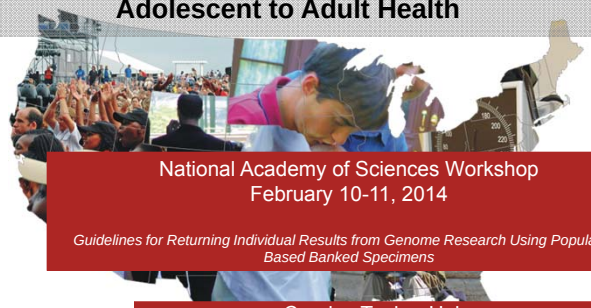
Add Health — *Social, Behavioral, and Biological Linkages Across the Life Course*

National Longitudinal Study of Adolescent to Adult Health



National Academy of Sciences Workshop
February 10-11, 2014

Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens

Carolyn Tucker Halpern
University of North Carolina at Chapel Hill

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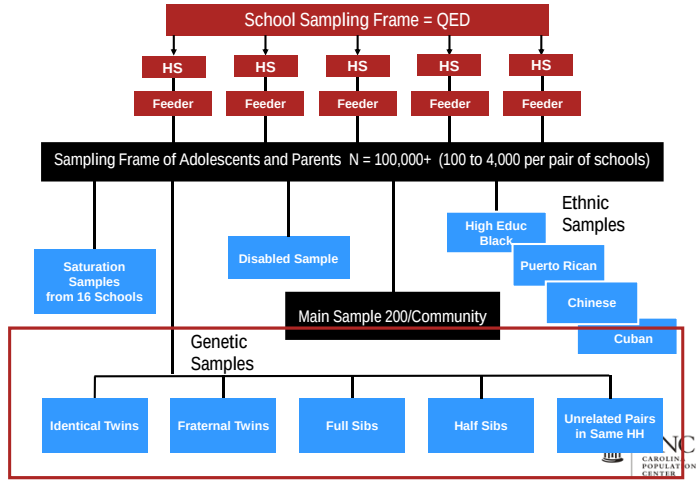
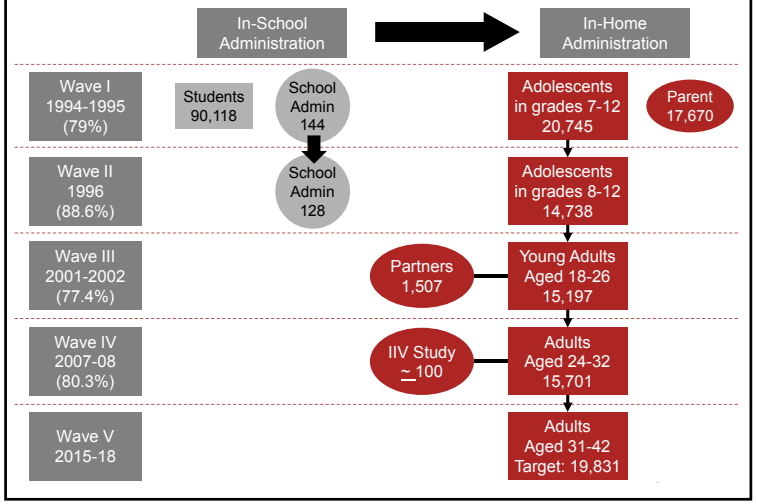
Add Health — *Social, Behavioral, and Biological Linkages Across the Life Course*



Add Health — *Social, Behavioral, and Biological Linkages Across the Life Course*



Add Health — *Social, Behavioral, and Biological Linkages Across the Life Course*

Race and Ethnic Diversity in Add Health

Race/Ethnicity	N	Unwtd. %
Mexico	1,767	8.5
Cuba	508	2.5
Central-South America	647	3.1
Puerto Rico	570	2.8
China	341	1.7
Philippines	643	3.1
Other Asia	601	2.9
Black (Africa/Afro-Caribbean)	4,601	22.2
Non-Hispanic White (Eur/Canada)	10,760	52.0
Native American (non-Hispanic)	248	1.2
Total N	**20,686**	**100.0**

Missing on race/ethnicity=59

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Biomarkers in Add Health

Biological Data across Waves

Adolescence →	Transition to Adulthood →	Young Adulthood →	Adulthood
Wave I-II (Ages 12-20)	Wave III (Ages 18-26)	Wave IV (Ages 24-32)	Wave V (Ages 31-42)
Embedded genetic sample of ~3,000 pairs →			
Physical development			
Height, weight	Height, weight	Height, weight, waist	Height, weight, waist
	STI tests (urine)	Metabolic	Metabolic
	HIV test (saliva)	Immune function	Immune function
	Genetic (buccal cell DNA)	Inflammation	Inflammation
		Cardiovascular	Cardiovascular
		Genetic (buccal cell DNA)	Genetic (whole blood)
		Medications	Medications
			Kidney

Non-Genetic Biospecimen Participation

- 99% Height, weight, waist (all Waves)
- 95% Saliva (Wave III; HIV)
- 92% Urine (Wave III; STIs)
- 99% Blood pressure (Wave IV)
- 94% Blood Spots (Wave IV; Metabolic, immune, inflammation; 76% archived)

Genetic Biospecimen Participation

- **Wave II**
  - Saliva: determine twin zygosity
  - Same-sex pairs in genetic sample
  - 66% participation
- **Wave III**
  - Buccal cells: candidate genes
  - Full sibs, twins in genetic sample
  - 83% participation
- **Wave IV**
  - Buccal cells: candidate genes and genome-wide analysis
  - Entire Add Health sample
  - 96% participation for candidate markers
  - 78% archived for GWAS

Evolving Content of DNA-Related Consent

- Wave II zygosity test (1 page)
  - "Receive results in about 6 weeks……all biological samples will be destroyed"
- Wave III (1 page)
- Wave IV (5 pages)
  - "Understand how variations in genetic make-up, in combination with environment and life experiences, may contribute to long term health"
  - "Storage for future research studies…also related to long term health, but would not be diagnostic tests to detect disease."

Wave III Candidate Markers

- **DAT1:** Dopamine transporter 40 base pair (bp) Variable Number Tandem Repeat (VNTR) in the 3' untranslated region of the gene
- **DRD4:** 48 bp VNTR in the third exon of the dopamine D4 receptor gene
- **5HTTLPR:** 43 bp addition/deletion in the 5' regulatory region of the serotonin transporter gene
- **MAOA:** 30 bp VNTR in the promoter region of the monoamine oxidase A gene
- **DRD2:** TaqIA single nucleotide polymorphism (SNP) in the dopamine D2 receptor
- **CYP2A6*2:** T→A substitution in exon 3 (rs1801272) of the cytochrome P450-2A6*2 gene
- **COMT:** val158met SNP (rs4680) in the catechol O-methyltransferase gene

Wave IV Candidate Markers

- VNTR and STR Genotyping
  - Monoamine Oxidase A Upstream VNTR
  - Dopamine D4 Receptor Exon 3 VNTR
  - Dopamine Transporter (*SLC6A3*) 3'-Untranslated Region VNTR
  - Serotonin Transporter-Linked Polymorphic Region
  - "Triallelic" HTTLPR alleles (LALGS; TRI)
  - Dopamine D5 Receptor Dinucleotide Repeat in the 5' Region
  - Monoamine Oxidase A Dinucleotide Repeat
- SNP Genotyping
  - Dopamine D2 Receptor TaqIA SNP rs1800497 in the 3' UTR
  - Catechol O-Methyltransferase (COMT) val158met SNP rs4680 (RS4680)
  - Serotonin Transporter (5HTT, Locus Symbol *SLC6A4*) rs12945042 (RS12945042)

Status of Genome-wide Genotyping

- 12,216 specimens were archived
- To date, ~9,500 specimens processed
  - Analysis of genetic pairs (~2000) complete
- ~2,500 additional specimens being processed
- Illumina HumanOmni1-Quad v1.0 and 2.5 Chips
- Near completion: Quality Control paper on pairs
- Preparing to deposit pairs GWAS data into dbGaP

Return of Biomarker Information to Add Health Respondents

- Wave II
  - Parents of twins received Zygosity information
- Wave III (Rs all 18+ years)
  - HIV
  - Gonorrhea and Chlamydia
- Wave IV
  - Blood pressure (& recommendations for follow-up)

BUT

  - No blood spot result data – tests considered experimental
  - No genetic data

Issues Regarding Return of Genetic Data in Research Studies

- Associations, not diagnostic
- Experimental methods
- Imprecision, inconsistency, risk of false positives
- Few markers are “clinically actionable”
- Could do more harm than good
  - Raise irrelevant concerns
  - Research needed: benefits/harm from returning results

Issues Regarding Return of Genetic Data in Research Studies

- Diverse, multi-racial/ethnic, genetically admixed populations
  - Strength of association may vary substantially among subpopulations
  - How to decide what is “important” for whom?
- Lack of resources to
  - Return results to participants
  - Answer questions that then arise
  - Provide tailored, professional counseling

Add Health Project Team

- Kathleen Mullan Harris, PI & Director
- Carolyn Tucker Halpern, Co-I & Deputy Director
- Eric Whitsel, Co-PI Biology Project
- Nancy Dole, Co-PI Biology Project
- Jon Hussey, Co-investigator
- Joyce Tabor, Add Health Data Manager
- Ley Killeya-Jones, Add Health Project Manager
- Sarah Dean, Assistant Project Manager

Add Health Co-Funders

- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development*
- National Cancer Institute*
- National Center for Health Statistics, Centers for Disease Control and Prevention, DHHS
- National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, DHHS*
- National Center for Minority Health and Health Disparities*
- National Institute of Allergy and Infectious Diseases*
- National Institute of Deafness and Other Communication Disorders*
- National Institute of General Medical Sciences
- National Institute of Mental Health
- National Institute of Nursing Research*
- National Institute on Aging*
- National Institute on Alcohol Abuse and Alcoholism*
- National Institute on Drug Abuse*
- National Science Foundation*
- Office of AIDS Research, NIH*
- Office of the Assistant Secretary for Planning and Evaluation, DHHS*
- Office of Behavioral and Social Sciences Research, NIH*
- Office of the Director, NIH
- Office of Minority Health, Centers for Disease Control and Prevention, DHHS
- Office of Minority Health, Office of Public Health and Science, DHHS
- Office of Population Affairs, DHHS*
- Office of Research on Women's Health, NIH*

*Wave 4 co-funders

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Add Health Web Page

http://www.cpc.unc.edu/projects/addhealth

- Online code books
- User guides to inform data analysis
- Bibliography of Add Health publications
- Information about the bi-annual Add Health Users Conference in Washington DC, June 2014
- Information about public-use and restricted-use data access

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Extra slides

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Pairs of Individuals in Embedded Genetic Sample, Add Health	
Sibling Type	N
Twin	784
Monozygotic	307
Dizygotic	452
Undetermined	25
Full Sibling	1251
Half Sibling	442
Non-related	662
Adopted (single individuals)	560

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Add Health Choice of Biological Data

- Biological states that are reasonably prevalent in the general population of youth & young adults
- Biological states and processes theoretically and/or empirically linked to future health
- Measures that can characterize those processes
- Feasible for a large scale, national field study
- Valid and reliable
- Appropriate for longitudinal designs
- Non-invasive, cost-efficient, practical

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Wave IV Consent for DNA Collection by race/ethnicity **n (%)***

Race/Ethnicity	To Collection	To Archive
Hispanic	2,393 (96%)	1,883 (75%)
Black, Non-Hispanic	3,348 (96%)	2,523 (72%)
White, Non-Hispanic	8,051 (97%)	6,822 (82%)
Other, Non-Hispanic†	1,335 (95%)	997 (71%)
All	15,140 (96%)‡	12,234 (78%)‡

*Unweighted number and percentage, excluding four incarcerated respondents for whom saliva collection was prohibited.
†Asian, American Indian, or other.
‡13 respondents with missing Wave I race are included in the Consent to Collection totals; 9 respondents missing Wave I race are included in the Consent to Archive totals.

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Behavioral, Social, Contextual Content Across Waves

Waves I, II

Demographic
Family, siblings, friends
Education, work
Physical and mental health
Daily activities and sleep
Relationships
Sexual, & fertility histories
Substance use
Delinquency and violence
Attitudes, religion
Economics, expectations
Psychological, personality

Wave III

Demographic
Family, siblings, friends
Education, work, military
Physical and mental health
Daily activities and sleep
Relationships
Sexual, & fertility histories
Substance use
Involvmt w/criminal justice sys
Attitudes, religion
Economics, expectations
Psychological, personality
Children and parenting
Civic participation
Gambling
Mentoring

Wave IV

Demographic
Family, siblings, friends
Educ, work, military (records)
Physical and mental health
Daily activities and sleep
Relationships
Sexual, & fertility histories
Substance use and abuse
Involvmt w/criminal justice sys
Work attitudes and chars, relig
Economics, expectations
Big 5 Personality, stressors
Children and parenting
Civic participation
Cognitive function
Psychosocial factors

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

Health and Retirement Study

David R. Weir
Principal Investigator

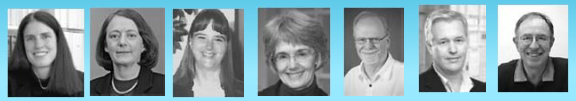
HRS exists to serve the needs of research on aging

- Created by US NIA(NIH) in 1992 in response to a review of research needs in late 1980s
- Congressional mandate to NIA to create it
- Michigan won a competitive bid to conduct it
- A cooperative agreement with NIA

HRS

HRS Co-Investigators

Charles C. Brown | Eileen M. Crimmins | Michael D. Hurd | Sharon L.R. Kardia | Kenneth M. Langa | Helen G. Levy | John J. McArdle



Kathleen McGarry | Olivia S. Mitchell | Mary Beth Ofstedal | Jacqui Smith | Robert B. Wallace | David R. Weir | Robert J. Willis

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HRS and NHANES

- ✓ Nationally representative sample
- ✓ Rapid public data release
- ✓ + Multi-disciplinary content
- ✓ - Population 50 and older
- ❑ Longitudinal study
- ❑ Under Michigan IRB, not PRA/OMB
- ✓ Confused about what results to report

HRS

Size

- From 1992 through 2012:
- Over 37,000 people were interviewed at least once
- 200,000 interviews were completed
- 8,000 workers retired
- 13,000 people have died
  - 10,500 interviews with their survivors

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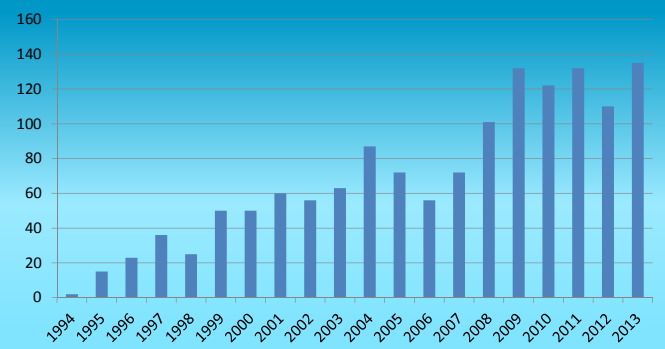
Impact: Number of New Peer-Reviewed Journal Articles per Year Using HRS



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Some key innovations

- Highly structured CAPI/CATI
  - Over 5,000 possible questions
    - Average interview gets about 400
- Administrative linkages to Social Security (earnings histories and benefits) and Medicare (health care)
- Biomarkers starting in 2006
  - Blood spots, physical performance
- Genetics data on ~20,000 people

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HRS philosophy: measure many things pretty well

- We don't aim to replace other national surveys on specific topics
- We do match them pretty closely

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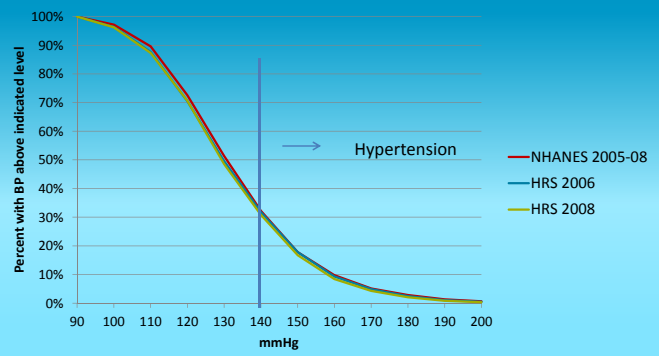
Systolic blood pressure: HRS vs NHANES



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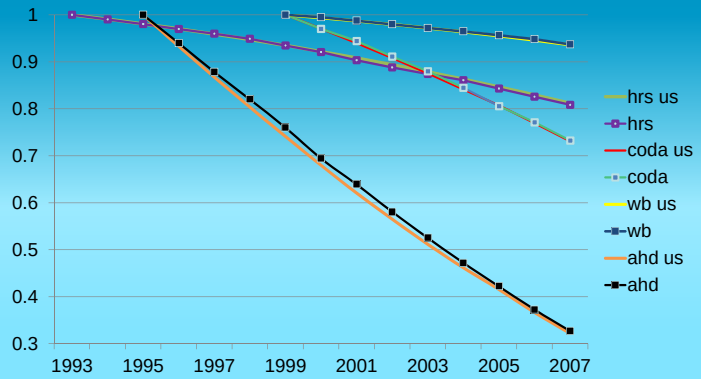
HRS Mortality by Cohort Compared with Life Tables



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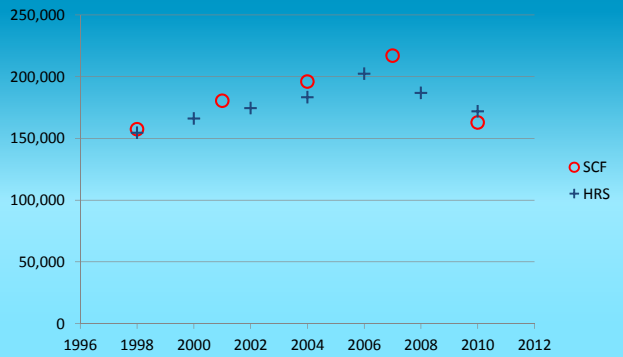
Median Wealth of Households 55 and Older—SCF and HRS (2008 dollars)



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Genetics in HRS

- Began collecting DNA in 2006
- Oragene (saliva)
- Stored in repository, no funding or definite plans for wide-scale use
- GWAS model identified as most appealing for HRS
  - Broad coverage of genome permits exploratory work in a wide range of health and behavioral phenotypes
    - Esp. longitudinally defined phenotypes
  - Rich genetic data for use in social science models
    - Instrumental variables, Mendelian randomization, etc
  - Preferable to do centrally, general access
  - Preserve samples in repository for future use

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ARRA

- NIA RC2 AG036495
- NIA RC4 AG039029 (Common Fund)
- Genotype samples collected in 2006, 2008, 2010, and 2012 ~ 20,000 total
- Illumina 2.5m SNP chip
- + exome chip
- CIDR for genotyping, U Washington for QC
  - And imputation to 1000 genomes 22 m SNPs

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Health and Retirement Study (HRS)

dbGaP Study Accession: phs000428.v1.p1

There are 76 authorized requests associated with this study.

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HRS Approach to Confidentiality

- Careful evaluation of risk
- Public data – low risk of re-identification, low to moderate sensitivity
  - Register on website, check box not to identify
- Sensitive data – low risk of re-identification, moderate to high sensitivity
  - e.g., cholesterol level, detailed Rx meds
  - Signed and countersigned agreement not to identify
- Restricted data – no direct identifiers but moderate risk of re-identification
  - E.g., de-identified Medicare records, de-identified GWAS
  - Onerous requirements

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HRS Policy on Reporting Results from Non-Genetic Data

- Separate signed consents for performance measures, blood spots, and DNA (saliva)
- We report blood pressure, HbA1c, total and HDL cholesterol (relatively quickly)
- We do not report CRP or cystatin-C
- Things that are well understood and commonly used in clinical practice are reported

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Consent and Reporting for DNA

- HRS adopted a broad general-use release
- DNA specimen collected separately, consented separately, no confusion about what biospecimen will be used for what purpose
- No return of genetic results is promised
- UM IRB determined that dbGaP represented a significant departure from information given to respondents in earlier consent
  - Revised consent for later years
  - Re-informed early participants, offered opt-out
  - About 100, fewer than 1% opted out

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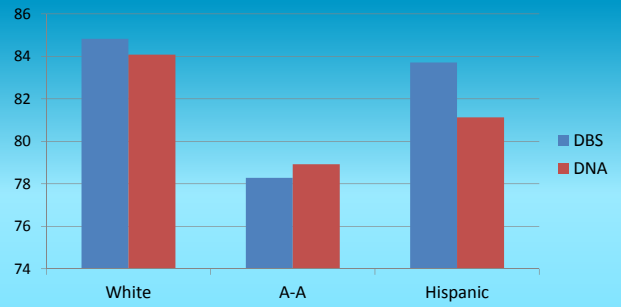
Consent Rates of New Respondents, by Race/Ethnicity (HRS 2010)



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Questions

- Clinical value of information contained in samples given at one point in time increases as time moves forward
  - How far back does obligation to report extend?
- Genome is heritable
  - Obligation to later generations vs privacy of participants?
- Population research studies don't advise people on their risks or how to manage them
  - How much genetic counseling to provide with results?
- No-return consent is an agreement, so criteria to violate that agreement should be higher than just some possible small benefit
  - How do we set a standard for compelling need to return?

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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/

Wisconsin Longitudinal Study

Center for the Demography of Health and Aging
University of Wisconsin-Madison
with support from the
National Institute on Aging since 1991

Agenda

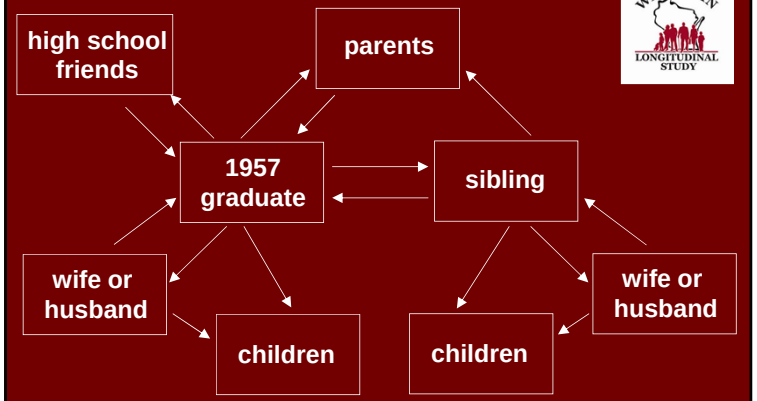
- Quick introduction to the WLS
  - Design and Data
- Genetic data
- Consent procedures
- Disclosure issues

what the WLS offers

- public longitudinal survey data following a cohort of 10,000+ Wisconsin high school graduates from ages ~18 to ~74 (and beyond?)
- survey data from multiple participants
- diverse administrative record data
- information about many domains of respondent lives, and those of other family members
- high response rates
- however: WLS respondents are all high school graduates and almost all whites (rather like 2/3 of Americans of their cohort, but *not* like everyone)

The "Happy Days" cohort

The “Happy Days” cohort

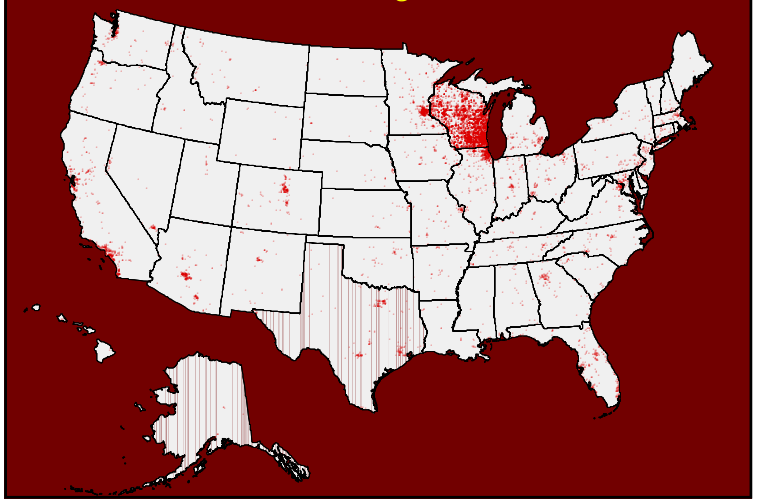


relational structure of data in the WLS

Survey Operations

- 1957 school survey
- 1964 parent post-card
- 1975 graduate telephone survey
- 1977 sibling telephone survey
- 1992-94 grad and sib telephone and mail
- 2004-06 grad, sib, and spouse telephone and mail
- 2007 onward – saliva collection
- 2010-12 grad, sib home interviews and mail

where are WLS graduates?



plus: much non-survey data:

- high school standardized test scores (Henmon-Nelson Test in freshman and junior years)
- high school class rank
- parents' occupation and income (tax records), 1957-60
- college and employer characteristics
- links to National Death Index
- geocodes of addresses
- elementary and high school resources (from state archives)
- high school yearbooks (for ~83% of all graduates)
- State disability claims
- DNA from Oragene for graduates and siblings (N = 9000+)
- And soon, Social Security earning and benefit histories and Medicare records

some domains where WLS data are especially strong

social/family background

educational history

employment history

job characteristics

marital history

children

physical/mental health

income and wealth

retirement and pensions

cognitive performance

leisure time activities

stressful life events

methodological features

- interviews by random replicates
- bracketing amounts with random anchors
- selecting special children (supplemental interview and survey)
- cognitive measurement
- health vignettes (WHS)
- recording interviews

biomarkers, and ...

- several measures of BMI
- facial characteristics: attractiveness, smiles, and facial mass (from high school yearbooks)
- DNA collection with Oragene saliva kits from grads (and siblings)
- experience with Medicare D
- home interviews of graduates and siblings with anthropometric and performance measures in the new round, 2010-11 (age 71-72)

WLS 2010-11 Leave Behind SAQ

- Repeat of previous measures
- Economic Literacy
- Economic Games
  - Subset of cases play for real-stakes
- Elder abuse
- Medication Inventory

Consent for Saliva Collection

- One of three signed consent forms
  - Medicare
  - Saliva
  - Social Security earnings
- Unrestricted use for group analyses
- Labs not qualified for medical diagnostics
- No competence to provide medical advice
- No information feedback, ever

Analyses of DNA

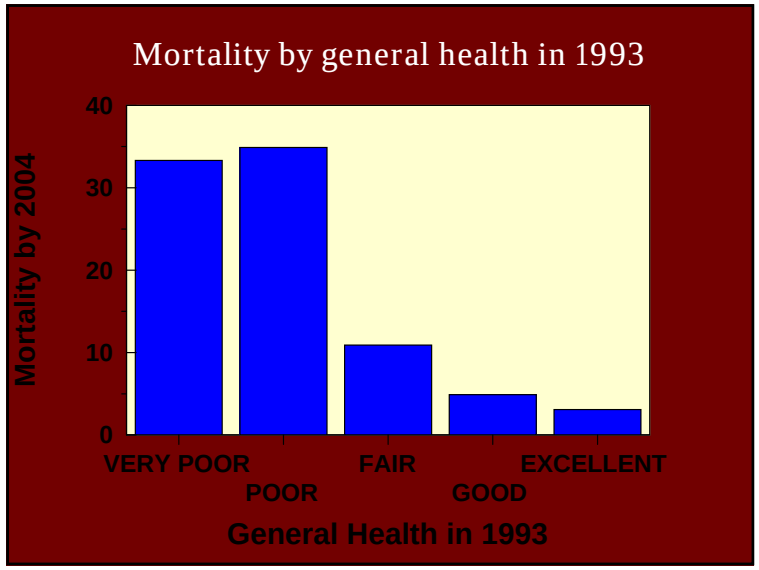
- Currently have 9000 samples from graduates, including ~2000 from sibling pairs
- Successful assays for graduates and siblings
- 95 SNPs for candidate genes related to AD, breast cancer, cognition, depression, diabetes, impulsivity, fertility, longevity, obesity, etc.
- Separate assays for FMR1 (Fragile X syndrome)
- Application underway for GWAS

availability/access of wls data

- commitment to easy public availability of all permissible data
- many tools on the web to facilitate use of WLS data and access to publications
- longitudinal data with a large sampling fraction provides particular challenges for maintaining confidentiality
- Genomic (and some other restricted) data may only be analyzed within a secure data enclave, whether at Madison or elsewhere

Disclosure Issues

- Suicidal ideation
- Child abuse
- Elder abuse
- Lake fish consumption
- End of life planning
- Symptoms
- Anesthesia
- General health
- Genetic information



WLS internet resources
(use Google)

- questions? write to wls@ssc.wisc.edu
- public data users
  - http://www.ssc.wisc.edu/wlsresearch/
  - documentation
  - bibliography and publications
  - variable search aids
  - downloadable data
- small grant program
  - http://www.ssc.wisc.edu/wlsresearch/pilot/
- private web
  - proposals, instruments, manuscripts
- respondent web
  - http://wisls.org

Wisconsin Longitudinal Study
Center for the Demography of Health and Aging
University of Wisconsin-Madison
Currently funded by National Institute on Aging

National Children's Study Presentation
for the
National Academy of Sciences Workshop
on
Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens

Jack Moye, Jr., MD
U.S. Department of Health and Human Services
National Institutes of Health
Centers for Disease Control and Prevention
U.S. Environmental Protection Agency

February 10-11, 2014

National Children's Study

- The National Children's Study is a national longitudinal study of environmental influences on children's health and development authorized by the Children's Health Act of 2000
- "Environmental influences" broadly defined to include physical, chemical, biological, and psychosocial
- A data acquisition resource and not a conventional study
- Majority of biospecimens and data intended to be analyzed in future

NCS Structure and Status

- Current major components of the NCS
  - Vanguard Study: pilot phase - runs for 21 years - began accrual 2009 - ~5,000 families in 40 locations throughout the U.S. currently enrolled
  - Main Study: exposure-response phase - runs for 21 years, several years time shifted from Vanguard Study
  - Substudies: studies within studies (e.g., recruitment, sampling)
  - Formative Research and Supplemental Methodological Studies: short term, limited studies focused on methods development to support and inform the Vanguard and Main Studies

Comparison of NCS with NHANES

	NCS	NHANES
Legislation	Children's Health Act of 2000	National Health Survey Act of 1956
Design	Longitudinal	Cross sectional
Sample size	100,000	10,000's
Entry age	Prenatal/newborn	Infant through adult
Stored sample types	Multiple	Serum, plasma, urine
Stored DNA/consent for genetic testing	All participants	Participants aged ≥20 years
Repository linkage	Unlinked	Linked
Pregnant participants	Many	Few
Child participants	Many	Few

Return of results continuum

Sisters, BioVU | NCS, NHANES | PGP

None	Some	All
"Research use only" (RUO)	How to choose? Who decides?	Equal partners

What can be done?
What should be done?
Who should decide?

Current NCS Return of Results Strategy: Informed Consent

- NCS consent process is designed to tell the participant
  - what we would like to collect and why,
  - how we would collect it, how we would protect it,
  - results we can share with them at the time of a given visit, and
  - when and under what circumstances we may contact participants to ask if they would like to receive individual research results

What you should know about joining the National Children's Study Vanguard Study

- **How can I find out about the results of the Study?**
- "…We will share what we learn from the Study as a whole. We will keep in touch through newsletters, on our Web site, and in other ways.
- "…We will share some information we learn about you and your child with you when it is available
- "…If we know the results from tests we do during a visit, we will share them with you then. For example, we will tell you information about your height, weight, and blood pressure…"

What you should know about joining the National Children's Study Vanguard Study

- **How can I find out about the results of the Study?**
- "…We plan to test most of your samples in the future
  - At this time, we do not know when these tests will be done, which tests will be done, and when information from the tests will be available
  - A committee of doctors, scientists and community members (the iSMOC) will advise the Study on which tests may provide information about participants' health
  - When test results related to your health and your child's health are available, we may ask you if you want to learn about them…"

National Children's Study: Vanguard Study Informed Consent for Pregnant Women's Study Participation

- "…I understand that these samples may be used for a variety of tests in the future, including genetic tests.
- "…I understand that I will not routinely get results back from tests done on the samples I give to the study
- "…I give my permission for the Study to use my biological samples to obtain my genetic information…"

Considerations Informing the NCS Approach to Return of Results

- Personal health information may be important to participants even if tests are conducted sometime in the future
- Some tests for the evaluation of samples are known at the time of collection; others are not yet determined
- Some tests require delayed or future laboratory analysis, others can be reported immediately
- Some tests could inform current medical care; others have unknown implications
- Availability and salience of testing can change over time

Current NCS Return of Results Strategy Considerations

- Current NCS return strategy is informed by:
  - Identification of analyses to be conducted with Study samples (what will be tested for)
  - Characteristics (certification, accreditation) of analysis source (how will testing be done)
  - Applicable clinical and regulatory standards and current practice
  - Timeframe in which analysis can be completed and research results made available for potential reporting
  - Potential health impact of research result based on clinical significance and medical actionability

Individual Research Result Health Impact Categories

Health Impact	Examples
Descriptive health information	Height, weight
Clinically non-significant	Routine genomic DNA copy number variation (e.g., AMY1)
Clinically significant • Medical actionable	Elevated BP, blood Pb; APC or BRCA gene mutations
• Not medically actionable	Alzheimer's, spinocerebellar ataxia
Unknown clinical significance	Environmental chemicals with no agreed upon critical values

Advice and Oversight for NCS Strategy on Return of Results

- Consultation with NCS Federal Advisory Committee and independent Study Monitoring and Oversight Committee (iSMOC)
- Return warranted if "clinically significant and medically actionable"
- Procedure: Recall/consent → repeat → refer
- Current experience limited to environmental contaminants and clinical chemistries – e.g., elevated blood metals, water contaminants exceeding EPA maximum contaminant level
- Further input sought for planned future analyses

Ongoing Development Process for NCS Return of Results Strategy

- The independent Study Monitoring and Oversight Committee (iSMOC) determines which, how, and when findings will be reported (including individuals, groups, communities)
- When iSMOC identifies an analysis, a standard, and determines if results are clinically actionable, a recommendation is made to the Study Director
- The Study Director, in consultation with others, determines if and how the recommendation should be implemented
  - This may include returning results to participants, consulting with and reporting to oversight bodies, revising the study protocol
- If the NCS Return of Results policy is revised, this information is incorporated into Study materials

NCS Repository Sample Receipt

National Children's Study Information

Visit the NCS Website

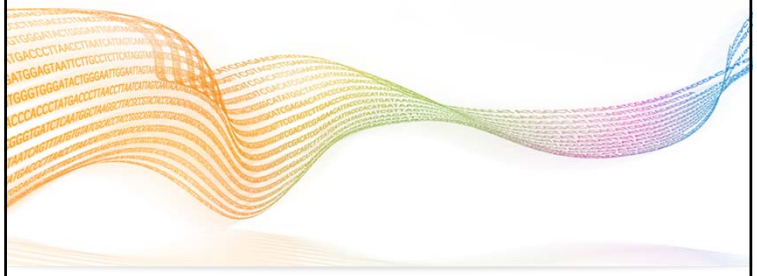
- http://www.nationalchildrensstudy.gov/

Contact us via email

- mailto:ContactNCS@nih.gov

Returning data to participants: Understand Your Genome Symposium

Tina Hambuch, PhD, dABMG
10 February 2014, NHANES



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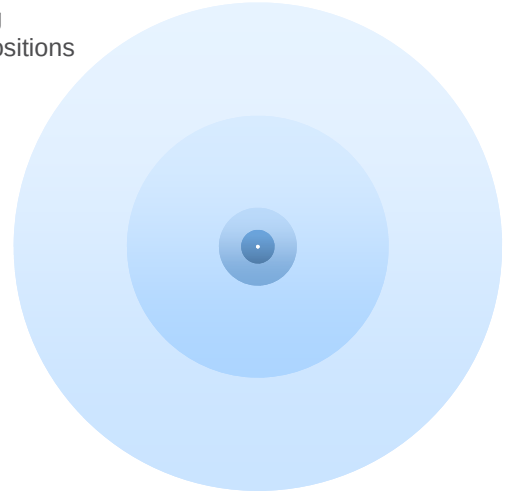
Genomes are big

3.1 Billion base positions

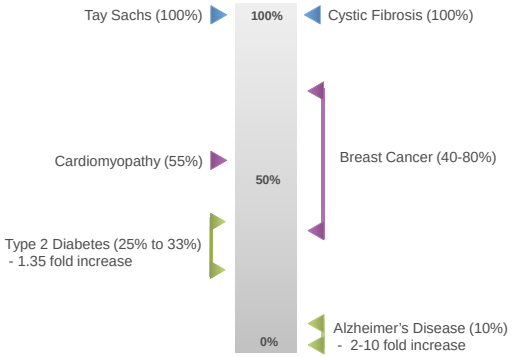
- 2.9 billion positions called
- 3.3 million variants
- 1.5 million variants in genes
- 21,000 coding
- 9,600 NS
- 73 Stop



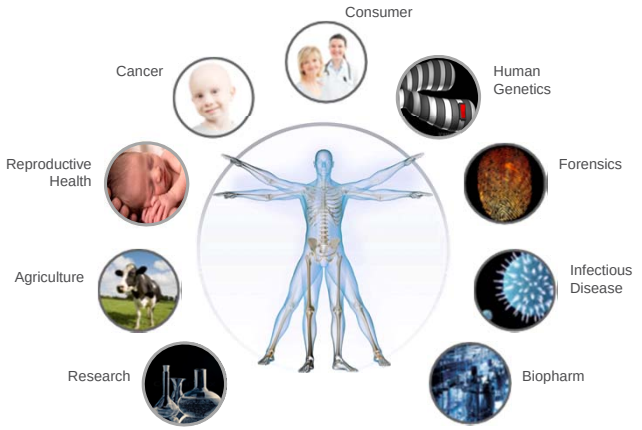
Genomes are complex

- Monogenic diseases
- Majority of disease risk by single gene
- Epigenetic disease(>1 gene + environment)

11% of the genes in the genome are tested for clinically today



Genomes are here



Genomes are being sequenced at the population level

Monday, 21 October 2013 10:22 KATE SWEENEY

ILLUMINA AND CAMBRIDGE SPEARHEAD GENOMICS REVOLUTION

U.K. Organizations Partner With Illumina To Sequence 10,000 Whole Genomes

Published on October 21, 2013 at 12:00 PM · No Comments

University of Cambridge, Genomics England Ltd., and Illumina Collaborate to Sequence 10,000 Whole Human Genomes for National Health Service Patients

Project Will Lay Foundation for Genomic Medicine

Initiative Will Sequence 10,000 Whole Genomes of People with Rare Genetic Diseases

BIOMEDICINE NEWS

Why the U.K. Wants a Genomic National Health Service

The U.K. plans to sequence 100,000 National Health Service patients by 2017—in a bold push to be a genomic medicine leader.

100,000 British Genomes

A new initiative lead by the UK's National Health Service aims to sequence the genomes of as many as 100,000 patients, a project that will cost £100 million.

The Million Veteran Program: Building VA's Mega-Database for Genomic Medicine

Personalis Awarded Contract From VA Million Veteran Program – Whole Genome Sequencing and Data Analysis for Over 1,000 Individuals

Sequencing the genome of an entire population

As the first country ever, the Faroe Islands are preparing to sequence the genetic material of its entire population. The FarGen project could become a model for personalised medicine throughout the world.

Goals of Understand Your Genome

- Informed conversation on opportunities and challenges associated with genomic medicine
- Experience physician-mediated personal genome sequencing
- Enable a network of stakeholders in genomic medicine
- Identify opportunities and efficiencies
- Identify concerns and challenges
- Identify policies and guidelines needs

Physicians
Genetic Counselors
Laboratory Directors
Policy Makers

Administrators
Entrepreneurs
Investors
Ethicists

Genomes in Healthcare

Require an informed community and robust processes

Step 1 physician/patient consent process

Step 2 Physician-Illumina Clinical Geneticist consultation as needed

Step 3 Sample blood collection

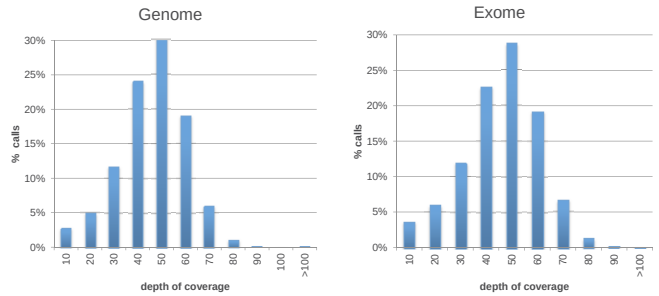
Step 4 Sequencing at Illumina's CLIA-certified, CAP-accredited lab

Step 5 Variants interpreted and reported to physician

Step 6 Physician-patient discussion regarding results and next steps in medical management

Accuracy, Interpretation and Reporting

Analytical Validity in ICL



Depth of coverage	Sensitivity	Specificity
30x	>99.9%	>99.99%
20x	99.5%	>99.99%
10x	98.0%	99.99%
5x	N/A	99.99%

Could this Variant Be Responsible for Disease?

THE CRIME

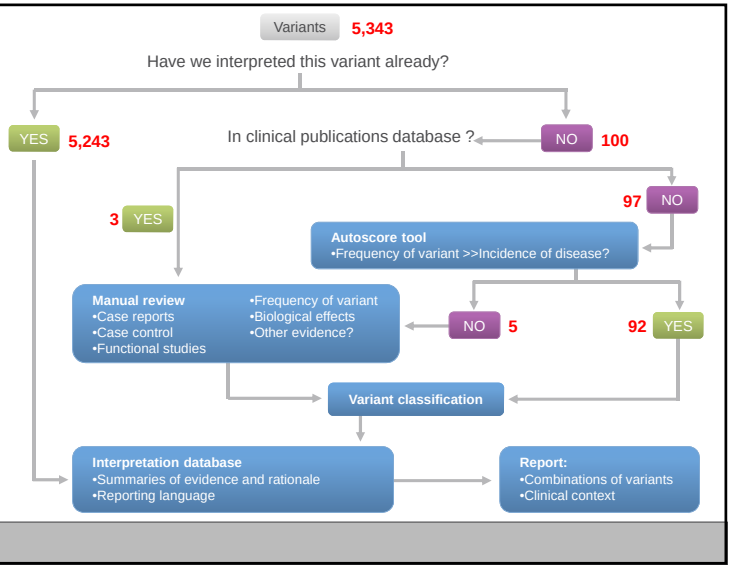
Genetic Disease

- How does it happen
  - Autosomal dominant, autosomal recessive, x-linked, other?
  - Early onset, late onset, penetrance
- How common is it?

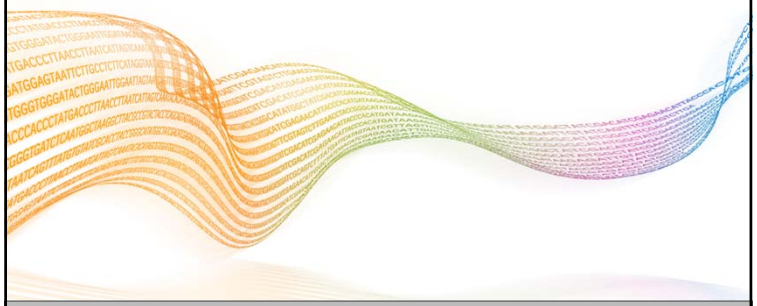
THE SUSPECT

A Genetic Variant

- What kind of variant is this?
- What is known about this variant?
- How common is this variant?
- Are there other genes or variants that could also be responsible?
- Is this variant the criminal or an accessory to the crime?



Policies



Reporting policy decisions

Secondary findings

No Predisposition/Carrier screenings available for minors

Clinical report includes pathogenic, likely pathogenic and VUS that are suspicious for pathogenicity

Appendix includes all annotated calls that passed quality, plus interpretations

Updates on interpretations

The power of numbers

Control populations

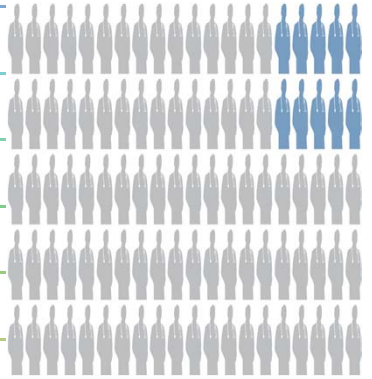
Identification of artifacts

Ethnic/population diversity

Higher quality calls

Improve efficiency for interpretation

Mitigate cost of entry



Patient/Participant requests

Explore data using other tools and software

- Research tools
- Assessment of parameter changes in algorithms

Evaluate additional genes/biomarkers

- Services that offer additional/alternative types of assessment (ancestry, traits)
- Annotation/interpretation software

Share with other individuals

- Specific individuals in community

Donate for further research

- Hospitals, such as Medical College of Wisconsin
- PGP

Policies that are needed

Printed clinical report only, or data passing quality metrics too?

New consents for every use case?

Do receivers of genomes require IRBs, and if so, how do participants navigate that process?

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