BIOGRAPHICAL SKETCH

NAME: Bethany J. Wolf

eRA COMMONS USER NAME (credential, e.g., agency login): WOLFB1

POSITION TITLE: Associate 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
Rice University, Houston TX	B.A.	1995	Chemistry Anthropology
University of North Carolina, Wilmington NC	M.S.	2000	Chemistry
Medical University of South Carolina, Charleston SC	Ph.D.	2010	Biostatistics

A. Personal Statement

A majority of my effort is focused on collaborations with clinical and basic science faculty at the Medical University of South Carolina (MUSC). During my tenure at MUSC, I have played a significant role in obtaining funded extramural research grants, including two 5-year NIH/NCATS U01 clinical and translational sciences awards which fund the South Carolina Clinical and Translational Research Institute (SCTR) and NIH/NIAMS P30 and P60 Multidisciplinary Center for Clinical Research (MCRC) and Core Centers for Clinical Research (CCCR) grants with the Division of Rheumatology. I am the Associate Director of the Methodologic Core for the CCCR and the Biostatistics Core for SCTR. The primary goals of the CCCR Methodologic Core and SCTR Biostatistics Cores are to provide statistical support for clinical and basic scientist across the MUSC campus, develop new statistical approaches to address methodology issues that arise during clinical collaborations, and to provide statistical education to non-statisticians across campus. Through my involvement in these cores, I have the opportunity to interact with faculty across a multitude of disciplines to design research studies, develop analysis plans for grant proposals, conduct data analysis, and collaborate in writing manuscripts. Additionally, I serve as the primary statistician for the Department of Anesthesia and Perioperative Medicine, providing statistical guidance in the design, implementation, evaluation, and dissemination of results for research projects conducted within the department. Since my faculty appointment, I have published more than 100 peer reviewed papers. Twenty-three of these manuscripts provide contributions to the fields of statistics and/or informatics and the remainder are collaborative clinical and basic science manuscripts, a majority of which I was the lead statistician. I am also a co-investigator 9 NIH, DOD, or VA funded grants, and as a result have consistently maintained over 90% funding through extramural grants and other funds.

I have been a driving force for methodology development for the CCCR and SCTR to address the statistical need of our collaborators. My three primary research areas for statistical methods are (1) rigorous and robust prediction model development, (2) statistical methods for genomic analysis, and (3) statistical evaluation of dichotomization for clinical decision making.

- *Prediction Modeling*: My research in prediction modeling focuses on rigorous development of prediction models and on advancing machine learning approaches to address data complexities such as repeated measures. There are often numerous therapeutics for treating specific diseases as patients do not always respond equally. Statistical approaches to optimize person-specific treatment recommendations must be sufficiently flexible to allow for complex relationships between predictors and the outcome to address heterogeneity, provide good prediction within and between treatment regimens, and allow for unbiased selection of an optimal subset of predictors. I have developed a unified modeling framework to address these issues by simultaneously applying multiple modeling approaches, cross-validated variable selection, and external model validation to yield robust, reproducible models developed in a rigorous manner while optimizing performance both across and within treatments. I have applied this approach to model of treatment response in lupus nephritis using histology information or urine biomarkers resulting in a publication in *Lupus Science & Medicine* and another manuscript recently published in *Kidney International*. I have also submitted an NIH R03 in collaboration with a clinical psychologist at MUSC to

apply this approach to data from a multi-center clinical trial comparing smoking cessation therapies to provide patient-specific treatment recommendations.

- Machine learning models offer greater flexibility compared to traditional regression models but often fail to address correlation between repeated outcome measures within patients. My former student, Dr. Jaime Speiser, and I extended decision tree and ensemble methods for application to repeatedly measured binary outcomes. We initially developed a decision tree framework for clustered and longitudinal binary outcomes by iterating between a decision tree model and a generalized linear mixed model to account for the correlation in the outcome, a method referred to as Binary Mixed Model Trees (BiMM Trees). This approach was further extended BiMM Tree o an ensemble framework. These methods have been published in *Communication in Statistics- Simulation and Computation* and *Chemometrics and Intelligent Laboratory Systems*.

- *Statistical Methods for Genomics*: Genome-wide association studies (GWAS) have been successful in finding thousands of disease-associated genetic variants. However, complex diseases are often associated with many single nucleotide polymorphisms (SNPs) with small effect sizes making associations difficult to detect. Current statistical methods are also limited in explaining the functional mechanisms through which SNPs are associated with diseases. To address these challenges, my former student, Dr. Aastha Khatiwada and I developed GPA-Tree, a statistical approach that utilizes a hierarchical model to integrate GWAS summary statistics and functional annotation information within a unified framework. In simulations, GPA-Tree shows increased area under the curve (AUC) and higher power to detect risk-associated SNPs. Furthermore, GPA-Tree is also able to identify combinations of functional annotations relevant to the risk SNPs and disease, facilitating understanding of potential mechanisms linking risk-associated SNPs with the complex diseases. This work has recently been resubmitted to *Bioinformatics* and an R-shiny app has been developed for easy implementation of the GPA-Tree software.

- *Dichotomization for Clinical Decision Making*: Despite ubiquitous use of dichotomization in clinical settings, criticisms based on statistical issues are widespread. However, given the widespread use in clinical practice, blanket dismissal of the practice of dichotomization may not be advisable. In statistical prediction, there is always loss of information when estimation is performed from a random sample from a population. However, dichotomizing does not always lead to a greater information loss compared to using a predictor in its continuous form. Quantification of information loss, especially when used to predict a binary outcome (e.g. disease status) could provide a formal rationale refuting or supporting the practice. My former student, Peter Greene, and I developed a parameter for quantifying the relative loss (*RL*) in information for estimating the probability of a binary outcome using the continuous and dichotomous versions or a predictor. As *RL* is not directly calculable, we also developed a statistic for estimating the relative loss and proposed a hypothesis testing framework for evaluating whether the continuous or dichotomous formulation of a predictor provides better estimation of a binary outcome. The hypothesis test was applied to evaluate dichotomizing age at first cannabis use for estimating the probability of psychotic experiences later in life and found that sufficient information was retained to discriminate risk of a psychotic experience when age at first use is dichotomized at $\geq$ 15 versus > 15. This work is currently under review in *Biometrics*.

B. Positions and Honors

Positions and Employment

1995-1997	Research Chemist, TBC-Brinadd, Houston, TX
1998-1999	Teaching Assistant, University of North Carolina, Wilmington
1999-2000	Research Assistant, University of North Carolina, Wilmington
2000-2005	Research Chemist, Sun Chemical, Charleston SC
2005-2010	Graduate Research Assistant, Medical University of South Carolina
2010	Post-doctoral Scholar, Medical University of South Carolina
2010-2017	Assistant Professor of Biostatistics, Medical University of South Carolina
2018-present	Associate Professor of Biostatistics, Medical University of South Carolina

Other Experience and Professional Memberships

2008-2015 Member American Statistical Association

Honors

1994-1995 Presidents Honor Roll
2002 Bayer award for performance "Above and Beyond"
2002-2005 Making Science Make Sense
2006 Awarded AAAS membership
2006 First Place, Student research day, PhD poster session 11
2008 First Place, Student research day, PhD oral session 7
2008 Awarded Sigma Xi membership
2008 Bioinformatics Award, MUSC student research day 2008
2014-present Chapter Representative for the South Carolina American Statistical Association

C. Contribution to Science

Translational Science: As a member of the Biostatistics, Epidemiology, and Design Core within MUSC's CTSA program, I have collaborated with basic science and clinical faculty in multiple disciplines. The work listed below provides recent collaborations with both clinical and basic science researchers at MUSC and collaborating institutions.

1. Khatiwada A, **Wolf BJ**, Mulligan J, Shary JR, Hewison M, Baatz JE, Newton DA, Hawrylowicz C, Hollis BW, Wagner CL (2021). Effects of Vitamin D Supplementation on Circulating Concentrations of Growth Factors and Immune-mediators in Healthy Women during Pregnancy. Pediatric Research, 89(3):554-562, . doi: 10.1038/s41390-020-0885-7.
2. Elmunzer BJ, **Wolf BJ**, Scheiman JM, Tierney WM, Taylor JR (2021). Association between pre-admission acid suppressive medication exposure and severity of illness in patients hospitalized with COVID-19. Gastroenterology, 160(4): 1414-1422, doi: 10.1053/j.gastro.2020.11.007, PMCID: PMC7659802.
3. Moake M, Presley BC, Hill JG, **Wolf BJ**, Kane ID, Busch CE, Jackson BF (2020). Point-of-Care Ultrasound to Assess Gastric Content in Pediatric Emergency Department Procedural Sedation Patients. Pediatric Emergency Care, doi: 10.1097/PEC.0000000000002198. Epub ahead of print. PMCID: PMC7854775.
4. Srivastava P, Solanki AK, Arif E, **Wolf BJ**, Janech MG, Budisavljevic MN, Kwon SH, Nihalani D (2019). Development of a novel cell-based assay to diagnose recurrent Focal and Segmental Glomerulosclerosis. Kidney International, 95(3):708-716. PMCID: PMC6396290.

Genetics and Genomics: Both my statistical methodology research and my clinical collaborations have involved development and application of statistical tools for analysis of genetics data. As faculty in the department of Public Health Sciences, I have engaged in collaborations examining improvements in genetic analysis through integrated genomic analysis pipelines. Additionally though MUSC's CTSA program I have collaborated on several studies that have led to discovery and validation of genetic markers of patient response in different patient populations. Examples of this work are provided below.

1. Khatiwada A, **Wolf BJ**, Yilmaz AS, Ramos PS, Pietrzak M, Lawson A, Hunt KJ, Kim HJ, Chung D. GPA-Tree: Statistical Approach for Functional-Annotation-Tree-Guided Prioritization of GWAS Results. *Bioinformatics,* 2021 Nov 26:btab802. doi: 10.1093/bioinformatics/btab802. Epub ahead of print. PMID: 34849578.
2. Hardiman G, Savage SJ, Hazard ES, daSilveira WA, Wilson RC, Caulder S, Ambrose L, Frey L, **Wolf B**, Gattoni-Celli S, Halbert CH. A precision medicine approach to interrogate gene expression patterns in African American men presenting with early stage prostate cancer. *Cancers*, 2021 Oct 14;13(20):5143. doi: 10.3390/cancers13205143. PMID: 34680291; PMCID: PMC8533960.
3. Rohrer B, Parsons N, Balasubramaniam A, Schnabolk G, Tomlinson S, **Wolf BJ** (2019). Association of age-related macular degeneration with complement activation products, smoking, and single nucleotide polymorphisms in South Carolinians of European and African descent. Molecular Vision, 25: 79-92, PMCID: PMC6377374.

4. **Wolf BJ**, Ramos PS, Nietert PJ, Hyer MJ, Ramakrishnan V, Gilkeson GS, Hardiman GT, Kamen DL (2018). An analytic approach using candidate gene selection and Logic Forest to identify gene by environment interactions (GxE) for systemic lupus erythematosus in African Americans. Genes, 9(10), 496; https://doi.org/10.3390/genes9100496, PMCID: PMC6211136.

Rheumatology: As the associate director of the Methodology core of MUSC's CCCR for Improving Minority Health in Rheumatic Diseases, I have collaborated with basic science and clinical faculty to improve understanding of the development and progression of rheumatologic diseases as well as a focus on identifying patient populations likely to respond to therapy. The work listed below provides examples of my collaborations with both clinical and basic science researchers from the rheumatology research base.

1. Ayoub I, **Wolf BJ**, Geng L, Song H, Khatiwada A, Tsao BP, Oates JC, Rovin BH (2021). Prediction Models of Treatment Response in Lupus Nephritis. *Kidney International*, 2021 Dec 3:S0085-2538(21)01079-6. doi: 10.1016/j.kint.2021.11.014. Epub ahead of print. PMID: 34871620.
2. Helget LN, Dillon DJ, **Wolf BJ**, Parks LP, Self SE, Bruner ET, Oates EE, Oates JC. Development of a lupus nephritis one-year outcome prediction tool using renal histopathologic and clinical laboratory variables at the time of diagnosis. Lupus Science & Medicine. 2021 Aug;8(1):e000489. doi: 10.1136/lupus-2021-000489. PMID: 34429335
3. Nowling TK, Kral M, **Wolf B**, Gilkeson G, Ruth NM (2021). Formal neurocognitive function and anti-N-methyl-D-aspartate receptor antibodies in paediatric lupus. Lupus Sci Med, 8(1):e000462, PMCID: PMC799320.
4. Nowling TK, Rodgers J, Thiyagarajan T, **Wolf B**, Bruner E, Sundararaj K, Molano I, Gilkeson G (2020). Targeting glycosphingolipid metabolism as a potential therapeutic approach for treating disease in female MRL/lpr lupus mice. PLoS One, 15(3), PMCID: PMC7080257.

Opiate and Addiction Research: I also work closely with the Department of Anesthesia and Perioperative Medicine and the Department of Psychiatry at MUSC. Predominant research foci include reduction of in-hospital opiate consumption during common surgical procedures, for example cesarean sections, and personalized medicine approaches for addiction. Examples of this work are provided below.

1. Luo Z, Fitting S, Robinson C, Benitez A, Li M, Wu Y, Fu X, Amato D, Ning W, Fundeburg N, Wang X, Zhou Z, Yu X, Wagner A, Cong X, Xu W, Maas K, **Wolf BJ**, Yu J, Scott A, Merae-Clark A, Hamlett E, Jiang W (2021). Chronic cannabis smoking-enriched oral pathobiont drives behavioral changes, macrophage infiltration, and increases β-amyloid protein production in the brain. EBioMedicine. 2021 Nov 23;74:103701. doi: 10.1016/j.ebiom.2021.103701. Epub ahead of print. PMID: 34826801; PMCID: PMC8626580.
2. Jones SK, **Wolf BJ**, Froeliger B, Wallace K, Carpenter M, Alberg AJ (2021). Nicotine metabolism predicted by CYP2A6 genotypes in relation to smoking cessation: A systematic review. Nicotine Tob Res. 2021 Sep 3:ntab175. doi: 10.1093/ntr/ntab175. Epub ahead of print. PMID: 34478556.
3. Killeen TK, **Wolf B**, Greer TL, Carmody T, Rethorst CD, Trivedi MH (2020). Gender and racial/ethnic differences in physiologic responses in the Stimulant Reduction Intervention using Dosed Exercise Study. Addict Behav. 2020 Nov;110:106546. doi: 10.1016/j.addbeh.2020.106546. PMCID: PMC7416606.
4. Wilson SH, **Wolf BJ**, Robinson S, Bingham KJ, Nelson C, Hebbar L (2019). Intravenous versus Oral Acetaminophen for Analgesia after Caesarean Delivery: A Randomized Trial. Pain Medicine, 20(8): 1584-1591, PMID: 30561704.

Statistical Methods. The main focus of my biostatistics methods research is on the development of novel statistical and machine learning methods for identifying complex relationships among risk factors for diseases with low heritability. Much of my methodology research focuses on decision tree-based methodology as decision trees are capable of modeling the complex interactions that occur between risk factors, for example biologic networks, that may predict disease outcomes. Additionally, I am working on developing efficient methods for developing diagnostic and prognostics tests for determining patient disease status based on multiple clinical markers. The articles listed below highlight some of the work in this area.

1. Khatiwada A, **Wolf BJ**, Yilmaz AS, Ramos PS, Pietrzak M, Lawson A, Hunt KJ, Kim HJ, Chung D. GPA-Tree: Statistical Approach for Functional-Annotation-Tree-Guided Prioritization of GWAS Results.

Bioinformatics, 2021 Nov 26:btab802. doi: 10.1093/bioinformatics/btab802. Epub ahead of print. PMID: 34849578.

2. **Wolf BJ,** Jiang Y, Wilson SH, Oates JC (2020). Variable selection methods for identifying predictor interactions in data with repeatedly measured binary outcomes. J Clin Transl Sci. 2020 Nov 16;5(1):e59. doi: 10.1017/cts.2020.556. PMCID: PMC8057419.
3. Speiser JL, **Wolf BJ**, Chung D, Karvellas C, Koch DG, Durkalski V (2019). BiMM forest: A random forest method for modeling clustered and longitudinal binary outcomes. Chemometrics and Intelligent Laboratory Systems, 185: 122-134; PMCID: PMC6813794.
4. **Wolf BJ**, Ramos PS, Nietert PJ, Hyer MJ, Ramakrishnan V, Gilkeson GS, Hadriman GT, Kamen DL. An analytic approach using candidate gene selection and Logic Forest to identify gene by environment interactions (GxE) for systemic lupus erythematosus in African Americans. Genes, 9(10), 496; https://doi.org/10.3390/genes9100496

Complete List of Published Work in MyBibliopgraphy:
https://www.ncbi.nlm.nih.gov/myncbi/bethany.wolf.1/bibliography/public/

D. Research Support

Ongoing Research Support

NIH P30AR072582 Gilkeson (PI: Gilkeson G) 09/01/2017 – 08/31/2022
CCCR Improving Minority Health on Rheumatic Diseases
Methodology Core (PI: Nietert/Wolf)
The goal of this MCRC is the advancement of knowledge with respect to African Americans who have, or who are at risk of developing, systemic lupus erythematosus, systemic sclerosis, and other debilitating rheumatic diseases. The overall objective of this Core is to provide rigorous methodological and biostatistical support to the MCRC investigators and to lead investigations into racial/ethnic components of rheumatic disease that are focused in methodological areas including studies of gene x gene and gene x environment interactions.
Role: Associate Director of the Methodology Core

1UL1TR001450-02 (PI: Brady K) 08/13/2015 – 03/31/2025
NIH/NCATS
South Carolina Clinical and Translational Research Institute (SCTR)
Methodologic Core (PI: Nietert/Wolf)
SCTR is the catalyst for changing the culture of biomedical research, facilitating sharing of resources and expertise, and streamlining research-related processes to bring about large-scale change in the clinical and translational research efforts in South Carolina.
Role: Co-investigator

R01 AR071947 (PI: Oates JC/Rovin BH/Tsao B) 05/27/2018 – 04/30/2023
NIH/NIAMS
Predictive Biomarkers for disease activity and organ damage in patients with lupus
Goals: The goal of this CCCR is the advancement of knowledge with respect to African Americans who have, or who are at risk of developing, systemic lupus erythematosus, systemic sclerosis, and other debilitating rheumatic diseases. The overall objective of this Core is to provide rigorous methodological and biostatistical support to the CCCR investigators and to lead investigations into racial/ethnic components of rheumatic disease that are focused in methodological areas including studies of gene x gene and gene x environment interactions.
Role: Co-investigator

U54GM104941 (PI: Hicks GE) 09/01/2013 – 05/31/2023
NIH/NCATS
Delaware Clinical and Translational Research Program (DE-CTR)
Goal: The overall goal the Delaware CTR is to provide a research infrastructure for clinical and translational research. MUSC is the out-of-state participant in a Delaware consortium. The objective of this infrastructure grant is to build the translational research infrastructure at each institution and establish new collaborative

research relationships between investigators from MUSC and the University of Delaware-led consortiumthus relieving the burden of increased health care costs for these patients and improving their quality of life.
Role: Co-Investigator

R56MH124744 (PI: Obeid J) 08/15/2017-06/30/2022
NIH/NIMH
Leveraging Deep Learning and Clinic Notes for Surveillance and Prediction of Intentional Self-Harm and Suicide
Goals: The aims in this project are to improve the phenotyping of suicidal behavior and to predict future suicidal behavior and suicide deaths by integrating mortality data with EHR data and leveraging state-of-the-art natural language computational approaches. We will also investigate methods for explain ability and interpretability of the models to improve future adoption by clinicians. Models will be validated by examining reproducibility and generalizability across two health systems using similar data at both sites.
Role: Co-Investigator

R21 CA263464 (PI: Angel P) 09/01/2021-08/30/2023
NIH/NCI
Cellular Sources of Pathological Stromal Variants
Goals: The goal is to identify collagen structure variants contributing to hepatocellular carcinoma pathology and outcomes.
Role: Co-Investigator

R01MD015395 (PI: Ramos P) 07/01/2021 – 06/30/2026
NIH
Social Factors, Epigenomics, and Lupus in African American women (SELA)
Goals: Systemic lupus erythematosus (SLE, or lupus) is a chronic multisystem autoimmune disease characterized by the production of autoantibodies, disproportionately affecting women and African Americans, with whom it is associated with significant mortality and morbidity, and without safe and effective treatments. This project seeks to identify and characterize the epigenetic mechanisms by which positive and negative social experiences affect gene function and thereby influence SLE in African American women.
Role: Co-Investigator

LRA (PI: Sanz I, Emory) 09/01/2021-08/31/2024
Lupus Research Alliance
Heterogeneity in African Ancestry SLE: Implications for Targeted Therapy
Goals: The over-arching goal is to elucidate the B cell undergirding of SLE heterogeneity in unique cohorts of African American patients (AA), a population with the highest concentration of severe disease. We shall: 1) determine the mechanistic contribution of B cells and PC to the clinical heterogeneity of SLE; 2) establish the value of phenotypic, functional and molecular B cell and PC profiles as biomarkers/correlates of different types of disease; and 3) demonstrate their utility to design and monitor targeted therapeutic strategies. Furthermore, we will determine the role of the microbiome in disease heterogeneity; and its correlation with B cell variables associated with disease heterogeneity.
Role: Co-Investigator

1R21AR079765 (PI: Feghali-Bostwick/Angel) 07/01/2018-06/30/2023
NIH
Development of proteomic-based ECM signatures for lung fibrosis
Major Goals: We propose to use a novel collagen-targeting proteomic approach to localize and measure collagen types and post-translational modifications within the lung tissues of patients with IPF and SSc, and examine the functional implications of these changes in primary fibroblasts.
Role: Co-Investigator

<u>Completed Research Support</u>
P60 AR062755 7/1/2012-6/30/2017

NIH/NIAMS PI: Gilkeson, G
MCRC for Rheumatic Diseases in African Americans: Methodology Core
The objective of this study is to advance the understanding of role of genetic and environmental factors play in development and progression of rheumatic diseases with particular focus on racial and geographic disparities.
Total Cost / Percent Effort: $911,728 / 20%
Role: Biostatistician

MUSC SCTR#1616 Spyropoulos (PI) 6/6/2016-6/5/2017
The Obesogenic Potential of DOSS: a Low-Risk/High-Benefit Approach to Managing Obesity.
Goals: The aim of this project is to study the contribution of DOSS Obesogen to maternal and offspring obesity. If DOSS is found to be a significant contributor, diet and exercise intervention studies can be augmented by controlling DOSS intake for the potential of a low-risk, high-benefit approach.
Role: Co-Investigator

UL1RR029882 12/6/10-3/31/2014
NIH/NCRR PI: Brady, K
South Carolina Clinical & Translational Research Institute (SCTR)
This project provides infrastructure to our university in order to advance clinical and translational research.
Total Cost: $20,827,235 / 60% FTE
Role: Biostatistician

NIH/NINDS/Emory University Frankel (PI) 10/2/14-4/30/17
BIO-ProTECT:
Biomarkers of Injury and Outcome in ProTECT III
Goals: The objective of the study is to provide statistical and data management support for the investigation of biomarkers associated with outcome following traumatic brain injury.
Role: Biostatistician

VA247-12-C-0289 09/30/2010 – 09/28/2014
VAMC PI: Oates, J.
Urine biomarkers of lupus nephritis pathology and response to therapy
The objective of this proposal is to identify noninvasive urine protein markers of disease that are indicative of renal pathology and response to therapy in lupus nephritis. Multiple low abundance proteins are also being analyzed. To increase predictive power in this heterogeneous disease, artificial neural network modeling is being used to create diagnostic and predictive models of disease and response to therapy.
Total Cost: $146,043 / 5% FTE
Role: Biostatistician

IRG-97-219-11 06/01/10-11/30/10
ACS-IRG PI: Kistner-Griffin, E
Exploring cancer pathways using ensembles of tree-based classifiers
This project develops, implements and evaluates new statistical methodology to explore gene-gene interactions for identification of genetic subpopulations among cancer patients.
Role: Post-Doctoral Scholar

T32GM074934 8/15/05-8/15/07
NIH/NIGMS PI: Slate, EH
Biostatistics Training for Basic Biomedical Research
This grant focused on training new biostatisticians to assume key roles in the "omics" era of biomedical research by stressing integration of biostatistical theory and methods with tools from bioinformatics to address quantitative frontiers in modern multi-disciplinary biological research.
Role: Graduate Research Assistant

K25DE016863 8/15/07-8/15/08