Biosocial 2.0: Future directions for integrating biological measures into population-based research

Thom McDade, PhD
Northwestern University, Department of Anthropology and Institute for Policy Research
All About The Human Genome Project (HGP)

The Human Genome Project (HGP) was one of the great feats of exploration in history - an inward voyage of discovery rather than an outward exploration of the planet or the cosmos; an international research effort to sequence and map all of the genes - together known as the genome - of members of our species, Homo sapiens. Completed in April 2003, the HGP gave us the ability, for the first time, to read nature's complete genetic blueprint for building a human being.

https://www.genome.gov/10001772/all-about-the--human-genome-project-hgp/

"It is humbling for me and awe inspiring to realise that we have caught the first glimpse of our own instruction book, previously known only to God."
Dr Francis Collins, Human Genome Project

"We've now got to the point in human history where for the first time we are going to hold in our hands the set of instructions to make a human being."
Dr John Sulston, UK Sanger Centre

"We now have the possibility of achieving all we ever hoped for from medicine."
UK Science Minister Lord Sainsbury
The case of the missing heritability

When scientists opened up the human genome, they expected to find the genetic components of common traits and diseases. But they were nowhere to be seen. Brendan Maher shines a light on six places where the missing loot could be stashed away.
Ten years after President Bill Clinton announced that the first draft of the human genome was complete, medicine has yet to see any large part of the promised benefits.

The failure of the genome

If inherited genes are not to blame for our most common illnesses, how can we find out what is?

Blogging the Human Genome: Was the Human Genome Project a failure?

According to his published DNA sequence, James Watson should be blind, deaf, and have a tiny head. Why doesn’t he?
Human genome: Downsized

Scientists still don’t agree on how many protein-making genes the human genome holds, but the range of their estimates has narrowed in recent years.

- Estimated value
- Range of estimates
- Launch of the Human Genome Project
- First draft of human genome released
- Refined analysis of complete genome

The latest count found 21,306 protein-coding genes

That the tomato and potato contain so many genes does not mean that they are more sophisticated than people but that they have chosen a different stratagem for managing their cells’ affairs.

More Genes Than Humans: The Tomato Decoded

By NICHOLAS WADE

The tomato, whose genome has just now been decoded, turns out to be one well-endowed vegetable, possessing 31,760 genes. This rich legacy, possibly a reflection of the disaster that killed off the dinosaurs, is some 7,000 more than that of a person, and presents a complex puzzle to scientists who hope to understand its secrets.
Scientists still don’t agree on how many protein-making genes the human genome holds, but the range of their estimates has narrowed in recent years.

1. Launch of the Human Genome Project
2. First draft of human genome released
3. Refined analysis of complete genome

The latest count found 21,306 protein-coding genes
Biosocial approach in population science

American Anthropologist 1912, 14(3)

CHANGES IN THE BODILY FORM OF DESCENDANTS OF IMMIGRANTS

BY FRANZ BOAS

UNDER this title I have published the results of my investigations on the anthropometry of immigrants and their descendants, undertaken for the United States Immigration Commission. A partial report was asked for by the Commission and submitted to Congress on December 16, 1909, and published about March, 1910. It was stated in the report (p. 6) that the investigation was not complete. An abstract of the complete report was submitted to Congress on December 3, 1910, and issued on March 17, 1911. The final report was presented on December 5, 1910, by the Secretary of the Commission, submitted to Congress on June 8, 1911, printed in September, 1911, and issued in May, 1912. It was reprinted and published by the Columbia University Press in New York in 1912.

I may summarize the principal results of this investigation as follows:

1. American-born descendants of immigrants differ in type from their foreign-born parents. The changes which occur among various European types are not all in the same direction. They develop in early childhood and persist throughout life (Partial Report, pp. 7-16; Abstract, pp. 11-28; Final Report, pp. 55-56, and tables, pp. 10-55).

2. The influence of American environment makes itself felt with increasing intensity, according to the time elapsed between the arrival of the mother and the birth of the child (Partial Report, pp. 17-22; Abstract, pp. 29-37; Final Report, pp. 57-64, 99-115).
Biosocial approach in population science
Biosocial perspective, defined

“...the dynamic, bidirectional interactions between biological phenomena and social relationships and contexts, which constitute processes of human development over the life course.”

— Harris and McDade, 2018 (p. 2)
Biosocial perspective, defined

- Political economy
  - Social structure and stratification
  - Neighborhoods and schools
  - Interpersonal relationships

- BRAIN and BODY
  - gestation
  - infancy
  - childhood
  - adolescence
  - adulthood
  - older adulthood

- Biochemical messengers
- Organs and tissues
- Physiological and neurological systems
- Genome and epigenome
A unique opportunity for biosocial applications in population science/health

- Large, diverse, representative samples
- Rich measures of context/experience/behavior
- Multiple measures across life stages
- Outcomes characterized across multiple dimensions
  - Anthropometric, physiologic, genetic measures
Bringing biology to population-based research

Demographic factors
- Age
- Gender
- Socioeconomic status
- Race/ethnicity

Psychosocial factors
- Social relationships
- Stressor exposure (e.g., life events, discrimination)
- Cognitive/affective traits

Community factors
- Geographic setting, location
- Social capital
- Infrastructure

Health care
- Access
- Knowledge/trust

Cultural factors
- Shared beliefs, values, models of behavior

Biological mechanisms
- Sympathetic adrenal medullary system
- Hypothalamic pituitary adrenal axis
- Cardiovascular system
- Metabolic processes
- Immune system
- Gonadal function, regn

Behavioral mechanisms
- Diet, physical activity
- Smoking, alcohol/drug abuse
- Sleep patterns
- Risk taking
- Use of health services

Health outcomes
- Mortality
- Morbidity
- Fecundity/fertility
- Functional loss

Socializing biology

**Biosocial 1.0** Borrow clinical biomarkers and apply them in population-based settings using prevailing conceptual and analytic frameworks.

**Biosocial 2.0** Challenge prevailing biomedical frameworks by broadening scientific and public understandings of human biology, development, and health.
The biomedical approach: Trapped inside the body

"It is humbling for me and awe inspiring to realise that we have caught the first glimpse of our own instruction book, previously known only to God."

– Dr Francis Collins, Human Genome Project

"We now have the possibility of achieving all we ever hoped for from medicine."

– UK Science Minister Lord Sainsbury

“...the natural inclination of medicine is to isolate the single factor that is most responsible for the observed behavior. . . . For infection, the target is the pathogen; for cancer, it is the tumor; and for gastrointestinal bleeding, it is the bleeding vessel or ulcer.”


“...many epidemiologic studies focus on individuals and individual risk factors. . . . This research might more properly be seen as clinical research in large groups of people.”

What determines health? Pre-class
Northwestern University: AND is in our DNA

491 views • Feb 1, 2019
Human biology is a social biology

Fig. 1. Level of social integration and age-adjusted mortality for males in five prospective studies. RR, the relative risk ratio of mortality at the lowest versus highest level of social integration.

Fig. 2. Prospective associations of social integration with biomarkers of physiological functioning over the life course. Results based on ordinary least squares (OLS) models of biomarkers at follow-up regressed on baseline social integration, adjusting for age, sex, and race. HRS and NSHAP findings are similar, so we present the larger HRS sample results.

Figure 1
Differential gene expression in high- versus low-lonely individuals. Genome-wide transcriptional profiles were assessed in peripheral blood leukocyte RNA samples collected from individuals in the top and bottom 15% of the distribution of subjective social isolation. Analysis by Affymetrix U133A high-density oligonucleotide arrays identified 229 transcripts showing >50% difference in mean expression levels across groups (green = over-expression in high-lonely, red = under-expression). High subjective social isolation is associated with a statistically significant net reduction in the number of expressed genes (13) down-regulated versus 78 up-regulated, p-value by exact binomial test.)
Human biology is a social biology

**Figure 1**
*Mortality Rate by Socioeconomic Status Level*

- CRP (mg/L)
- DNAm in association with SES
Socializing biology

**Biosocial 2.0**  
Attend to developments in the clinical sciences; borrow as needed.

Broaden scientific and public understandings of human biology

- *Field-friendly methods for studying biology in “free-ranging” humans*
- *Using biology to document the impact of social context and experience*
- *Challenge simplistic understandings of biological causation*
Measuring the body in free-ranging humans
Measuring the body in free-ranging humans

Saliva
- DNA
- Reproductive hormones
- Stress hormones
- Immune factors
- HIV

Urine
- Reproductive hormones
- Stress hormones
- Renal function
- STIs
- Drug metabolites

Anthropometry
- Ht, wt, body comp
- Blood pressure

Point-of-care assessment
- Blood smears
- Capillary tubes
- Dried blood spots

Capillary tubes
Dried blood spots
State of the Science in Dried Blood Spots

Jeffrey D. Freeman,* Lori M. Rosman,1 Jeremy D. Ratcliff,2 Paul T. Strickland,3 David R. Graham,4 and Ellen K. Silbergeld4

BACKGROUND: Advancements in the quality and availability of highly sensitive analytical instrumentation and methodologies have led to increased interest in the use of microsamples. Among microsamples, dried blood spots (DBS) are the most well-known. Although there have been a variety of review papers published on DBS, there has been no attempt at describing the full range of analytes measurable in DBS, or any systematic approach published for characterizing the strengths and weaknesses associated with adoption of DBS analyses.

CONTENT: A scoping review of reviews methodology was used for characterizing the state of the science in DBS. We identified 2018 analytes measured in DBS and found every common analytic method applied to traditional liquid samples had been applied to DBS samples. Analytes covered a broad range of biomarkers that included genes, transcripts, proteins, and metabolites. Strengths of DBS enable its application in most clinical and laboratory settings, and the removal of phlebotomy and the need for refrigeration have expanded biosampling to hard-to-reach and vulnerable populations. Weaknesses may limit adoption in the near term because DBS is a nontraditional sample often requiring conversion of measurements to plasma or serum values. Opportunities presented by novel methodologies may obviate many of the current limitations, but threats around the ethical use of residual samples must be considered by potential adopters.

SUMMARY: DBS provide a wide range of potential applications that extend beyond the reach of traditional samples. Current limitations are serious but not intractable.

Technological advancements will likely continue to minimize constraints around DBS adoption.

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Recent advancements in the quality and availability of highly sensitive analytical instrumentation have led to increased interest in the use of microsamples (i.e., biological samples of <50 µL) (1–3). Microsamples have been applied for basic and clinical research, public health, and clinical medicine (4–9). Interest in microsampling has been driven, in part, by the development of sophisticated computer software programs and methodological platforms for improved qualitative and quantitative analysis (10–13). Among microsampling methods, dried blood spots (DBS) are the most well-known and researched. DBS are a minimally invasive method for the collection of small quantities of whole blood from finger or heel stick with application to specially prepared filter paper for drying (14, 15). DBS samples do not require phlebotomy, and DBS can be stored and shipped under ambient conditions, although a comprehensive assessment of analyte stability has not been performed (16, 17). Existing stability studies for DBS, although limited, have demonstrated analyte stability across a wide range of storage conditions (18).

To date, DBS have a range of applications in clinical practice, basic research, and population-based research (4, 5, 15, 19, 20). The most common and widely accepted clinical use of DBS is for newborn screening programs, which are primarily concerned with the detection of metabolic disorders (21). Other clinical applications in the published literature have focused on HIV surveillance, therapeutic drug monitoring, and clinical chemistry (8, 21–24). Basic research applications for DBS include biomarker development and validation, drug discovery and development, forensic science, systems biology, and toxicology (5, 17, 25–27). Population-based research applications are variable but may be broadly categorized into human epidemiological studies and environmental population studies (5, 17, 26, 29).

1 National Health Mission Area, Johns Hopkins University Applied Physics Laboratory, Laurel, MD. 2 Welch Medical Library, Johns Hopkins University, Baltimore, MD. 3 Public Health Studies Program, Krieger School of Arts and Sciences, Johns Hopkins University, Baltimore, MD. 4 Department of Environmental Health and Engineering, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD. 5 Department of Molecular and Comparative Pathobiology, School of Medicine, Johns Hopkins University, Baltimore, MD.

* Address correspondence to this author at: JHUPL, 11100 Johns Hopkins Road, Room 21-3360, Laurel, MD 20723. Fax 410-955-6010; e-mail jeffrey.freeman@jhuapl.edu. Received May 9, 2017; accepted September 26, 2017.

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6 Nonstandard abbreviations: DBS, dried blood spots; SIR, scoping review of reviews; SWOT, Strengths, Weaknesses, Opportunities, and Threats; VOC, volatile organic compound.
Compliance: DBS vs. income
Self-collected dried blood spots as a tool for measuring ovarian reserve in young female cancer survivors

S.C. Roberts¹, S.M. Seav¹, T.W. McDade², S.A. Dominick¹, J.R. Gorman³, B.W. Whitcomb⁴, and H.I. Su¹,*

2) Clean Hands and Prepare Finger
- Wash your hands with hot water to remove any dirt or other substances. Also this helps to make sure your hands are very warm before starting the collection.
- Stand in front of the flat surface or table top with the collection materials in front of you.
- Choose your non-wringing hand to use for the collection.
- Shake your chosen hand downward for about 15 seconds to get the blood to collect in your fingers.
- Wipe the fleshy side of either your middle or ring finger of your chosen hand with the alcohol wipe.

3) Remove Cap from Lancet
- Twist the cap one full turn and pull until the cap comes off.

4) Performing the Finger Prick
- Place the lancet on the fleshy side (closer to the pinky rather than the thumb) of the chosen finger. By pricking the fleshy side facing the pinky, your hand will be in a more comfortable position to let the blood drops fall from your finger.
- Do NOT place the lancet in the middle of the finger pad or near the nail.
- Bring the thumb of the chosen hand up to tip of the chosen finger. Use the thumb to make the prick surface stretched tight.
- Hold lancet firmly against the fleshy portion of the chosen finger. Press lancet down until it "clicks".
- Milk the finger to make sure blood is flowing freely. To milk your finger, place your thumb at the bottom of the chosen finger, gently press down and slide your thumb up to the finger pad. Continue to slide your thumb up from the bottom to the finger pad.
- Using one gauze pad, wipe away the first drop of blood from the pricked finger.

5) Collecting the Blood Sample
- Gently milk the pricked finger and hold over one of the circles on the collection card.
- Wait for one large drop of blood to form. Let the blood drop fall to the middle of one of the circles on the collection card.
- Do NOT bring the paper up to catch the drop. Do NOT smear, blot, or place a second drop in a circle.
- Follow the steps above until all 5 circles have been filled with ONE large drop of blood per circle.

6) Mailing the Blood Sample
- Allow the collection card to air dry at least 2 hours at room temperature. If necessary, allow the card to dry overnight at room temperature.
- Place the collection card in the foil bag with the absorbent pouch.

Figure 1 Flow of the DBS study participants.

Thank you!
Bringing biology to population-based research

>50,000 DBS samples in past 15 years
DBS: New directions

Genome-Wide Profiling of RNA from Dried Blood Spots: Convergence with Bioinformatic Results Derived from Whole Venous Blood and Peripheral Blood Mononuclear Cells

Thomas W. McDade\textsuperscript{a,b,c}, Kharah M. Ross\textsuperscript{d}, Ruby L. Fried\textsuperscript{a}, Jesusa M. G. Arevalo\textsuperscript{a}, Jeffrey Ma\textsuperscript{a}, Gregory E. Miller\textsuperscript{a,b}, and Steve W. Cole\textsuperscript{a,f}

McDade et al. (2019). *J DOHaD.*

Use of Dried Blood Spots for Estimating Children’s Exposures to Heavy Metals in Epidemiological Research

William E Funk\textsuperscript{a}, Joachim D Pleil\textsuperscript{a}, Dana J Sauter\textsuperscript{a}, Thomas W McDade\textsuperscript{a} and Jane L Holl\textsuperscript{a}

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\textsuperscript{b}United States Environmental Protection Agency, National Exposure Research Laboratory/ORD, Research Triangle Park, NC, USA
\textsuperscript{c}Cabot Microelectronics, Aurora, IL USA
\textsuperscript{d}Department of Anthropology and Institute for Policy Research, Northwestern University, Evanston, IL, USA
Socializing biology

**Biosocial 2.0**  
Attend to developments in the clinical sciences; borrow as needed.

Broaden scientific and public understandings of human biology

- **Field-friendly methods for studying biology in “free-ranging” humans**
  - Get out of the clinic to foreground contextual factors as determinants of human biology, development, and health
  - Recruit more diverse and representative samples; engage communities in formulating questions, collecting data, and interpreting results
  - Ask novel research questions that are facilitated by methodological innovation
Socializing biology

**Biosocial 2.0**  
Attend to developments in the clinical sciences; borrow as needed.

Broaden scientific and public understandings of human biology

- Field-friendly methods for studying biology in “free-ranging” humans
- Using biology to document the impact of context and experience
Bringing biology to population-based research

Demographic factors
- Age
- Gender
- Socioeconomic status
- Race/ethnicity

Psychosocial factors
- Social relationships
- Stressor exposure (e.g., life events, discrimination)
- Cognitive/affective traits

Community factors
- Geographic setting, location
- Social capital
- Infrastructure

Health care
- Access
- Knowledge/trust

Cultural factors
- Shared beliefs, values, models of behavior

Biological mechanisms
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- Hypothalamic pituitary adrenal axis
- Cardiovascular system
- Metabolic processes
- Immune system
- Gonadal fn, regn

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- Diet, physical activity
- Smoking, alcohol/drug abuse
- Sleep patterns
- Risk taking
- Use of health services

Health outcomes
- Mortality
- Morbidity
- Fecundity/fertility
- Functional loss

Education is good for your health (but not for everyone?)

Depressive symptoms

Metabolic Syndrome by Race/Ethnicity

Biomarkers of CVD/diabetes

Gaydosh et al. (2017). *PNAS*.

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**The New York Times**

THE GREAT DIVIDE

Can Upward Mobility Cost You Your Health?

By GREGORY E. MILLER, EDITH CHEN and GENE H. BRODY

January 4, 2014 2:30 pm

The Great Divide is a series about inequality.

Americans love a good rags-to-riches story. Even in an age of soaring inequality, we like to think that people can still make it big here if they work hard and stay out of trouble. The socioeconomic reality of most of the last four decades — stagnant wages, soaring income and wealth inequality, and reduced equality of opportunity — have dented, but not destroyed, the appeal of the American dream.

Those who do climb the ladder, against the odds, often pay a little-known price: Success at school and in the workplace can exact a toll on the body that may have long-term repercussions for health.

Among American children there are wide socioeconomic gaps on many dimensions of well-being: school achievement, mental health, drug use, teenage pregnancy and juvenile incarceration, to name just a few. Despite the risks that lower-income children face, we also know that a significant minority beat the odds. They perform admirably in school, avoid drugs and go on to college.

Psychologists refer to these children as resilient, because they achieve positive outcomes in adverse circumstances. They do so in part by cultivating a kind of determined persistence. Often with nurturing from a parent, relative or mentor, they set goals for the future, work diligently toward them, navigate setbacks, stay focused on the long term and resist temptations that might knock them off the ladder to success.
**Socializing biology**

**Biosocial 2.0**

- Attend to developments in the clinical sciences; borrow as needed.

Broaden scientific and public understandings of human biology

- **Field-friendly methods for studying biology in “free-ranging” humans**
- **Using biology to document the impact of context and experience.**

  **Biomarkers as ethnographic tools to generate insight into the quality of social environments**

  **Identify subgroups of more vulnerable individuals, heterogeneity in responses to similar experiences**

  **Policy evaluation: Near term impacts and unintended consequences**
Socializing biology

**Biosocial 2.0**  ➔ Attend to developments in the clinical sciences; borrow as needed.

Broaden scientific and public understandings of human biology

- *Field-friendly methods for studying biology in “free-ranging” humans*
- *Using biology to document the impact of social context and experience*
- *Challenge simplistic understandings of biological causation*
RESEARCH ARTICLE

Genome-wide analysis of DNA methylation in relation to socioeconomic status during development and early adulthood

Thomas W. McDade\textsuperscript{1,2,3} | Calen P. Ryan\textsuperscript{1} | Meaghan J. Jones\textsuperscript{4,5,6} | Morgan K. Hoke\textsuperscript{7,8} | Judith Borja\textsuperscript{9,10} | Gregory E. Miller\textsuperscript{2,11} | Christopher W. Kuzawa\textsuperscript{1,2} | Michael S. Kobor\textsuperscript{3,4,5}
Epigenetics and the biological embedding of experience
Are molecular signatures of low SES detectable in the epigenome?
Cebu Longitudinal Health and Nutrition Survey

|---------|-------|-------|-------|-------|------|------|------|

Gen 2
n=3080

gestation → infancy → childhood → adolescence → adulthood

education, hh income, hh assets

DNA methylation (Illumina 450k array)
Results: SES and DNA methylation

Comparing low/low vs. high/high SES:

Total of 1,537 genes

1,777 CpG sites with increased methylation in low/low

769 CpG sites with reduced methylation in low/low

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**General themes**

- **Immune function**
- **Skeletal development**
- **Nervous system development**
Scientists still don’t agree on how many protein-making genes the human genome holds, but the range of their estimates has narrowed in recent years.

2,546 CpG sites across 1,537 genes
Genome-wide analysis of DNA methylation in relation to socioeconomic status during development and early adulthood

Thomas W. McDade1,2,3 | Calen P. Ryan1 | Meaghan J. Jones4,5,6 |
Morgan K. Hoke7,8 | Judith Borja9,10 | Gregory E. Miller2,11 | Christopher W. Kuzawa1,2 |
Michael S. Kobor3,4,5

Northwestern Now (//)

Poverty leaves a mark on our genes

Study's findings challenge understandings of genes as fixed features of our biology
April 05, 2019 | By Hilary Hurd Anyaso (//for-journalists/staff-page/showhilary-anyaso)

Poverty leaves a mark on nearly 10 percent of the genes in the genome.

A new Northwestern University study challenges prevailing understandings of genes as immutable features of biology that are fixed at conception.

Poverty plays role in DNA structure changes, study involving Northwestern professor finds

Children play in a slum in Cabu City, Philippines, the location of a study in which Northwestern anthropology professor Thomas McDade has been involved for nearly two decades. (Universal Images Group 2004)

By Elvia Malagon
Chicago Tribune
APRIL 5, 2019, 2:30 PM

Growing up in poverty can have such a lasting effect on a person's health that researchers have now determined it contributes to changing the person's gene structure, according to a newly published study co-authored by a Northwestern University professor.
Hi Dr. McDade:

I have a couple of follow up questions.

1) Study doesn't use the word, but would it be correct to conclude that the effect of poverty on genes is harmful? Why or why not?
2) Do you hope that this research will begin to make poverty viewed as a public health issue, similar to addiction? That is, that this is not just a personal failing or even strictly environmental but a biological component and must be addressed as such?

Thanks alot!

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CULTURE | PSYCHOLOGY

Why Poverty Is Like a Disease

Emerging science is putting the lie to American meritocracy.

BY CHRISTIAN H. COOPER
PHOTOGRAPHY BY NATHAN COOPER
APRIL 20, 2017
Socializing biology

Biosocial 2.0

Attend to developments in the clinical sciences; borrow as needed.

Broaden scientific and public understandings of human biology

- Field-friendly methods for studying biology in “free-ranging” humans
- Using biology to document the impact of social context and experience
- Challenge simplistic understandings of biological causation

Much work to be done here!
What determines health? Pre-class
What determines health? Post-class
Acknowledgments

Office of Population Studies, U San Carlos, Cebu

Institute for Policy Research, Northwestern

Canadian Institute for Advance Research

Research in Cebu

NIH (RO1 HL085144; RO1 TW05596; R01-AG039443)

NSF Physical Anthropology (BCS 1440564)