BIOGRAPHICAL SKETCH

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NAME: Horvath, Steve

eRA COMMONS USER NAME (credential, e.g., agency login): Horvath2

POSITION TITLE: Professor of Human Genetics and Biostatistics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Berlin, Berlin, Germany	BSc	06/1989	Mathematics/Physics
University of North Carolina, Chapel Hill, NC, USA	PhD	07/1995	Mathematics
Harvard School of Public Health, Boston, MA, USA	ScD	07/2000	Biostatistics

A. Personal statement.

Nature magazine published a feature article on my work entitled "Biomarker of ageing: The clock-watcher". I think the term "clock watcher" adequately captures my passion for developing molecular biomarkers of aging. My team published the first DNAm based biomarkers of aging in 2011. Two years later, I published the multi-tissue DNAm age estimator which has since been established as one of the most accurate and reproducible molecular biomarkers (Horvath 2013). Our recent results (Marioni, et al. 2015, Chen 2016) provide irrefutable evidence that DNAm biomarker must at least be indicators of fundamental aging processes that play a causative role in human aging. My lab is working on enhancing DNAm age estimators along multiple dimensions including a) to make them more predictive of health span, b) to make them more robust for in vitro studies, c) to understand the underlying molecular mechanism — the clockwork, and d) to adapt them to model organisms.

I have had the privilege of working with an extraordinary team of collaborators on molecular biomarkers of aging, human cohorts, genomics, anti-aging interventions, and a host of age related conditions. Since the development of the epigenetic clock method, I have co-authored 46 scientific articles on DNAm age estimators that cover many topics including Alzheimer's disease, Huntington's disease, heart disease, cancer, centenarians, cellular senescence, diet, Down syndrome, frailty, GWAS, HIV infection, menopausal hormone treatments, mortality prediction, obesity, progeria, stem cell transplantation, and telomeres.

I am also an epidemiologist and biostatistician/bioinformaticist. My group developed powerful prediction methods and systems biologic data mining methods, e.g. Weighted Correlation Network Analysis (WGCNA).

I have extensive experience analyzing a wide variety of different data including DNA methylation-, miRNA, copy number variation-, SNP-, tissue microarray-, proteomics-, RNA-seq data.

My group at UCLA has now developed a custom Mammalian Array on the Illumina platform that can be used to estimate the DNAm age across mammalian species. This has turned out to be an ideal tool for the aging study in mice, rats, dogs, swine, sheep, and other mammalian species.

1. Horvath S, Raj K DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nat Rev Genet. 2018 Jun;19(6):371-384. doi: 10.1038/s41576-018-0004-3. PMID: 29643443 PMCID: not yet available
2. Lu AT, Xue L, Salfati EL, Chen BH, Ferrucci L, Levy D, Joehanes R, Murabito JM, Kiel DP, Tsai PC, Yet I, Bell JT, Mangino M, Tanaka T, McRae AF, Marioni RE, Visscher PM, Wray NR, Deary IJ, Levine ME, Quach A, et al, Whitsel EA, Aviv A, Cardona A, Day FR, Wareham NJ, Perry JRB, Ong KK, Raj K, Lunetta KL, **Horvath** S (2018) GWAS of epigenetic aging rates in blood reveals a critical role for TERT.

Nat Commun. 2018 Jan 26;9(1):387. doi: 10.1038/s41467-017-02697-5. PMID: 29374233 PMCID: PMC5786029
3. Chen BH, Marioni RE, Colicino E, Peters MJ, Ward-Caviness CK, Tsai PC, Roetker NS, Just AC, Demerath EW, Guan W, Bressler J, Fornage M, Studenski S, Vandiver AR, Moore AZ, Tanaka T, Kiel DP, Liang L, Vokonas P, Schwartz J, Lunetta KL, Murabito JM, Bandinelli S, Hernandez DG, Melzer D, Nalls M, Pilling LC, Price TR, Singleton AB, et al, Absher D, Assimes T, Levine ME, Lu AT, Tsao PS, Hou L, Manson JE, Carty CL, LaCroix AZ, Reiner AP, Spector TD, Feinberg AP, Levy D, Baccarelli A, van Meurs J, Bell JT, Peters A, Deary IJ, Pankow JS, Ferrucci L, **Horvath** S (2016) DNA methylation-based measures of biological age: meta-analysis predicting time to death. Aging (Albany NY). 2016 Sep 28;8(9):1844-1865. doi: 10.18632/aging.101020. PMID: 27690265 PMCID: PMC5076441
4. **Horvath** S (2013) DNA methylation age of human tissues and cell types. Genome Biol. 2013 Oct 21;14(10):R115. PMCID: PMC4015143

B. Positions and Honors

Positions and Employment

12/1999–10/2000 Visiting Scientist (Postdoc level), Inst. for Medical Statistics University of Bonn
11/2000–07/2005 Assistant Professor in the Depts. of Hum Genetics & Biostats, Univ. of Calif., LA
08/2005–06/2009 Tenured Associate Professor in the Depts. of Hum Genetics & Biostats, Univ. of Calif., LA
07/2009–present Full Professor in the Depts. of Hum Genetics & Biostats, Univ. of Calif., LA

Honors

2014 Nature magazine published a feature article. http://www.nature.com/news/biomarkers-and-ageing-the-clock-watcher-1.15014
2016 Aging Cell Best Paper Prize 2015 for the article Horvath (2015) Accelerated Epigenetic Aging in Down Syndrome. Aging Cell. PMID: 25678027
2016 June 15, 2016 Presenter for the NIH Wednesday Afternoon Lecture Series on aging research
2017 April 2017. Allen Distinguished Investigator award for developing a universal epigenetic clock for vertebrates.

C. Contribution to Science

1. I have developed systems biologic methods for genomic data such as weighted correlation network analysis (WGCNA). I have written a Springer book entitled "Weighted Network Analysis: Applications in Genomics and Systems Biology" and offer a summer workshop on these methods. These network methods have been applied to a variety of different high dimensional data sets including gene expression data (both microarray based on RNA-seq based), gene methylation data, and proteomics data.

a. Zhang B, Horvath S (2005) A General Framework for Weighted Gene Co-Expression Network Analysis. Statistical Applications in Genetics and Molecular Biology. Vol. 4: No. 1, Article 17.
b. Horvath S, Dong J (2008) Geometric Interpretation of Gene Co-Expression Network Analysis. PLoS Computational Biology. 4(8): e1000117. PMCID: PMC2446438
c. Langfelder P, Horvath S (2008) WGCNA: an R package for Weighted Correlation Network Analysis. BMC Bioinformatics. 2008 Dec 29;9(1):559. PMCID: PMC2631488
d. Parikshak NN, Luo R, Zhang A, Won H, Lowe JK, Chandran V, Horvath S, Geschwind DH. Integrative functional genomic analyses implicate specific molecular pathways and circuits in autism. Cell. 2013 Nov 21;155(5):1008-21. PMCID: PMC3934107

2. I have developed several powerful epigenetic biomarkers of aging based on DNA methylation levels. The first publication described an epigenetic age predictor in saliva. After realizing that many aging effects are preserved between blood and brain tissue, I turned to the development of an age estimation method that applies to most human tissues and cell types. The resulting epigenetic clock method is the first age prediction method based on DNAm levels that accurately predicts age in more than one tissue or fluid. In the original article (Horvath 2013 PMC4015143), I presented several novel findings including the following

I. stem cells and iPS cells are perfectly young,
II. the epigenetic clock works in chimpanzees,

III. age acceleration effects (measured by the clock) are highly heritable,
IV. normal female breast tissue (adjacent to tumor) exhibits positive age acceleration effects while heart tissue appears younger,
V. cell passaging increases DNAm age,
VI. the ticking rate of the epigenetic clock is fastest during development,
VII. mutations in steroid receptors are associated with lower age acceleration effects in breast cancer tissue.

3. Using this epigenetic biomarker of aging, I was a first or senior author on articles that presented the first evidence that obesity accelerates the epigenetic age of liver tissue, that the epigenetic age of blood predicts all-cause mortality in later life, that HIV infection accelerates age, that the cerebellum ages more slowly than other brain regions, that menopause accelerates aging, and to find genome wide significant SNPs for epigenetic aging rates.

a. Horvath S, Erhart W, Brosch M, Ammerpohl O, von Schönfels W, Ahrens M, Heits N, Bell JT, Tsai PC, Spector TD, Deloukas P, Siebert R, Sipos B, Becker T, Röcken C, Schafmayer C, Hampe J (2014) Obesity accelerates epigenetic aging of human liver. Proc Natl Acad Sci U S A. 2014 Oct 13. PMCID: PMC4217403
b. Horvath S, Levine AJ (2015) HIV-1 infection accelerates age according to the epigenetic clock. J Infectious Diseases. 2015, Nov 15;212(10):1563-73. PMCID: PMC4621253
c. Horvath S, Mah V, Lu AT, Woo JS, Choi OW, Jasinska AJ, Riancho JA, Tung S, Coles NS, Braun J, Vinters HV, Coles LS (2015). The cerebellum ages slowly according to the epigenetic clock. Aging (Albany NY) Vol 7, No 5. PMCID: PMC4468311
d. Lu AT, Hannon E, Levine ME, Hao K, Crimmins EM, Lunnon K, Kozlenkov A, Mill J, Dracheva S, Horvath S (2016) Genetic variants near MLST8 and DHX57 affect the epigenetic age of the cerebellum. Nat Commun. 2016 Feb 2;7:10561. doi: 10.1038/ncomms10561. PMID: 26830004 PMCID: PMC4740877

Complete list of published work (more than 200 papers):
https://www.ncbi.nlm.nih.gov/pubmed/?term=Steve+Horvath%5BAuthor+-+Full%5D

D. Research Support

Ongoing Research Support

1U01AG060908 - 01 (PI: Horvath) 10/01/2018-09/30/2023
NIH/NIA
Validation and optimization of epigenetic clocks
The goal of the project is to validate and optimize human DNA methylation based biomarkers of aging for human interventional studies.

12349 Horvath (PI) 05/01/2017-05/01/2020
Paul G. Allen Family Foundation
Universal Epigenetic Aging Clock for Vertebrates
The goal of this project is to identify epigenetic biomarkers for aging that are conserved across mammals

U34AG051425-01 (PI: Horvath) 10/01/2015 - 09/30/2018
NIH/NIA
The epiGenetIcs Leads to aGe-relAted diseases (GILGA-mesh) Network
Goal: As part of this planning grant, we aim to design comprehensive and rigorous human studies that allow one to evaluate whether epigenetic mechanisms mediate the effect of chronological age on chronic diseases.

R01AG057912 (PI: Levine) 09/30/2017 - 05/31/2022
NIH/NIA
Molecular Networks Underlying Resilience to Alzheimer's Disease Among APOE E4 Carriers

Annual Direct Costs $1,189,957
Goal: We aim to identify molecular pathways and networks that confer protection against Alzheimer's Disease among individuals with at least one ApoE e4 allele. Toward this end, Dr Horvath will carry out statistical analyses and consult on the analysis of high-dimensional omics data from multiple-tissues and with respect to state-of-the-art systems biology approaches applies to epigenomic, transcriptomic, and proteomic profiles of resilient ApoE e4 carriers (those who escape AD) to carriers who develop AD.

R21 PA-16-161 (PI: Schaenman) 07/01/1706/30/19

NIH/NIAID

Evaluation of Epigenetic Markers of Biologic Age to Predict Adverse Outcomes after Transplantation

Goal: This project seeks to evaluate the immunologic and epigenetic changes in the older transplant recipient.

Role: Biostatistician

Completed Research Support

1R21AG049400 Horvath (PI) 06/01/16 – 05/30/18 (NCTE)
NIH/NIA
Epigenetic clock for measuring the DNA methylation age of mouse tissues
The goal of this study is to develop an epigenetic clock for mouse tissues.
Role: PI

R01AG042511 Horvath (PI) 07/01/13 – 06/30/17
NIH/NIA
Systems genetic and reverse phenotypic analysis of age and retirement
The goal of this study is to analyze SNP data from the Health and Retirement study (HRS) based on systems biologic methods (e.g. gene sets found in orthogonal genomic data).
Role: PI

R21AG046954 Horvath (PI) 09/15/15 – 09/15/17
NIH/NIA
Cross-Tissue Study of an Accelerated Epigenetic Aging Mechanism Caused by HIV
This proposal leverages the tissue samples from deceased HIV+ and HIV- subjects and the latest version of the well-validated Ilumina Infinium 450K array, allowing high-resolution genome wide DNAm profiles. Our overarching goal is to show that accelerated cellular aging, as measured by DNAm, has clinical relevance in the context of HIV/HANA.
Role: PI

P50CA092131 (Reiter) 07/01/13 – 08/31/18
NIH/NCI
UCLA SPORE in Prostate Cancer
The goal is to develop treatments and diagnostics for prostate cancer patients. As the director of the biostatistics and bioinformatics core, I am in charge of the analysis of related data, e.g. immunohistochemical data, RNA seq data, and designing clinical studies.
Role: Co-investigator

R25GM103774 (Papp) 05/01/13 – 04/30/17
NIH/NIGMS
Statistical Genomics and Systems Biology Workshop

The goal of this project is to organize yearly workshops on network methods and statistical genetics methods.
Role: As co-investigator, I am in charge of organizing several week-long network analysis workshops to be held at UCLA.

R21ES024356 Horvath (PI) 08/06/14 – 07/31/16
NIH/NIEHS
Environmental Exposure, DNA Methylation, and Parkinson's Disease
We refer to this as leaving a 'biological signature' evoked by exposures which we hypothesize to still be present when disease is diagnosed. Here we propose to use a powerful new tool and systems biology analytic methods to identify signatures for toxic exposures that evoke long-term biologic responses.
Role: PI