Yizhe (Crystal) Xu

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Education

Ph.D. in Population Health Sciences, with Emphasis in Biostatistics: University of Utah. 2016.8 – 2020.8

- Dissertation:
    - Chapter I: *Estimating the Optimal Individualized Treatment Rule from A Cost-Effectiveness Perspective with An Application to the Systolic Blood Pressure Intervention Trial (SPRINT).*
    - Chapter II: *A Conditional Random Forest Approach to Estimating the Most Cost-effective Individualized Treatment Rule with An Application to Treating Patients in High Cardiovascular Risk Condition with Standard or Intensive Blood Pressure Control.*
    - Chapter III: *Covariate Selection for Statistical Adjustment in Cost-effectiveness Analysis.*
- Mentors: Jincheng Shen and Tom Greene.
- Coursework: Modern Causal Inference (Applied & Theory), Machine Learning, Analysis of Secondary Data, Multilevel data, Grant Writing, etc.

M.S. in Biostatistics: University of Utah. 2014.8 – 2016.12

- Coursework: Linear Models, Survival Analysis, Longitudinal Data Analysis, Categorical Data Analysis, Advanced Research Design, Epidemiology, etc.

B.S. in Nursing: Liaoning Medical University. 2008.9 – 2012.6

Awards

1. Joint Statistical Meeting, Student Paper Award, Health Policy Statistics Section, Virtual Conference, 2021
2. Student Travel Award, ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop Program, Washington D.C., USA, 2019.
3. The University of Utah, Master of Statistics-Biostatistics Student of the Year, 2017.
4. Liaoning Medical University, Student of the Year, 2011.

Work Experience

Stanford University: Center for Biomedical Informatics Research (BMIR). Postdoc for applying statistical learning tools to personalize cardiovascular treatment funded by the R01 grant (NHLBI R01). 2020.11 – now.

University of Utah: Department of Population Health Sciences (PHS). Postdoc for the Optimize-SPRINT study and SPRINT-MIND study funded by the R01 grant (HL139837 01). 2020.8 – 2020. 10.

University of Utah: Department of Population Health Sciences (PHS). Graduate assistant for the Optimize-SPRINT study funded by the R01 grant (HL139837 01). 2018.5 – 2020.8.

Veteran Affairs (Salt Lake City): Value & Epidemiology Research Using Causal Inference and Data Science (VERITAS). Research assistant. 2017.5 – 2020.8.

University of Utah: Study Design and Biostatistics Center (SDBC). Graduate assistant. 2016.6 – 2019.4.

University of Utah: Department of Family and Preventive Medicine (FPMD). Research assistant. 2014.5 – 2016.5

Feng Tian Hospital (China): Registered nurse. 2011.7 – 2012.5

Research Interests

- <u>Precision medicine</u>: heterogeneous treatment effect (HTE), individualized treatment rule (ITR) in randomized controlled trials and observational studies
- <u>Causal inference</u>: Propensity score matching/weighing, doubly robust estimation (DR), dynamic treatment regime (DTR), etc.;
- <u>Statistical machine learning</u>: random (survival) forest, causal (survival) forest, Bayesian additive regression tree, gradient boosting machine, elastic-net, deep neural network, etc.;
- <u>Survival analysis</u>;
- Cost-effectiveness analysis;
- <u>Applied Statistics</u>: cardiovascular disease, comparative effectiveness research, pharmaco-epidemiological studies.

Skills

- Proficient in statistical software R, SAS, and Stata. Basic use of Python and SQL.
- Proficient in high-performance computing using SLURM and Putty (for analyzing large-scale datasets or developing extensive simulations).
- Proficient in LaTeX.
- Comprehensive training in scientific writing and grant writing.
- Advanced Chinese and English (conversation, reading, and writing).

Research Experience

University of Utah (SDBC & Department of PHS):

1. Dissertation Chapter I: Estimating the Optimal Individualized Treatment Rule from A Cost-Effectiveness Perspective.

   - **Summary**: The aim is to estimate the most cost-effective treatment rule that considers the trade-off between health gains and added costs of interventions while accounting for individual heterogeneity. I extend the idea of an individualized treatment rule (ITR) to a cost-effectiveness (CE) study and propose a weighted decision-tree-based classification method to provide a nonparametric estimation of the optimal ITR. I define the classification weights using a net-monetary-benefit (NMB)-based reward and propose approaches to estimating the weights as a function of subject characteristics.

2. Dissertation Chapter II: A Conditional Random Forest Approach to Estimating the Most Cost-effective Individualized Treatment Rule.

   - **Summary**: The goal is to improve the performance of the proposed method in Dissertation Chapter I for estimating the optimal individualized treatment rule. I propose an advanced NMB-based classification algorithm to identify the optimal CE ITR, where a conditional random forest method is applied to prevent overfitting and instability and ensure estimation performance. Furthermore, I propose two partitioned estimators for the subject-specific classification weights to effectively incorporate information from censored subjects, thus improving estimation efficiency.

3. Dissertation Chapter III: Covariate Selection for Statistical Adjustment in Cost-effectiveness Analysis.

   - **Summary**: I extend the causal graph theory and graphical separation rules to a cost-effectiveness study to identify a sufficient covariate set that attenuates structural bias. I use Directed Acyclic Graphs and causal graphical separation rules to demonstrate the causal structures of cost-effectiveness studies and the resulting sources of bias. I extend the back-door path criterion to CE analyses and propose two covariate selection strategies for adjustment by considering the relationships between the sufficient covariate adjustment sets for quality-adjusted-life-years and cost.

4. Adam P. Bress, Tom Greene, Catherine G. Derington, Jincheng Shen, **Yizhe Xu**, Yiyi Zhang, Jian Ying, Brandon Bellows, Rachel Hess, Jennifer Herrick, Zugui Zhang, Paul Kolm, Robert Yeh, Sanjay Basu, William S. Weintraub, and Andrew E. Moran; for the SPRINT Research Group. Patient Selection for Intensive Blood Pressure Treatment Based on Benefit and Harm in Systolic Blood Pressure Intervention Trial (SPRINT) (R01 grant (HL139837 01)).

   - **Summary**: The goal of this study is to develop and validate a clinical decision tool that accurately discriminates between expected magnitude of benefit and harm with intensive vs. standard systolic blood pressure (SBP) treatment. We built survival models using SPRINT participant-level data for two benefit outcomes, cardiovascular disease composite outcome and all-cause mortality, and one harm outcome, treatment-related serious adverse events (SAEs). Elastic net Cox regression predicted the absolute risk of each outcome with intensive vs. standard SBP treatment from 36 baseline factors and related the predicted absolute risk of each outcome to the effect of the treatment, expressed as the risk difference between intensive vs. standard SBP treatment.

   - **Conclusion**: SPRINT participants exhibited little predictable variation in the ratio of the magnitude of benefit to harm with intensive vs. standard SBP treatment. Most participants with a high predicted benefit profile were also at high risk of harm. Selection of patients for

intensive SBP treatment should prioritize high probability of benefit since SAEs in SPRINT were generally transient.

5. Tom Green, Jian Ying, **Yizhe Xu**, Jincheng Shen. Evaluating Heterogeneity in Treatment Effects in the SPRINT Study Using Elastic-net Versus Causal Forest.

- **Summary**: Our study compares the performance of two machine learning methods, elastic-net and causal forest, in estimating the heterogeneous treatment effects (HTEs) in the Systolic Blood Pressure Interventional Trial (SPRINT). We conduct simulation studies to explore the specific conditions, such as sample size and amount of effect modification, for these two data-driven methods to perform well. Under the sample size of the SPRINT trial, the Elastic-net outperformed the causal forest method in detecting HTEs, and the causal forest did not improve upon the standard intention-to-treat estimate.

Veteran Affairs (SLC):

1. Grant W. Cannon, Wei Chen, **Yizhe Xu**, Jincheng Shen, Neil A. Accortt, David H. Collier, Brian C. Sauer. Empirical Evidence of Disease Activity Thresholds Used to Indicate Need for Major Therapeutic Change: An Observational Study in US Veterans with Rheumatoid Arthritis.

- **Summary**: Our study aims to determine disease activity thresholds associated with a decision by providers to initiate a major therapeutic change (MTC) in patients with rheumatoid arthritis (RA) and to report the impact of that change on RA disease activity. The study population included US Veterans enrolled in the Veterans Affairs RA (VARA) registry between 1/1/2006 and 9/30/2017. The disease activity measures (DAMs) are extracted from medical notes stored in the VA Corporate Data Warehouse (CDW) using validated extraction algorithms or data entered manually into the VARA registry database. Other patient data extracted from the CDW include pharmacy, laboratory, and outpatient diagnoses. We estimated the marginal and conditional effects of MTC on ACR20 response with established disease activity level combined with the empirical thresholds from Youden analysis.

- **Conclusion**: MTC was associated with clinical improvement across all DAMs with the greatest change in patients with RA disease activity above the Youden thresholds identified in this work.

2. Identifying the Optimal Risk for MRSA for Initiating Anti-MRSA Therapy for Community Onset Pneumonia.

- **Summary**: The overuse of empiric antibiotics may lead to poor outcomes of community-acquired pneumonia and increase the risk of infection with drug-resistant organisms (DROs). Our study investigates the DROs that related to methicillin-resistant Staphylococcus aureus (MRSA) infection and determines the optimal level of MRSA risk to initiate the anti-MRSA therapy to reduce 30-day mortality. We define a pneumonia hospitalization using ICD9 codes and extract patient demographics, clinical information, and medication administration data from electronic health records (EHRs). Death data were obtained from the VA Vital Status File. This is an ongoing project.

3. **Yizhe Xu**, Wei Chen, Brian C. Sauer. A Closer Look at Unnecessary Adjustment When the Target Parameter Is the Marginal Causal Effect.

- **Summary**: Simplified approaches to covariate selection recommend adjusting for all risk factors or all pre-treatment variables. Our study aims to clarify that, for noncollapsible

models, analytical bias may appear in estimating marginal treatment effects when adjusting for pure risk factors or instrumental variables even with no unmeasured confounding. We develop simulation studies to compare the regression approach with the inverse probability of treatment weighting (IPTW) method for covariate adjustment, and we demonstrate that the IPTW method provides unbiased estimates under most scenarios.

4. **Yizhe Xu**, Yan Cheng, Wei Chen, Marlene Egger, Joanne LaFleur, Brian C. Sauer. A Simulation Study to Compare Methods in Estimating Treatment/Adherence Effects When Intermediator Is Also a Time-Dependent Confounder.

   - **Summary**: A time-dependent confounder is a covariate that varies over time and a common cause of treatment and outcome. Our study aims to demonstrate the issues of using traditional regression to estimate treatment effects when time-dependent confounding exists. We design simulations with two treatment stages under an HIV study context. Our simulations show that the regression approach yields biased results regardless of the model types or covariate sets. The marginal structural models (MSMs) with the inverse probability treatment weighting (IPTW) method provides unbiased estimates.

University of Utah (Department of FPMD):

1. The Enrollment, Childbearing Motivations, and Intentions of Couples in the Creighton Model Effectiveness, Intentions, and Behaviors Assessment (CEIBA) Study.

   - **Summary**: The Creighton Model FertilityCareTM System (CrM) is a standardized approach for educating women about the biomarkers of their fertility. Couples can use this information for timing intercourse during "fertile" or "infertile" days to try to conceive or to avoid pregnancy. This multi-site study aims to assess fertility motivations, intentions, fertility-related sexual behaviors, and their impact on effectiveness to avoid and to conceive among new users of the CrM. As a research assistant, I have helped with data preprocessing (fusing and cleaning data (remove duplicate records, correct data typo, backtrack missing data), data subsetting), chart and questionnaire review, and statistical analysis.

Publications

(in chronological order)

1. **Y. Xu**, T.H. Greene, Y. Zhang, B.C. Sauer, A.P. Bress, W.S. Weintraub, and J. Shen. Estimating the Optimal Individualized Treatment Rule from A Cost-Effectiveness Perspective. *Biometrics*. 2020; DOI: 10.1111/biom.13406.
2. Adam P. Bress, Tom Greene, Catherine G. Derington, Jincheng Shen, **Yizhe Xu**, Yiyi Zhang, Jian Ying, Brandon Bellows, Rachel Hess, Jennifer Herrick, Zugui Zhang, Paul Kolm, Robert Yeh, Sanjay Basu, William S. Weintraub, and Andrew E. Moran; for the SPRINT Research Group. Patient Selection for Intensive Blood Pressure Treatment Based on Benefit and Harm in Systolic Blood Pressure Intervention Trial (SPRINT). *Journal of the American College of Cardiology*. Submitted 2021.
3. Grant W. Cannon, Wei Chen, **Yizhe Xu**, Jincheng Shen, Neil A. Accortt, David H. Collier, Brian C. Sauer. Empirical Evidence of Disease Activity Thresholds Used to Indicate Need for Major Therapeutic Change: An Observational Study in US Veterans with Rheumatoid Arthritis. *Arthritis Research and Therapy.* 2020 Oct.

4. Kelly L. Corbett, Angela P. Presson, Chong Zhang, **Yizhe Xu**, Susan L. Bratton S, Rebecca R. Dixon. Does Non-Neurologic Multiorgan Dysfunction After Out-of-Hospital Cardiac Arrest Among Children Admitted in Coma Predict Outcome 1 Year Later? *Journal of Pediatric Intensive Care*. 2020. DOI: 10.1055/s-0040-1715850

5. Bailey TL, Stephens AR, Adeyemi TF, **Xu Y**, Presson AP, Aoki SK, Maak TG. Traction Time, Force and Postoperative Nerve Block Significantly Influence the Development and Duration of Neuropathy Following Hip Arthroscopy. *Arthroscopy*. 2019 Oct;35(10):2825-2831.

6. Tin A, Marten J, Halperin Kuhns VL, Li Y, Wuttke M, Kirsten H, Sieber KB, Qiu C, Gorski M, Yu Z, Giri A, Sveinbjornsson G, Li M, Chu AY, Hoppmann A, O'Connor LJ, Prins B, Nutile T, Noce D, Akiyama M, Cocca M, Ghasemi S, van der Most PJ, Horn K, **Xu Y**, Fuchsberger C, Sedaghat S, Afaq S, Amin N, Ärnlöv J, Bakker SJL, et al. Target genes, variants, tissues and transcriptional pathways influencing human serum urate levels. *Nature Genetics*. 2019 Oct. 51(10): 1459–1474

7. Teumer A, Li Y, Ghasemi S, Prins BP, Wuttke M, Hermle T, Giri A, Sieber KB, Qiu C, Kirsten H, Tin A, Chu AY, Bansal N, Feitosa MF, Wang L, Chai JF, Cocca M, Fuchsberger C, Gorski M, Hoppmann A, Horn K, Li M, Marten J, Noce D, Nutile T, Sedaghat S, Sveinbjornsson G, Tayo BO, van der Most PJ, **Xu Y**, Yu Z, Gerstner L, Ärnlöv J, Bakker SJL, Baptista D, Biggs ML, Boerwinkle E, Brenner H, et al. Genome-wide association meta-analyses and fine-mapping elucidate pathways influencing albuminuria. *Nature Communications*. 2019 Sep;10(1):4130.

8. Wuttke M, Li Y, Li M, Sieber KB, Feitosa MF, Gorski M, Tin A, Wang L, Chu AY, Hoppmann A, Kirsten H, Giri A, Chai JF, Sveinbjornsson G, Tayo BO, Nutile T, Fuchsberger C, Marten J, Cocca M, Ghasemi S, **Xu Y**, Horn K, Noce D, van der Most PJ, Sedaghat S, Yu Z, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nature Genetics*. 2019 Jun;51(6):957-972.

9. Kazmers NH, Stephens AR, Presson AP, **Xu Y**, Feller RJ, Tyser AR. Comparison of Direct Surgical Costs for Proximal Row Carpectomy and Four-Corner Arthrodesis. *Journal of Wrist Surgery*. 2019 Feb;8(1):66-71.

10. Kazmers NH, Presson AP, **Xu Y**, Howenstein A, Tyser AR. Cost Implications of Varying the Surgical Technique, Surgical Setting, and Anesthesia Type for Carpal Tunnel Release Surgery. *American Journal of Hand Surgery*. 2018 Nov;43(11):971-977.

11. Kwok AC, Edwards K, Donato DP, Tatro E, **Xu Y**, Presson AP, Agarwal JP. Operative Time and Flap Failure in Unilateral and Bilateral Free Flap Breast Reconstruction. *Journal Reconstructive Microsurgery*. 2018 Jul;34(6):428-435.

12. Kazmers NH, Judson CH, Presson AP, **Xu Y**, Tyser AR. Evaluation of Factors Driving Cost Variation for Distal Radius Fracture Open Reduction Internal Fixation. *The Journal of Hand Surgery*. 2018 Jul; 43(7): 606-614.

13. **Yizhe Xu**, Joseph B. Stanford, Kristina Allen-Brady, Nan Hu. Optimal Study Design for Diagnostic Accuracy Studies: Differential Verification versus Partial Verification. *Journal of Clinical and Translational Science*. 2017 Sep; 1(1): 28-29.

14. Pirozzi CS, Mendoza DL, **Xu Y**, Zhang Y, Scholand MB, Baughman RP. Short-Term Particulate Air Pollution Exposure is Associated with Increased Severity of Respiratory and Quality of Life Symptoms in Patients with Fibrotic Sarcoidosis. *International Journal of Environmental Research and Public Health*. 2018 May;15(6).

15. Workman JK, Wilkes J, Presson AP, **Xu Y**, Heflin JA, Smith JT. Variation in Adolescent Idiopathic Scoliosis Surgery: Implications for Improving Healthcare Value. *Journal of Pediatrics*. 2018 Apr;195:213-219.

16. Keihani S, **Xu Y**, Presson AP, Hotaling JM, Nirula R, Piotrowski J, Dodgion CM, Black CM, Mukherjee K, Morris BJ, Majercik S, Smith BP, Schwartz I, Elliott SP, DeSoucy ES, Zakaluzny S, Thomsen PB, Erickson BA, Baradaran N, Breyer BN, Miller B, Santucci RA, Carrick MM, Hewitt T, Burks FN, Kocik JF, Askari R, Myers JB; Genito-Urinary Trauma Study Group. Contemporary management of high-grade renal trauma: Results from the American Association for the Surgery of Trauma Genitourinary Trauma study. *Journal of Trauma and Acute Care Surgery*. 2018 Mar;84(3):418-425.
17. Dena M. Elkeeb, **Yizhe Xu**, Angela P. Presson, Marta J. Petersen, John J. Zone, Aaron M. Secrest. Nonmodifiable patient characteristics as predictors of patient satisfaction in dermatology. *Journal of the American Academy of Dermatology*. 2017 Jun; 76(6): AB181.
18. Awad AW, Karsy M, Sanai N, Spetzler R, Zhang Y, **Xu Y**, Mahan MA. Impact of removed tumor volume and location on patient outcome in glioblastoma. *Journal of Neuro-Oncology*. 2017 Oct;135(1):161-171.
19. Sorena Keihani, **Yizhe Xu**, Angela P. Presson, Brian P. Smith, Patrick M. Reilly, Xian Luo-Owen, Kaushik Mukherjee, Bradley J. Morris, Sarah Majercik, Peter B. Thomsen, Bradley A. Erickson, Benjamin N. Breyer, Gregory Murphy, Barbara A. Shaffer, Matthew M. Carrick, Brandi Miller, Richard A. Santucci, Timothy Hewitt, Frank N. Burks, Erik S. DeSoucy, Scott A. Zakaluzny, LaDonna Allen, Jurek F. Kocik, Raminder Nirula, and Jeremy B. Myers. MP79-01 Nephrectomy after high-grade renal trauma: Results from the American Association for the Surgery of Trauma (AAST) Genitourinary Trauma Study. *Journal of Urology*. 2017 Apr.; 197(4S): e1072-e1073.

Papers Under Review

1. **Y. Xu**, J. Shen, A.P. Bress, B.K. Bellows, and T.H. Greene. A Conditional Random Forest Approach to Estimating the Most Cost-effective Individualized Treatment Rule. *Statistical Methods in Medical Research*. Submitted 2020+.

Presentations

1. "A Conditional Random Forest Approach to Estimating the Most Cost-effective Individualized Treatment Rule "

   Aug 2021 in Journal of Statistical Meetings (JSM) Health Policy Statistics Section, Seattle, USA

2. "Estimating the Optimal Individualized Treatment Rule from A Cost-Effectiveness Perspective."

   Sep 2019 in American Statistical Association (ASA) Biopharmaceutical Section Regulatory-Industry Statistics Workshop Program, Washington D.C., USA.

3. "Random-Forest Based Personalized Treatment Rule Optimization form A Cost-Effectiveness Perspective with An Application to the SPRINT Study."

   Sep 2019 in the 3rd Annual Translational Hypertension Symposium and Early-Stage Investigator Workshop, Utah, USA.

4. "Was the Effect of Intensive Blood Pressure Intervention on CVD Risk Heterogeneous in the SPRINT Study?"

Sep 2018 in the 2nd Annual Translational Hypertension Symposium and Early-Stage Investigator Workshop, Utah, USA.

5. "Optimal study design for Diagnostic Accuracy Studies: Differential verification Versus partial verification."

   Sep 2017 in Association for Clinical and Translational Science, Washington D.C., USA.

Software

1. CEAOptimalITR on GitHub for estimating the optimal individualized treatment rule (ITR) from a cost-effectiveness perspective.
2. CEAOptimalITREfficient on GitHub is an improved version of CEAOptimalITR, and it provides more accurate estimates of the optimal cost-effective ITR with less variability.
3. RFPredPower on GitHub is a sample size and power calculation software using machine learning methods.

Tutoring

1. Undergraduate level: College Algebra (Math 1050), Trigonometry (Math 1060), Introduction to Statistics (Math 2040), Calculus I to III (Math 2210).
2. Master level: Introduction to Probability (Math 5010), Statistics Inference I (Math 5080), Statistics Inference II (Math 5090).

References

1. Jincheng Shen, Ph.D., assistant professor, Department of Population Health Science, University of Utah, Utah. 801-213-4007, jincheng.shen@hsc.utah.edu.
2. Tom Greene, Ph.D., professor, Department of Population Health Science, University of Utah, Utah. 801-213-3741, Tom.Greene@hsc.utah.edu.
3. Brian Sauer, Ph.D., assistant professor, Department of Epidemiology, University of Utah, Utah. 801-582-1565, brian.sauer@utah.edu.

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