a **polygenic risk score (PRS)**
- A PRS aggregates millions of individual loci across the human genome and weights them by the strength of their association to produce a single quantitative measure of genetic risk
  - PRS: Weighted average across the number of SNPs (*n*) of the number of reference alleles *x* (0,1 or 2) at that SNP multiplied by the score for that SNP (ß):

$$PRS_i = \sum_{j=1}^{n} (\beta_j x_{ij})$$

Source: Schmitz & Conley 2015

Attractive features of a PRS

- Hypothesis-free measures
  - Ex ante knowledge about the biological processes involved is not needed to estimate a score for a particular phenotype
  - Allows researchers to explore how genes operate within environments where the biological mechanisms are not fully understood (Belsky & Israel 2014)
- Maximizes statistical power when modeling gene-environment (G x E) interactions
  - PRSs use the raw statistical power from huge consortia to generate one measure of genetic risk
  - The statistical power needed to model a candidate G x E study for biologically distal, social phenotypes is not possible in social surveys that contain the level of detailed information about respondents that motivates GxE inquiry (Belsky, Moffitt, & Caspi 2013)

Issues to consider when constructing PRSs

- Constructing a PRS based off of a GWAS your study is in
  - Mathematically remove your study (see attached PowerPoint)
    - Problems: dealing with adjustment for genomic inflation, incorporation of stratified meta-analyses (e.g. sex-specific scores)
  - Approach consortia to rerun meta-analysis without your study
- If there is no seminal GWAS on a particular phenotype
- If your study does not have the related phenotype
- Size of the study, discovery, replication, meta-analysis or joint analysis for selection of appropriate beta weights or effect sizes
- HRS is currently in the process of designing the methods and pipeline to create publicly available PRSs

HRS – PRS in Development

- Will be a public data release (summer 2016)
- 1st priority (Data publicly available)
  Psychiatric Genomics Consortium (PGC)
  BMI – Locke (2015)
  Alzheimer's Disease - IGAP
  Height – HapMap GIANT – (2014)
  Waist – GIANT
  Waist to hip – GIANT
  Educational attainment

- 2nd priority (Need additional data)
  Blood Pressure (ICBP)
  Smoking
  Longevity
  General cognition (Davies)
  Subjective Wellbeing
  Kidney Function (Cystatin C)

HRS | HEALTH AND RETIREMENT STUDY
A Longitudinal Study of Health, Retirement, and Aging
Sponsored by the National Institute on Aging

THANK YOU !

http://hrsonline.isr.umich.edu/