Investigating Factors Contributing to the Implementation of Personalized Medicine Practices in Clinical Oncology

Leveraging Spatial Relationships Between Immune Cells within the Tumor Microenvironment to Predict Response to Immunotherapy Treatment

Investigating Factors Contributing to the Implementation of Personalized Medicine Practices in Clinical Oncology

> A Sociotechnical Synthesis In STS 4500 Presented to The Faculty of the School of Engineering and Applied Science University of Virginia In Partial Fulfillment of the Requirements for the Degree Bachelor of Science in Biomedical Engineering

> > By Kate Goundry

May 9, 2024 On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

ADVISORS

Caitlin Wylie, Department of Engineering and Society

Sepideh Dolatshahi, PhD, Department of Biomedical Engineering

Contents

A Computational Framework for Deriving Mechanistic Hypotheses about Immune Interactions in the Tumor Microenvironment from Multiplex Immunohistochemistry Images

Investigating Factors Contributing to the Implementation of Personalized Medicine Practices in Clinical Oncology

Prospectus

Sociotechnical Synthesis

Chemotherapy and radiation have been long standing treatments for a wide array of cancers and have largely been harmful to patients. Their major aim has been to kill malignant cells by means of cytotoxicity. However, this leaves healthy cells in the body to be killed or harmed alongside them. Their use is toxic to patients and overall contributes to a decreased quality of life and has limited efficacy in extending survival and curing patients. In the last twenty years, immunotherapy gained traction as a feasible and effective form of therapy. Instead of using cytotoxic mechanisms to kill cells, it breaks down barriers that cancerous cells put up to suppress the immune system. Upon activation, the immune system effectively destroys the tumor without destroying uninvolved tissue. While immunotherapy has the power to completely transform the current landscape of cancer treatment, there are technical and sociotechnical barriers to immunotherapy completely transforming cancer treatment as we know it. My technical problem looks to improve the informed selection of immunotherapy treatment to improve clinic use. My STS project focuses on the cultural and organizational factors surrounding the uptake of similar implementations of precision medicine cancer therapy into the clinic, so that precision immunotherapy may be modeled in an educated way.

A limitation of immunotherapy is its unpredictable efficacy. Pembrolizumab, the world's leading immunotherapy treatment, can be used in cancers of many different tissues, but it is only effective in approximately 40% of patients. Clinicians are unable to predict based on clinical features and biomarker tests which patients are more likely to respond to treatment. If patients could be appropriately prescribed immunotherapy treatment, or directed towards more fitting immunotherapy or chemotherapy treatments, efficacy and implementation of immunotherapy could quickly increase. My technical project looked to measure and leverage the spatial associations between immune cells in patient biopsies of the tumor microenvironment. The purpose of this is to associate the local architecture of the immune system with response to immunotherapy treatment.

To that end, we have built a successful metric, by leveraging these spatial relationships as quantitative features which were then input into supervised machine learning analysis. We have built models that differentiated regions of interest based on their response to treatment with 92% cross-validation accuracy. While the preliminary results of the model proved to be effective, this work was done on a small scale of patients, and to build an effective and trustworthy model, future researchers will be tasked to increase the power of the model by increasing the number of patients being used. In addition, this project could be improved by substituting alternative methods of spatial quantification and machine learning analysis.

To accelerate the introduction of immunotherapy and to maximize the benefits of the advancement of immunotherapy, my STS project focused on the field of implementation science to anticipate how biomarker-guided immunotherapy treatment based on biopsy results might be implemented. Implementation science is the study of the social factors that impact the uptake of new practices by users. We decided to investigate the implementation of a prior advancement of precision medicine in the hopes that we could provide suggestions for future implementation at the cross-section of immunotherapy and precision medicine. We focused on the cultural, organizational, and technical components and their role in affecting the speed of implementation of genetic testing in chemotherapy selection which had been done previously. This investigation yielded results from multiple peer-reviewed journals examining the implementation of the technique in studies consisting of physician interviews, large-scale multi-center data analyses,

and observational studies. From our analysis, we found that physician relationships, comprehensive and simplified education for physicians, and working on cost and payment coverage plans could most rapidly improve the downstream implementation. In the future, it would be advantageous for researchers to investigate these effects into initial implementations of precision medicine in immunotherapy and leverage it to improve later implementation.

I would like to acknowledge Sepideh Dolatshahi for her mentorship, new ideas, and teaching. I would like to thank Gabe Hanson, Remziye Wessel, and the members of the Dolatshahi lab for their thoughtful discourse and work on the project, and I would like to thank the Biomedical Engineering Department at UVA for the support and education required to complete this project. I would like to acknowledge Professor Caitlin Wylie for her comments and discourse surrounding the sociotechnical project mentioned above. I hope to pursue similar projects with equally inspiring goals in the future stages of my career.