Development of a urine assay for IL-33 and sST2 as biomarkers for acute kidney injury
(Technical Project)

Dialysis Disparities: Using Actor-Network Theory to Frame Genetic, Social, and Environmental Contributors to Unequal Health Outcomes
(STS Project)

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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

The kidney is one of the most important organs in the body, as it filters out toxins from the blood and regulates salt and fluid balance to maintain homeostasis. As such, the kidney receives anywhere from 20-25% of the total blood that the heart pumps out to the rest of the body. The kidney has high oxygen requirements, so it is extremely important that this blood flow be maintained to filter the body's blood and maintain the kidney's function (*Kidney Blood Flow - an Overview | ScienceDirect Topics*, n.d.). Chronic kidney disease, or CKD, is a highly prevalent disease throughout the world. The global prevalence is estimated at 13.4% (Lv & Zhang, 2019). CKD often originates as an acute kidney injury (AKI), which occurs when the kidney undergoes ischemia–meaning it does not get enough blood flow for a prolonged period of time–such as in the case of heart surgery. Due to lack of nutrients and oxygen reaching kidney cells that are needed to filter blood, these cells die off. If acute kidney injury is not properly and quickly treated, this damage becomes permanent and the kidney irreplacably loses its blood filtering function, which is otherwise defined as CKD (Makris & Spanou, 2016). Thus, the final product for technical project will be a standardized protocol for an assay for early and sensitive detetction of biomarkers that indicate AKI as well as a technical report on the success of this biomarker-based assay.

When CKD worsens, it proceeds to a further stage of kidney disease called end-stage renal disease (ESRD), in which most if not all patients require renal replacement therapies (RRT) such as dialysis or kidney transplantation. These therapies essentially replace the kidney and are a necessity for survival in end-stage patients. Certain types of simpler, at-home dialysis options such as home hemodialysis and home peritoneal dialysis exist, but in the United States, most people still travel to dialysis centers three times a week to receive in-center hemodialysis (Flanagin et al., 2020). Additionally, patients are often fatigued after dialysis and need someone to drive them

home. Factoring in travel time and fatigue, those on dialysis often cannot maintain a full-time job. All these complications provide a way for socioeconomic and racial disparities to arise. These disparities are proven by the fact that African Americans and other minority groups have poorer outcomes in CKD and dialysis care (*Chronic Kidney Disease in African-Americans*, 2018). Some contributors to these disparities are genetic, however the primary factors are social determinants (MD, 2021). Several human and non-human actors are equivalent participants in such networks that exacerbate disparities in the utilization and outcomes of dialysis technology. Such connections between existing actors of social inequality and discrimination and exacerbatory aspects of CKD care may help provide explanations for why these disparities exist. As such, actor network theory will be utilized as a framework for sociotechnical analysis in this field. The deliverable for this component of the project will be a report on sociotechnical aspects of CKD and dialysis care.

TECHNICAL

One of the most common complications during heart surgery is acute kidney injury (AKI), which occurs in as much as 31% of patients (Ramos & Dias, 2018). AKI is a condition in which the kidney undergoes an abrupt reduction in function. In cardiac surgeries, AKI is often caused by ischemia, in which the amount of blood and oxygen that is delivered to the kidney is highly reduced (Makris & Spanou, 2016). If the diagnosis and treatment of AKI are prolonged, the cells in the kidney will experience greater damage, and the chance for the kidneys to recover decreases. AKI leads to CKD that can worsen to end-stage renal disease, requiring RRTs such as dialysis. Currently, AKI is primarily diagnosed with a blood or urine test to measure levels of a biomarker called creatinine. However, creatinine tests are imperfect due to the lack of specificity and sensitivity (Zhou et al., 2006). Thus, creatinine levels cannot indicate AKI in the early stages. Better biomarkers and rapid urine tests are needed to detect AKI earlier and more accurately.

The team will focus on two novel biomarkers for AKI that are found in the urine: Interleukin 33 (IL-33) and soluble Suppressor of Tumorigenicity 2 (sST2). IL-33 is a molecule released by damaged cells that signals and recruits a certain type of immune cell to the site of injury (Stremska et al., 2017). Previous studies show that IL-33 is involved in ischemia, the type of injury that occurs in the kidneys of cardiac surgery patients. IL-33 is released by the cells of the blood vessels in the kidney and is found in especially elevated concentrations in damaged areas of the kidney (Ferhat et al., 2018). sST2 on the other hand, is a receptor molecule that binds IL-33 and is present in the blood. It has also been found to be in elevated concentrations in patients with poor cardiac surgery outcomes and kidney damage (Patel et al., 2020; Plawecki et al., 2018).

The main objective of this project is to develop an assay to effectively detect IL-33 and sST2 in urine samples from cardiac surgery patients. The results from this assay will be correlated to clinical diagnoses of AKI to confirm IL-33 and sST2 as biomarkers for AKI. Simultaneous detection of IL-33 and sST2 will help measure kidney damage and immune cell activation to design appropriate treatment strategies. This assay will then be simplified and consolidated into a diagnostic tool for AKI, such as a chip, which will allow healthcare providers to administer treatment in the vital early stages. As such, CKD and devolvement into ESRD requiring dialysis can be prevented. This assay and a technical report will be the final deliverables for this project.

STS TOPIC

The number of people with ESRD who require RRT is estimated to be between 5 and 7 million globally (Lv & Zhang, 2019). Thus, kidney disease is a huge social and economic burden for families throughout the world. Particularly in the United States, there are large racial, ethnic, and geographic disparities in CKD burden, treatment, and outcomes. African Americans are more likely to have suboptimal dialysis effectiveness and CKD outcomes (Crews et al., 2014). Racial

and ethnic minorities are 1.4 to 4 times more likely to require RRT such as dialysis, and there are many biological and social factors that contribute to this disparity; biologically, African Americans have greater incidence of anemia and mineral and bone disease, which could contribute to disparities (Norris et al., 2017). Some social factors that contribute to such disparities are implicit clinician bias or bias in testing criteria, disparities in type of dialysis access (i.e. arteriovenous fistula vs. catheter), unequal distribution of dialysis care facilities, reduced access to more convenient forms of dialysis, and greater exposure to environmental pollution.

The factors that contribute to dialysis disparities begin at the clinical level. Diagnosis of CKD is accomplished by a measure of kidney function known as estimated glomerular filtration rate, or eGFR. However, an outdated correction factor used to calculate eGFR for black people overestimates their kidney function, as such makes them less likely to be diagnosed with CKD. In turn, physicians may be less likely to refer black people for dialysis care even though they may require it ("Push to Remove Racist Bias from Kidney Testing Gains New Ground," 2020). As dialysis filters the blood extracorporeally (outside of the body), it requires an access point, or simply an "access" to draw blood from. There are a couple ways an access is created, but the main methods are an intravascular catheter, which is a tube placed permanently in the veins, and an arteriovenous fistula, a graft between an artery and a vein in the arm that allows increased blood flow and easier accessibility. Catheters have a greater risk for infection, and it has been shown that using a fistula for dialysis access has improved survival and outcomes. It was found that white patients have a 32% higher chance of initiating dialysis with a fistula, increasing their chances of survival over minorities (Zarkowsky et al., 2015). Another contributing factor is travel distance to dialysis facilities and accessibility of at-home dialysis modalities. Although in-center hemodialysis is still the most common dialysis modality, there are certain home modalities such as home

hemodialysis and home peritoneal dialysis. It has been found that not only are dialysis centers more sparsely located in African American-populated areas, but that African Americans also have reduced access to at-home dialysis modalities that have been proven to be more convenient have better survival rates (Prakash et al., 2014; Rydell et al., 2019). Additionally, minorities such as African Americans, Hispanics, and Asians have been found to be libr in areas with greater risk for exposure to hazardous air pollutants, particularly as a result of historical residential segregation practices (*Disparities in the Impact of Air Pollution*, n.d.). It has been proven that increased exposure to pollutants exacerbates CKD, so it is clear how pollution can also contribute to worse dialysis outcomes as well (Tsai et al., 2021).

The human and non-human factors leading to the above-mentioned disparities will be framed as actors in a sociotechnical network that perpetuates inequalities in dialysis care. Actor network theory (ANT) is a sociotechnical theory that was first developed by French sociologist Bruno Latour. This theory focuses on both human and inanimate actors and their effects on social processes. ANT "move[s] away from the idea that technology impacts on humans as an external force, to the view that technology emerged from social interests (e.g. economic, professional) and that it thus has the potential to shape social interactions" (Cresswell et al., 2010, p.). Critics of ANT, such as Langdon Winner, are apprehensive towards the fact that ANT does not consider the intentionality of human actors compared to non-human actors. When considering dialysis disparities, however, it is close to impossible to determine whether the intentionality of human actors causes them to have a greater effect on disparities than non-human actors, and thus makes it most efficient to not distinguish the intentionality of human actors. In the STS paper, the variety of factors involved in dialysis disparities that are mentioned above will be framed using ANT. Their causes, such as physician bias, discriminatory public policy, etc. will be described as actors

in this network, and the interconnected network that perpetuates disparities in dialysis will be examined.

METHODOLOGIES

Research question: How do sociotechnical factors create disparities in health outcomes in dialysis care in the United States?

This research will explore the question of how human and non-human actors interconnect to create disparities in dialysis care. The research will primarily be conducted through documentary methods. The preliminary work of researching studies with specific statistics on disparities and factors contributing to them has already been completed for the prospectus. This research will serve to establishe the context and main points of disparity that will be elaborated on. Further documentary research will be done in order to elucidate the causes of these factors, and to describe these causes as actors in the context of ANT. For example, if documentary research uncovered that implicit physician bias contributed to whether a dialysis patient received a cather or a fistula as their dialysis access, it would confirm the physican as a human actor in this network. These documentary sources will most likely come from cohort or cross-sectional studies on dialysis patients published in medical and public journals found on databases such as Pubmed.

As an extension of documentary research, policy analysis will be done to find further root causes. For example, there is evidence to suggest that policies such as redlining have contributed to minorities more commonly living in more polluted neighborhoods (Manke|, 2019). Policy analysis methods will help reveal this information, and confirm that politicians and specific policies are actors in this network. Some important keywords that will be used during the documentary and policy research processes are implicit bias, redlining, residential segregation, and environmental discrimination. Finally, interviews and observation of interactions between

healthcare workers and patients in dialysis clinics will be used to inform this research. On top of documentary research and policy analysis, direct conversation with those who are in a dialysis clinic on a regular basis as well those on dialysis will more strongly inform the microscale social processes that take effect in the dialysis clinic that lead to such strong disparities. As a result of these three research methods, the root causes of the main points of disparity that were described in the STS Topic will be found and framed as actors in the context of ANT. The information will be organized by each of these points of disparities, and finally the relationships between all of them will be described and brought together. Framing the issue with ANT will help in concluding how social factors have affected the development and utilization of the technology of dialysis, and how the rules of dialysis technology shape the lives of those who require it. A report will be written on framing the sociotechnical factors contributing to dialysis factors in the context of ANT.

CONCLUSION

This prospectus targets the development of acute kidney injury, or AKI, in cardiac surgery patients. The current standard of blood/urine creatinine measurement cannot detect AKI in the important early stages when it must be treated. As such, the team will focus on two new biomarkers, IL-33 and sST2, which have been found to be elevated in AKI. The team will develop a standardized protocol for an assay to detect these molecules in existing urine samples from cardiac surgery patients, and correlating measurements of these molecules to clinical diagnosis of AKI. The assay will then be simplified onto a rapid tool such as a chip that i easily used in clinical settings. If successful, the application of such a test in clinical settings will enable accurate and rapid detection of AKI and inform physicians to form a treatment plan, making it more likely to prevent progression into chronic kidney disease.

If AKI is not treated in the early stages and continues to worsen, it becomes chronic kidney disease and the kidneys will eventually fail, causing patients to require renal replacement therapy, primarily through dialysis. In America, not only do African Americans have higher rates of CKD than white people, but they have poorer dialysis effectiveness and worse health outcomes. A variety of factors, both human and non-human, contribute to these disparities, including physician bias in diagnosing CKD and choosing dialysis and access modalities, geographic accessibility of dialysis centers, and environmental pollution in minority neighborhoods. These are driven by interconnected actors such as genetics, physicians, politicians, public policy such as redlining, etc. This paper will focus on framing these actors using actor-network theory, and will use documentary research methods, public policy analysis, and interviews to accomplish this goal. Describing such a network will emphasize the main interconnected actors that create disparities and highlight how changes can be made to affect these actors and thus transform the entire network towards solving these disparities.

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