**Computational Modeling for Ex Vivo Analysis of Fibrosis, Hypertrophy and Proliferation in Heart Disease**
(Technical Project)

**The Affordable Care Act's Mandatory Health Insurance Requirement and Penalties and the Causes for Its Abolition**
(STS Project)

A Thesis Prospectus
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

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October 27, 2023

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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.

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## INTRODUCTION

While the United States's healthcare system ranks first in the world in science and technology and sixth overall, everyone does not equally feel the benefits of these advancements (Roy, 2021). High cost of procedures and medications limit their accessibility to certain regions of the country or groups of people, particularly racial minorities (Riley, 2012). The rise in healthcare costs in the United States in the past few decades can be partly attributed to the increased development of new medical technology. While improving clinical outcomes in many cases, they are expensive to produce and implement, which results in an increased financial burden for patients. The structure of the US healthcare system encourages the insertion of new medical technologies wherever possible as a result of "reimbursement systems, professional reward structures, legal considerations, and patient demands" (Neumann & Weinstein, 1991). Health insurance, therefore, is crucial in shielding patients from having to cover the entire cost of treatment themselves. Congress enacted the Affordable Care Act (ACA) in 2010 to provide public health insurance to those in poverty or near-poverty to lower the number of uninsured Americans. The ACA included a provision that made having health insurance, either public or private, mandatory under penalty of fines. This provision, however, was later lifted starting in 2019 under the Trump Administration (McIntyre & Song, 2019).

In this prospectus, I will propose technical and science, technology, and society (STS) projects to address the issue of healthcare accessibility. In my technical project, we will be developing a cell imaging pipeline using machine learning techniques to objectively quantify hypertrophy, cell proliferation, and fibrosis in mouse heart cross-sections. By creating this automated pipeline, researchers studying heart disease and failure will be able to quickly perform high throughput testing of new drugs and treatments, accelerate drug development, and make the process less expensive. My STS project will examine the ACA and the social and cultural attitude shifts that resulted in the lifting of the mandatory health insurance requirement. Initially, the government wished to compel individuals to obtain insurance, but as of the end of 2018, citizens are no longer forced to buy insurance if they do not wish to. Through an investigation of this topic, I aim to elucidate the arguments for and against the requirement and what caused it to be deemed no longer necessary.

**TECHNICAL PROJECT**

When blood flow is blocked to regions of the heart, starving the cells of oxygen, the cardiomyocytes (CMCs) begin to undergo apoptosis (coordinated cell death), which are the cells responsible for the contractions of the heart (van Empel et al., 2005). In a failing heart, the CMCs die off and are replaced by other cells flooding into the empty space, such as immune cells and fibroblasts. These fibroblasts produce scar tissue, which can transmit force but not generate its own. This weakens the heart and leads to other pathological changes which can result in the death of the patient. Fibrosis is a major concern in the natural regeneration of any tissue. The overproduction of extracellular matrix (ECM) in response to inflammation, while closing the injured area quickly, prevents new functional cells from navigating and proliferating in the wound. In the heart, excessive collagen and other ECM protein deposition can alter the architecture of the heart itself, further leading to its dysfunction (Travers et al., 2016). In response to the weakening during CMC death and fibrosis, because CMCs do not normally replenish themselves in adults, the remaining CMCs will hypertrophy to compensate the lost strength in what is called hypertrophic cardiomyopathy (HCM). The asymmetric remodeling and the stiffening of the heart tissue due to HCM leads to a plethora of other complications, such as diastolic dysfunction, obstructions, and arrythmias (Marian & Braunwald, 2017). In the case of a diseased heart, being able to observe and quantify the proliferation of fibroblasts and immune cells in an area of injury, as well as the hypertrophy and potential replenishment of cardiomyocytes, is critical in the future development of treatments and medications to limit fibrotic response and promote heart regeneration.

Machine learning techniques are already in wide usage within the medical field, being applied to subjects such as X-ray imaging, computerized tomography (CT) scanning, and mammographs, as well as others (Puttagunta & Ravi, 2021). Deep learning and neural networks have also been applied to histopathology, which is the field of imaging tissue slices to quantify and potentially diagnose diseases; however, the application of these techniques has yet to be done for in vivo analysis of cardiac tissue slices to quantify fibrosis, hypertrophy, and cell proliferation in heart failure.

For the technical project, my group will be working alongside other labs at the University of Virginia to aid in the discovery of new ways to objectively measure the cell proliferation patterns in tissue slices of mouse hearts. To achieve this goal, my group will be using machine learning techniques to develop an automated pipeline that is capable of differentiating cell types and their stage of development/replication. This will involve cell imaging of the mouse hearts and labeling of the cells to create training sets for the computer program to learn on. The pipeline will be able to report to the researcher the number and size of the cells, the types of cells present, and identify cells entering the cell cycle (i.e., replicating). It will also be able to quantify fibrosis and hypertrophy in the tissue cross-sections, which can be used to measure the amount of damage sustained by the organ. From there, researchers may use the pipeline to perform tests to observe the effects of various drugs and treatment conditions to discover new potential treatment methods for heart disease.

Our project will save time and cost for testing and developing drugs for treating heart disease and fibrosis by automating the process of cell counting and measurement and objectifying previously subjective measurements. The current method being deployed by Dr. Wolf's lab at the University of Virginia is to randomly select 30 cells in the image and measure them by hand, which is time consuming and potentially inconsistent depending on which researcher performs the measurements. Achievement of our project objectives will enable the creation and development of life-saving drugs and regenerative medicine solutions to heart disease and failure. By creating a pipeline to make this procedure more efficient, biomedical researchers and pharmaceutical companies will benefit from the ability to cheaply and easily perform high throughput testing and iteration of design. The project aims to address the issue of accessibility by making the drug development process cheaper and faster, thus making these treatments more available and affordable to the public.

**STS PROJECT**

President Obama originally signed the ACA into effect in 2010, which expanded the Medicaid program for seniors and offered a state-sponsored, affordable, taxpayer-funded health insurance for those in poverty or near-poverty (Rosenbaum, 2011). Initially, the ACA included compulsory penalties for not having any health insurance, although exemptions existed. Starting in 2019, the Tax Cuts and Jobs Act lowered the penalty for being uninsured to $0, alleviating the uninsured from facing this punishment (McIntyre & Song, 2019). This change in doctrine could either be seen as an effort to undermine the ACA and the universal healthcare initiative or as abolishing a practice that unfairly punished individuals for making a personal decision. Therefore, in this STS project, I will answer the question: how did changes in social, economic, and political attitudes result in the repeal of the federal mandatory healthcare insurance requirement in 2019?

The original reasons for instituting the ACA provide insight into why the creators implemented the penalties in the first place. If an individual is in a high-risk group, it is often difficult to obtain good health insurance, and many low-income jobs do not offer benefits. Failures in the market, such as insurance brokers not acting in their clients' best interests and the fierce advertising of prescription drugs elevating demand, also showed weaknesses in the American system that the ACA hoped to address (Silvers, 2013). In 2009, 15.4% of the population was uninsured, with 19.4% having been without insurance at some point in the past year. Additionally, there were, and still are, major racial disparities when it comes to coverage. In 2009, Hispanics had by far the highest percentage of uninsured at 31.2% (Cohen et al., 2019). Therefore, to aggressively combat the economic, social, and racial issues in healthcare, the penalty was used as the 'stick' to maximize the effect of the program.

The current status of the US healthcare system is a mix of public and private health insurance options. Private insurance remains dominant, however, with 66.0% having private insurance and 34.7% having public coverage. In 2018, before the mandate was repealed, 8.5% of people were uninsured, and in 2021, 8.3% of people were uninsured, which, while an improvement from before the ACA, still represents 28.3 million uninsured (Berchick et al., 2019; Kiesler-Starkey & Bunch, 2022). The widespread implementation of technology into the field has greatly increased America's medical capabilities, but technology is also a leading driver of healthcare costs (Goyen & Debatin, 2009). This plays a part in the disparities we see in healthcare affordability and accessibility. Certain regions of the US experience higher healthcare costs than others, and minority groups are at an increased risk for health inequalities because of differences in healthcare utilization (Chang et al., 2023). While the ACA was intended to address the issues of an uninsured population, healthcare cost, and healthcare inequalities, these problems remain over a decade later.

To justify implementing penalties for what would otherwise be a personal decision, there must have been a compelling interest that involved greater societal costs should people elect to remain uninsured. Patients without health insurance pose a serious financial risk to healthcare providers due to the lack of assurance of payment for services, and as a result, many practices refuse to take on new patients who are uninsured, and in most cases when they do, patients are required to pay in full at the time of service (O'Toole et al., 2001). High out-of-pocket costs and limited payment plans for uninsured patients has led to the accumulation of medical debt, which in turn is associated with reduced healthcare use. In June 2020, 17.8% of patients in the US had medical debt collections (Kluender et al., 2021). While debt itself can put strains on the economy, healthcare-related loss of productivity has massive financial implications for the country. An estimated $260 billion is lost due to health-related work losses each year, and this does not include the medical costs themselves (Mitchell & Bates, 2011). Therefore, the implementation of the penalties was not merely for the sake of the uninsured individual but had major social and economic implications for the country as well.

To explore this question further in my STS project, I intend to conduct a literature review of sources pertaining to the ACA, its mandatory insurance provision, and this provision's elimination. I will consult studies, interviews, editorials, and legal documents to gather information on the ACA penalty and shifts in opinion about it. I will collect these resources from academic journals, government sources, and news outlets and will span from around the time of the ACA's implementation (2010) to when the penalty was lifted (2019). I plan to apply the ideas of actor-network theory (ANT) to the analysis of the issue. ANT will elucidate how the ACA exists within a broader network of social relationships and infrastructures that both influences and is influenced by healthcare interactions between people. Additionally, it will allow analysis on how the state of the healthcare market in the US catalyzed the creation of the ACA's insurance requirement and its subsequent removal. Lastly, I can deploy ANT to study how the penalty to enforce insurance was used to govern and shape people's behavior within the healthcare infrastructure.

**CONCLUSION**

For my technical project, we hope to output an automated cell imaging pipeline that can quantify cardiomyocyte and fibroblast populations, nuclei, and collagen content. Medical researchers and pharmaceutical manufacturers will benefit from my project through the ability to conduct high-throughput studies of drug effects in vivo, and patients will benefit from the improved drug development and cheaper development process. From the analysis of the imposition and relinquishment of the ACA's mandatory insurance requirement in my STS project, government officials and policy makers, healthcare providers, and patients will benefit due to a better understanding of sociological conditions that govern the implementation, effectiveness, and public opinion of policy decisions. The technical and STS projects combine to address accessibility issues in healthcare, and their completion will expand the quality and affordability of treatment as well as equity in healthcare, respectively.

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