BIOGRAPHICAL SKETCH

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NAME: Witte, John Stuart

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

POSITION TITLE: Professor

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 California, Santa Barbara	BS	06/86	Mathematical Sciences
University of California, Berkeley	MS	05/88	Industrial Engineering & Operations Research
University of California, Los Angeles	PhD	04/94	Epidemiology
University of Southern California, Los Angeles	Postdoctoral	10/95	Biostatistics

A. Personal Statement

I have the appropriate scientific background and initiative for this project. Relevant to my role, I have extensive experience designing and undertaking large-scale genetic epidemiologic studies such as proposed here. My research program encompasses a synthesis of applied and methodological work, with the overall aim of deciphering the mechanisms underlying complex diseases and traits. My research is focused on evaluating pleiotropy, polygenic risk scores, and prostate cancer in large-scale cohorts of diverse populations.

Ongoing projects include:

- Understanding the **shared genetic basis of different cancers and diseases** (pleiotropy).
- Evaluating the contribution of **polygenic risk scores** to cancer risk and their transferability across diverse populations.
- Determining the **genetic basis of prostate cancer risk and aggressiveness** including across **ethnically diverse populations**.
- Developing **methods** for undertaking analyses of large data sets to detect genetic factors underlying complex phenotypes.

Other projects include searching for genes that impact drug / treatment response and evaluating the use of cell free DNA (liquid biopsies) to predict cancer risk and progression. In addition, I am a committed educator and have mentored over 50 pre- and post-doctoral fellows and direct courses in genetic epidemiology. In summary, I have the expertise, leadership, training, expertise and motivation necessary to successfully carry out the proposed research project.

Key ongoing and recently completed projects include:

R01 CA241410 (Witte) 4/1/2020-3/31/2024
NIH/NCI
Precision Prostate Cancer Screening with Genetically Adjusted Prostate-Specific Antigen Levels.
This project is undertaking a large-scale study to determine the genetic factors that predispose individuals to high prostate specific antigen levels independently of prostate cancer. With this information we can account for these genetic factors to personalize prostate specific antigen screening.
Role: PI

R01CA 201358 (Witte/Sakoda - MPI) 7/1/2016-6/30/2022
NIH/NCI
Genome-wide Pleiotropy Scan across Multiple Cancers
Growing evidence suggests that the same genetic risk factors may impact risk of multiple different cancers. We are investigating this by studying the co-inheritance and shared genetic basis of a large number of cancers from large cohort studies.
Role: PI.

U01 CA261339 (Conti/Witte MPI) 6/1/2021-5/31/2026
NIH / NCI
Title: Leveraging diversity in cancer epidemiology cohorts and novel methods to improve polygenic risk scores
The goal of this project is to address the need for appropriate PRS construction and evaluation across multiple race/ethnic groups by applying new PRS approaches to large-scale, longstanding cohorts.

P50CA180995 (Catalona-Prime PI) 9/25/2015 – 8/31/2021
Northwestern Univ. (NIH/NCI)
Impact of germline genetic variants and failure of active surveillance for prostate cancer
We propose to use genetics to gain clinically useful information concerning which men diagnosed with low-risk PC can be safely managed with AS and which should have early treatment.
Role: PI of subcontract, co-leader of Project 1.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021-present	Professor and Vice Chair, Department of Epidemiology & Population Health, Stanford University
2021-present	Professor, Department of Biomedical Data Science, Stanford University
2003-present	Professor, Department of Epidemiology & Biostatistics, UC San Francisco (UCSF)
2018-2021	Vice Chair, Department of Epidemiology and Biostatistics, UCSF
2008-2021	Head, Division of Cancer Epidemiology, UCSF
2005-2021	Co-Leader, Program in Molecular Oncology, Comprehensive Cancer Center, UCSF
1999-2003	Associate Professor, Division of Genetic and Molecular Epidemiology, Case Western Reserve
1995-1999	Assistant Professor, Division of Genetic and Molecular Epidemiology, Case Western Reserve

Other Experience

2013	Visiting Academic, Quantitative Genetics Group, University of Queensland
2011-present	Member, Editorial Board, Genetic Epidemiology
2008-present	Senior Editor, Cancer Epidemiology, Biomarkers & Prevention (Methods Section)
2008-2014	Member / Chair, CIDR Access Study Section, NIH
2007-2013	Board / Secretary, International Genetic Epidemiology Society
2004-2005	Editorial Board, Statistics in Medicine
2002-2006	Member, Epidemiology of Cancer Study Section (EPIC), NIH
2002-2003	Visiting Scientist, Genetic Epidemiology Group, IARC, Lyon, France
1996	Visiting Research Fellow, Genetic Epidemiology Unit, University of Melbourne, Australia

Honors

2018	Leadership Award, International Genetic Epidemiology Society
2017	Bob Millikan Memorial Lecture, University of North Carolina, Chapel Hill
2016	Up for a Challenge Award (leader of 'Team UCSF'), National Cancer Institute
2011	Stephen B. Hulley Award for Excellence in Teaching, UCSF
2002-2003	Visiting Scientist Award, International Agency for Research on Cancer
1999-2000	Glennan Fellow Award, Case Western Reserve University
1994	Ruth F. Richards Outstanding Student Award, UCLA School of Public Health
1989-1994	National Research Service Award, NIH
1986	Undergraduate Honors, University of California, Santa Barbara

C. Contributions to Science

1. **Deciphering the shared genetics underlying different cancers and traits**
   Another key aspect of my research is leveraging data from large population-based cohorts to demonstrate the extensive shared genetic basis of different cancers and other traits (pleiotropy). We have developed methods for studying pleiotropy and illustrated that individual variants and genomic regions show widespread pleiotropy, which may be leveraged to understand the biological basis of disease and improve screening and treatment.
   a. Majumdar A. Haldar T, Bhattacharya S, **Witte JS**. An efficient Bayesian meta-analysis approach for studying cross-phenotype genetic associations. PLoS Genetics 2018; 12;14(2):e1007139. PMCID: PMC5825176
   b. Wu YH, Graff RE, Passarelli MN, Hoffman JD, Ziv E, Hoffmann TJ, **Witte JS**. Identification of pleiotropic cancer susceptibility variants from genome-wide association studies reveals functional characteristics. Cancer Epidemiol Biomarkers Prev. 2018;27(1):75-85. PMCID: PMC5760292
   c. Rashkin SR, Graff RE, Kachuri L, Thai KK, Alexeeff SE, Blatchins MA, Cavazos TB, Corley DA, Emami NC, Hoffman JD, Jorgenson E, Kushi LH, Meyers TJ, Van Den Eeden SK, Ziv E, Habel LA, Hoffmann TJ, Sakoda LC, **Witte JS**. Pan-cancer study detects genetic risk variants and shared genetic basis in two large cohorts. Nat Commun. 2020;11:4423. PMCID: PMC7473862
   d. Kachuri L, Francis SS, Morrison M, Wendt GA, Bosse, Y, Cavazos TB, Rashkin SR, Ziv E, **Witte JS.** The landscape of host genetic factors involved in infection to common viruses. Genome Med 2020;12:93. PMCID: PMC7273301

2. **Polygenic Risk scores**
   My research program is also focused on evaluating the contribution of polygenic risk scores to cancer risk and their transferability across diverse populations. We have shown that polygenic risk scores can substantially improve prediction beyond modifiable risk factors, developed novel approaches to better characterize genetic variants exhibiting pleiotropy, and shown how incorporating ancestral information into analyses may improve the portability of PRS across populations to increase accuracy in ethnically diverse cohorts.
   a. Kachuri L, Graff RE, Smith-Byrne K, Meyers TJ, Rashkin SR, Ziv E, **Witte JS**, Johansson M. Integration of polygenic risk scores with modifiable risk factors improves risk prediction: results from a pan-cancer analysis. Nat Commun 2020; 11, 6084. PMCID: PMC7695829
   b. Mefford J, Park D, Zheng Z, Ko A, Ala-Korpela M, Laakso M, Pajukanta P, Yang J, **Witte J**, Zaitlen N. Efficient Estimation and Applications of Cross-Validated Genetic Predictions to Polygenic Risk Scores and Linear Mixed Models. J Comput Biol. 2020;27:4. PMID: 32077750
   c. Cavazos TB, **Witte JS**. Inclusion of Variants Discovered from Diverse Populations Improves Polygenic Risk Score Transferability. Human Genetics and Genomics Advances 2021; 2:1. PMCID: in process
   d. Graff RE, Cavazos TB, Thai KK, Kachuri L, Rashkin SR, Hoffman JD, Alexeeff SE, Blatchins M, Meyers TJ, Leong L, Tai CG, Emami NC, Corley DA, Kushi LH, Ziv E, Van Den Eeden SK, Jorgenson E, Hoffmann TJ, Habel LA, **Witte JS**, Sakoda LC. Cross-Cancer Evaluation of Polygenic Risk Scores for 17 Cancer Types in Two Large Cohorts. Nat Commun. 2021; 12:970. PMCID: in process. PMCID: PMC7869832.

3. **Prostate cancer: Genetics of prostate cancer development, aggressiveness, and disparities**
   I have led a series of projects delineating the genetic basis of prostate cancer. This includes comprehensive genome-wide studies of germline genetics and somatic genomics that have successfully detected loci underlying phenotypic variation in this complex disease. A key aspect of this work has been showing why African American men have increased prostate cancer risk and mortality.
   a. Hoffmann TJ, …, **Witte JS**. A large multi-ethnic genome-wide association study of prostate cancer identifies novel risk variants and substantial ethnic differences. Cancer Discovery 2015;5:878-891. PMCID: PMC4527942.
   b. Lindquist KJ, …, **Witte JS**. Mutational landscape of aggressive prostate tumors in African American men. Cancer Res; 2016;76:1860-18688. PMCID: PMC4772140.

c. Emami, NC, Kachuri L, Meyers TJ, Das R, Hoffman JD, Hoffmann TJ, Hu D, Shan J, Feng FY, Ziv E, **Witte JS**. Association of imputed prostate cancer transcriptome with disease risk reveals novel mechanisms. Nature Comm, 2019;15;10:3107. PMCID: PMC6629701
d. Emami NC, … , **Witte JS**. A large-scale association study detects novel rare variants, risk genes, functional elements, and polygenic architecture of prostate cancer susceptibility. Cancer Res. 2021; 81;7:1695-1703. PMCID: PMC8137514.

4. Methods for gene discovery

Another facet of my research is focused on statistical and epidemiologic methods for detecting genes underlying complex traits. This includes developing Bayesian hierarchical modeling and other tools to improve on conventional analyses of genetic association studies, and using machine learning to optimize sequence panels for genomic studies.

a. Conti DV, **Witte JS**. Hierarchical modeling of linkage disequilibrium: genetic structure and spatial relations. Am J Hum Genet 2003;72:351-363. PMCID: PMC379228.
b. Chen GK, **Witte JS**. Enriching the analysis of genomewide association studies with hierarchical modeling. Am J Hum Genet. 2007;81:397-404. PMCID: PMC1950795.
c. **Witte JS**, Visscher PM, Wray NR. The contribution of genetic variants to disease depends on the ruler. Nat Rev Genet. 2014;15(11):765-76. PMCID: PMC4412738.
d. Cario CL, Chen E, Leong L, Emami NC, Lopez K, Tenggara I, Simko JP, Friedlander TW, Li PS, Paris PL, Carroll PR, **Witte JS**. A machine learning approach to optimizing cell-free DNA sequencing panels: with an application to prostate cancer. BMC Cancer 2020; 20, 820. PMCID: PMC7456018

A comprehensive list of publications is available at: http://www.ncbi.nlm.nih.gov/sites/myncbi/1RuH-szbF9bQv/bibliography/47734976/public/?sort=date&direction=ascending.