GENETIC, SOCIAL, AND ENVIRONMENTAL CONTRIBUTORS TO UNEQUAL OUTCOMES OF KIDNEY DISEASE

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By

Ashwin Swaminathan

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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.

ADVISOR
Catherine D. Baritaud, Department of Engineering and Society

What is the body's most important organ? Perhaps it is the heart, which constantly pumps blood, or maybe it is the brain, which is necessary to control the rest of our body. An argument can be made that the kidney is paramount. As the kidney receives 20-25% of the body's entire blood flow, controls fluids and electrolytes, and filters out toxins, kidney health is crucial (Sharfuddin & Molitoris, 2008). One common complication that occurs in procedures like cardiac surgery is acute kidney injury (AKI), which can occur in up to 31% of patients due to reduced blood flow to the kidneys during the operation (Makris & Spanou, 2016). The technical section of this project is in collaboration with Autumn Blackshear and under the guidance of Dr. Sharma. The project aims to develop a test to measure the biomarkers IL-33 and sST2, which may indicate kidney injury. This diagnostic uses an enzyme-linked immunosorbent assay (ELISA), in which antibodies bind to the molecules of interest in urine samples, displaying a color visible to the eye. The final deliverable for the technical project is a protocol for carrying out this assay. Such a diagnostic would overtake the current standard of diagnosis, plasma creatinine, which is imperfect due to its lack of specificity and sensitivity (Zhou et al., 2006). This assay can be applied at the bedside to quickly diagnose AKI and allow clinicians to intervene early to prevent long-term complications.

If left untreated, AKI can deteriorate into chronic kidney disease, or CKD, a long-term condition that affects 13.4% of people worldwide. In late-stage CKD, the kidney irreplaceably loses its blood filtering function, forcing patients to permanently reorient their lives around dialysis, which draws blood out of the body to filter it through a dialyzer (Lv & Zhang, 2019). Although dialysis is a therapy that promotes patient survival, the average lifespan for someone on dialysis is only 3 years and worsens if dialysis is not consistent (Stokes, 2011).

Figure 1 highlights how CKD patients can end up on dialysis while on kidney transplant waitlists for years. During this time, confounding factors such as stress, distance to care centers, cost, loss of a regular job, lack of family support, and more can increase likelihood of death (K. Norris et al., 2008).

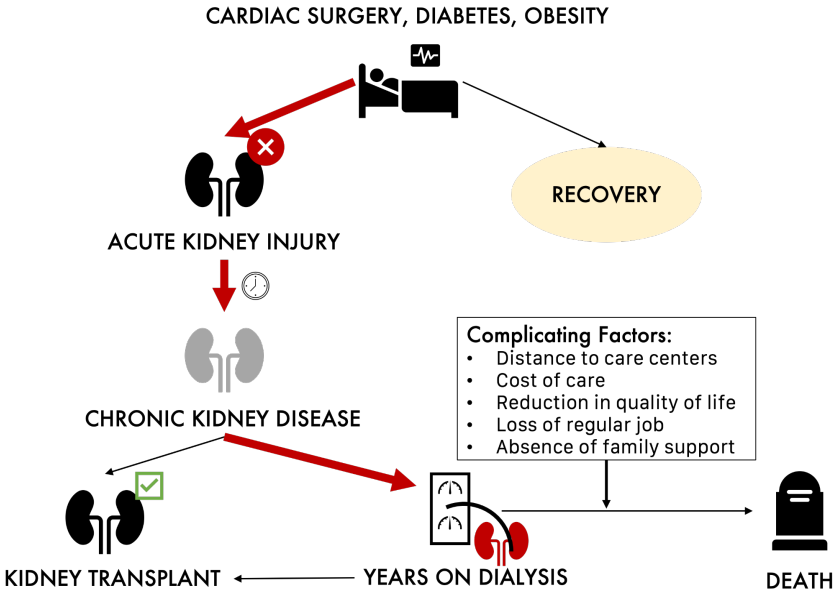

Figure 1: The CKD/Dialysis Pipeline: A flowchart showing possible trajectories for development and outcomes of kidney disease. The path shown in red is most common, with patients spending years on dialysis with a high likelihood of death (Swaminathan, 2022).

Given that CKD patients require close attention from doctors and regular dialysis for their treatment to be effective, any disparities in their medical care are highly detrimental to survival. It has been proven that certain groups have consistently worse access to dialysis care and poorer health outcomes, caused by various genetic, environmental, and social reasons; African Americans in particular are 1.4 to 4 times more likely than white Americans to require dialysis care, as highlighted by Keith Norris, a CKD clinician at the University of California, Los Angeles (K. C. Norris et al., 2017). As such, it is evident that the burden of the kidney disease is borne unevenly across racial boundaries in the United States. When creating a new technology such as the biomarker assay proposed in the technical project, it is vital to consider the social

factors around which this technology can be applied. Understanding existing racial disparities in medical technologies such as dialysis can bring to light a better understanding of the structural issues that must be navigated to bring about equitable application of technology.

In this research paper, Actor-Network Theory (ANT) is applied as an explanatory model of the various human and non-human actors and the ways in which these actors interconnect to contribute to dialysis disparities. ANT is a sociotechnical framework that was originally developed in the 1980s by Bruno Latour. The key idea of ANT is that "actors" need not be human, nor must they act intentionally (Latour, 2007). This allows for entities such as air pollution, more tangible biological components like DNA, and healthcare workers in the clinic to stand on equal footing as actors that produce some effect on the network. Here, "actors" are defined as the root causes of issues that worsen dialysis outcomes; the tangible or non-tangible entities that "tug" on the network to pull it in a particular direction. Using actor-network theory as an analytical framework in tandem with documentary research methods, the following question is addressed: *how do sociotechnical factors interconnect to create disparities in health outcomes in dialysis care in the United States*? The paper will first focus on genetic and biological arguments for poorer CKD outcomes in Black patients. Then, clinical factors and environmental/geographic factors will be considered. The paper will then focus on interconnections between these factors through the lens of ANT. In particularly, the paper will focus on disparities that affect the African American community, and the salience of social and environmental factors over purely biological explanations for disparities. Through addressing the above research question, this loosely-coupled STS paper will bring forward key points of action for alleviating or avoiding inequities when bringing forth new medical technologies, particularly in the field of kidney disease.

GENETIC CONTRIBUTORS AND BIOLOGICAL RESPONSES

Despite constituting 13.4% of the US population, African Americans consist of about 36% of patients currently on dialysis. As such, clinicians and medical researchers sometimes contend that genetics is the sole or primary contributor to the disproportionate burden of kidney disease. Several case-control and population-based studies have been conducted on the genomic contributors to elevated CKD in African Americans, including a study by Foster et al. at Tufts University. Foster's study found that changes in the gene apolipoprotein L1 (APOL1) may account for up to 70% of the disparity between Blacks and whites in the development of non-diabetic end-stage CKD. They also uncovered that carrying 2 high-risk APOL1 alleles corresponded with a 1.49-fold increase in CKD risk and a 1.88-fold increase in the risk of end-stage kidney disease (Foster et al., 2013). This gene contains several loci thought to be related to kidney function. As many African Americans carry 1 or 2 high-risk alleles within this gene locus, their risk for CKD is significantly elevated. As explained by Ebele Umeukeje and Bessie Young, doctors at the Vanderbilt University Medical center, APOL1 is a gene that produces a protective protein against trypanosomes, a type of parasite found in the "trypanosome belt" of Africa. Thus, it is likely that ancestors of African Americans developed APOL1 as a survival factor against trypanosomes, with the unwanted side effect of increased renal disease risk passed down their genetic lineage (Umeukeje & Young, 2019).

In addition to elevated rates of kidney diseases, African Americans also bear a disproportionate burden of conditions such as obesity and diabetes. All types of diabetes are 1.6 times more prevalent in African Americans. Additionally, nearly 48% of African American adults are obese while the same statistic is 32% for whites, as found on the American Psychological Association's (APA) website. There is no consensus on why this is the case,

however, many experts suggest that it is related to the "thrifty" gene, a genetic factor that evolved to favor efficient fat storage in African Americans. Such a gene may have been vital centuries ago in West Africa where food was far scarcer but acts as a detriment when paired with the modern abundance of food–particularly cheap, unhealthy food–in the United States. The APA also explains how other contributing factors may include lack of exercise and hereditary insulin resistance (*Ethnicity and Health in America Series*, n.d.; Marshall, 2005). This is an important consideration because both diabetes and obesity are significant comorbidities–i.e., confounding factors–for CKD. Studies show that diabetes and obesity significantly reduce the quality of life for CKD patients, largely due to cardiovascular complications. In addition, clinical outcomes are significantly worse for diabetic kidney disease patients on dialysis (Soleymanian et al., 2017).

One elusive biological contributor to disparate health outcomes is stress, which is a component that can also be strongly tied to social factors. Work by Karen Hye-cheon Kim at the University of Arkansas for Medical Sciences has linked increased stress to poorer weight management, and obesity is strongly linked with Type 2 Diabetes (Kim et al., 2009). As elaborated above, there is a strong link between diabetes, obesity, and worsening outcomes in CKD and dialysis. Expanding on this, Clark et al. propose a biopsychosocial model, where systemic racism in America and socioeconomic struggle contribute to greater stress and poorer clinical outcomes (Clark et al., 1999). This model contradicts some claims that disparities are only linked to the genetic traits of African Americans. Data points to an interplay of risk introduced by the APOL1 gene, a greater tendency to develop comorbid diabetes and obesity due to the Thrifty gene, as well as racism-induced stress. These effects combine to put African

Americans at greater risk to struggle with kidney disease even before other social factors are considered.

CLINICAL-LEVEL CONTRIBUTORS

The actions of doctors, nurses, and other healthcare workers in the clinic have a significant impact on patients' healthcare outcomes. Nwamaka Denise Eneanya and colleagues at the University of Pennsylvania outline the avenues through which disparities seep into the clinic. As of 2019, clinical diagnosis of kidney disease is still informed by racial information. Although there is no direct way to measure kidney function, one indirect quantity of importance is estimated glomerular filtration rate, or eGFR. eGFR is based on measurements of a protein found in blood called creatinine that is associated with kidney function; greater creatinine in the blood indicates worse kidney function. A racial coefficient increases the eGFR estimate for Black patients by around 16%, based on inconclusive evidence that Black people have greater muscle mass and thus release more creatinine into their bloodstream (Eneanya et al., 2019). There are severe clinical implications for such differences in eGFR due to the racial coefficient. A 16% higher eGFR for a Black patient could keep them above the threshold for CKD diagnosis even if their kidneys are likely deteriorating. As a result, the patient would be unable to receive necessary treatment that a white patient with the same creatinine measurements would. They would also be ineligible for kidney transplant waitlists. Informed by this non-factual correction factor, clinicians may be less likely to refer black people for dialysis care that they may require ("Push to Remove Racist Bias from Kidney Testing Gains New Ground," 2020). Due to the racial correction, individuals who require treatment are denied it, ignoring the evidence that greater variation in kidney function is found between individuals of the same race than across

racial boundaries (Eneanya et al., 2019). This racial correction factor only becomes more problematic when considering broader social contexts around which it is applied. Consider a biracial patient with no prior medical record who comes to a nephrologist to get her kidneys tested. Based on the patient's skin tone, some doctors may categorize her as white while others categorize her as black. If this patient truly has poor kidney function and requires a transplant or dialysis, the only deciding factor in her receiving treatment is the doctor's subjective assessment of her racial identity.

Another factor that can influence a patient's CKD outcomes is their type of dialysis access. In order to receive dialysis, every patient must have some sort of access point through which they can be hooked up to dialysis tubing so their blood can flow through the dialyzer. As seen below in Figure 2, there are three common types of dialysis access modalities. One modality is the arteriovenous (AV) fistula, which is a surgical connection between an artery and vein in the forearm that causes increased blood pressure in this vessel and makes it easier to access and connect the bloodstream to the dialysis tubing with a needle. Another access modality is an AV graft, which achieves the same purpose as a fistula–connecting an artery and a vein–but does so through a synthetic tube instead of a surgical connection. Lastly, the most common dialysis access modality is a central venous catheter (CVC). This consists of an exposed set of two tubes that connect to the dialysis tubing on one end, and on the other end traveling through the arm to attach to a vein near the heart. Despite being the most ubiquitous, the CVC is most prone to infection due to its two exposed ends, and such an infection can also travel into the bloodstream. Additionally, as found by Jeffrey Lawson at the Department of Surgery at Duke University, CVCs can cause blood clots during dialysis which can be fatal to the patient (Lawson et al., 2020). As such, the fistula is the most preferred form of dialysis access due to its safety.

Unfortunately, studies show that Black people are not only 10% less likely than white people to receive an AV fistula, but they are also 12% less likely to have a successful and usable fistula after placement. Clinical factors such as the lower likelihood of clinicians referring Black patients to receive a fistula, greater apprehension in Black patients towards fistulas, and smaller vein diameters likely all play into this disparity (Qian et al., 2020).

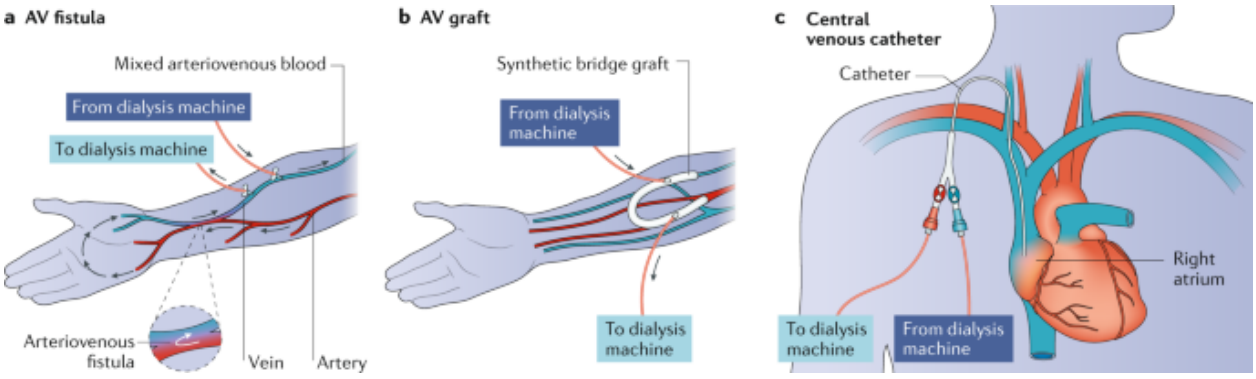

Figure 2: Dialysis Access Modalities: This figure illustrates the three common types of dialysis access modalities and how they connect to the patient's bloodstream (Lawson et al., 2020).

ENVIRONMENTAL AND GEOGRAPHIC CONTRIBUTORS

Geography and urban organization greatly influence access to necessary care for those of all racial and ethnic backgrounds. Considering that patients who are on traditional dialysis care must travel to a care center three times a week for a three-hour session each day, being closer to a quality dialysis center makes this whole process easier. Due to fatigue after dialysis, traveling to centers further away requires some form of transportation, e.g., a supportive family member to drive there and back or enough money to regularly travel on public transportation. These considerations are important with regard to traditional in-center dialysis. However, newer dialysis modalities that are more portable and accessible at home have come to the forefront: peritoneal dialysis and home hemodialysis. Peritoneal dialysis allows patients to hook up to a dialyzer overnight and filter their blood without having to route blood flow out of their bodies.

Home hemodialysis, on the other hand, offers patients with a portable form of the usual dialyzer machine to use at home, preventing travel times and allowing people to use it at times that work with their schedule. Both modalities greatly improve quality of life, and as such are vital for improving adherence to dialysis routines and overall dialysis outcomes. This is confirmed by a 2019 study by Helena Rydell et al. at Lund University in Sweden that showed that patients on home hemodialysis were more likely to stay on the same modality, had better survival, and had a higher likelihood of receiving a kidney transplant (Rydell et al., 2019). A retrospective cohort study by Prakash et al. found that, understandably, patients in rural areas had the poorest access to peritoneal or home hemodialysis and had to travel farther distances to reach dialysis care centers. They also found that patients in minority racial groups were less likely to have access to home hemodialysis compared to white patients (Prakash et al., 2014).

Residential segregation plays a key role in poorer access to dialysis care for minority communities. A 2007 study by Dr. Rudolph Rodriguez, a professor at the University of Washington School of Medicine, addresses this. Rodriguez found that dialysis centers located in ZIP codes with predominantly Black populations were of poorer quality; they had higher mortality rates and failed to meet performance standards. In addition, patients living in predominantly Black ZIP codes had longer times to transplantation, increasing the risk of mortality during this timeframe (Rodriguez et al., 2007). Since home hemodialysis is not as readily available to them, Black CKD patients are faced with the troublesome choice of either having to go to a poor dialysis center nearby or spend gas or transportation money to regularly go to a distant dialysis center of a higher quality. It can be seen how the stress of such a dilemma can pile on and contribute to worsening outcomes as well.

In addition to diminished access to dialysis centers and effective modalities, people of color (POC) living in predominantly POC neighborhoods are exposed to more environmental pollutants, particularly for those living in predominantly Black neighborhoods. Such exposure to hazardous environmental pollutants greatly increases the likelihood of premature death. According to the American Lung Association, this is likely because "due to decades of residential segregation, African Americans tend to live where there is greater exposure to air pollution" (*Disparities in the Impact of Air Pollution*, n.d., n.p.). In addition to residential segregation, pollution sources are also often located closer to disadvantaged communities. Several such pollutants found in the water have been proven to exacerbate kidney disease. For example, one study relates compounds such as arsenic, lead, and particulate matter to worsening CKD (Tsai et al., 2021).

Why do African American individuals consistently live in areas where access to dialysis or pollution is worse? As hinted to above, this phenomenon is largely tied to decades of residential segregation practices that disenfranchised black families and prevented them from purchasing homes in certain communities through predatory lending practices. One historical practice was known as redlining, which consisted of categorizing predominantly Black neighborhoods as "hazardous." This reduced home values in these neighborhoods and blocked Black families from getting loans to purchase houses, thereby preventing wealth accumulation, essentially trapping black families in these "lower-valued" communities for generations. Groundbreaking work by Nardone et al. at the University of California, San Francisco in 2020 examined redlining maps created by the Home Owners' Loan Corporation (HOLC) in California and examined it through the lens of geographic variation in asthma prevalence. This group found that neighborhoods assigned a higher risk level in the HOLC maps had higher proportions of

Black residents, a significant increase in exhaust particle emissions, and increased emergency department visits due to asthma (Nardone et al., 2020). Although in the context of a different disease, this study brings to light the effect that historically discriminatory practices still have on society today, particularly on worsening health outcomes for disenfranchised communities. In the context of CKD, the "entrapment" of Black communities into these "poorer" residential areas causes more difficulty in accessing high-quality dialysis care and increases exposure to pollutants, thereby reducing their prognosis for survival with kidney disease.

FRAMING INTERCONNECTIONS WITH ACTOR-NETWORK THEORY

POINTS OF ACTION

Now that the various contributors to disparities in kidney disease have been elaborated on and explained, Actor-Network Theory can be used to separate effects from actors. Through this, one can elucidate these actors as points of action to alleviate disparities. In Figure 3 on page 13, a model is proposed for how the three groups of factors explained above interconnect and impact each other, coming together as a network to cause poorer outcomes for black and brown people facing long-term kidney disease. Using Actor-Network Theory, these interconnections can be considered, whether they be intentional or unintentional (Latour, 2007). Figure 3 is organized by categories of factors; within each category are listed various effects. For example, one effect of genetic factors is "greater incidence of diabetes" while one effect of clinical factors is "differences in access modality." At the center of these categories are the "effectors" or actors that produce these effects and tug on the network. These effects not only impact patient outcomes but also relate to each other, as depicted by interconnected arrows. Within genetic factors, greater incidence of diabetes and obesity are tied together through the APOL1 and

Thrifty genes and both contribute to a greater likelihood of requiring dialysis. Within clinical factors, outdated diagnosis criteria cause clinicians to diagnose Black patients in a biased manner, while their continued bias validates these criteria. In turn, clinician bias and diagnosis criteria contribute to a difference in dialysis access modalities for Black patients. Within environmental factors, greater distance from quality dialysis centers also makes it more difficult for Black patients to access at-home dialysis modalities. These connections also exist across different categories of effects. For example, since genetics contribute to a greater incidence of CKD within the Black community, this also informs racial diagnosis criteria that underdiagnose kidney disease for Black people. Clinician bias is also involved with Black patients' poor access to at-home dialysis care. Greater exposure to pollutants is also related to an increased likelihood of requiring dialysis as it worsens kidney function, and clinician bias is involved in poorer access to more effective at-home dialysis modalities.

These primary actors within this network are listed at the bottom of Figure 3. Genetic actors are the evolutionarily developed APOL1 and Thrifty genes, which cause greater incidence of diabetes, obesity, and greater reliance on dialysis for Black people. Clinical actors are current healthcare workers who use biased eGFR criteria for differentially diagnosing and prescribing treatment for patients of different racial backgrounds as well as the historical clinicians who initially developed the racial correction factors that introduce clinical bias today. Environmental actors are historical and current policymakers who implement residential segregation through redlining and place sources of pollution closer to POC communities. Air and water pollutants are also considered actors, as they cause biological changes within Black individuals residing near pollution sources. This example highlights the versatility of Actor-Network Theory, allowing the consideration of the effects of non-intentional entities such as pollutant particles.

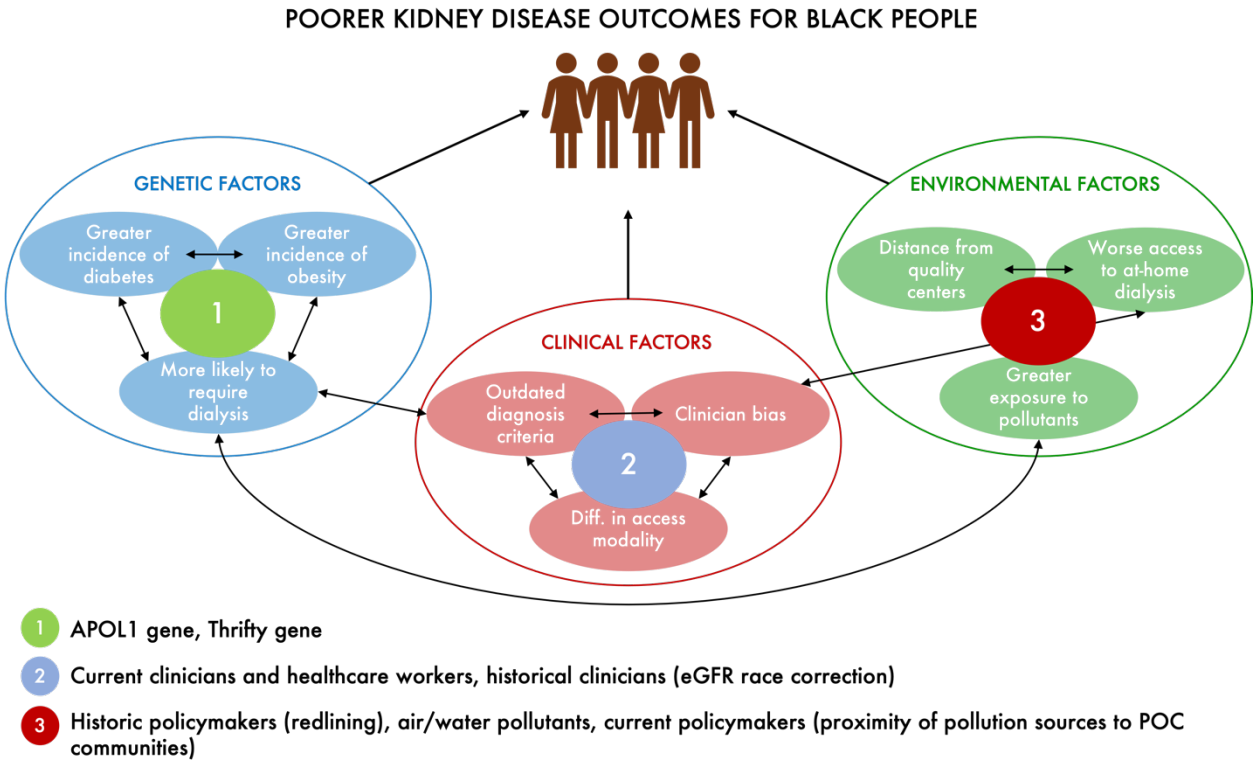

Figure 3: ANT Perspective of CKD Disparities: A network analysis of the various groups of contributors to kidney disease disparities. The interconnections between these factors and their impact on each other are particularly important (Swaminathan, 2022).

When considering interventions to alleviate these disparities, the focus falls primarily on clinical and environmental factors, as it is currently difficult to meaningfully change genetic predispositions. Many interventions to these issues could be policy-based. For example, policies could be implemented to remediate the displacement of POC from certain neighborhoods and make it easier for Black families to relocate and gain generational wealth. This would improve proximity to dialysis centers, lessen the risk of environmental pollution, and increase access to at-home dialysis. One example of such a policy is the recent "Combatting Redlining Initiative" announced by the U.S. Department of Justice in October 2021. This initiative aims to enforce fair lending practices for both depository and non-depository lenders (*Justice Department Announces New Initiative to Combat Redlining*, 2021). In the clinical scope, approaches must also be taken to eliminate outdated criteria that place black people in a bucket, particularly when educating

new doctors. This can slowly prevent the underdiagnosis of Black people. Data-driven approaches should be taken to decouple these correction factors from just racial criteria, and instead shift focus to a patient-specific approach. An example of such an approach is the work done by the National Kidney Foundation and American Society of Nephrology Task Force, who in December 2021 recommended a refit equation for eGFR that excluded the race correction factor and showed that this new equation promoted more racial equity (Delgado et al., 2021).

ENSURING EQUITABLE OUTCOMES

Actor-Network Theory shows how biological factors, clinician bias, decades-old policies, and outdated clinical criteria all contribute to these impactful disparities in kidney disease. This work highlights how interventions at the clinical and political levels can help society take a step toward making amends. When bringing a new product, such as a diagnostic for kidney disease, to market, it is essential to navigate the network of disparities and eliminate the factors that contribute to inequities in the current system. For example, diagnosis criteria for a new assay should not include racial corrections such as those currently used to calculate eGFR from creatinine. The distribution of such a product should be managed such that it is equitably distributed to clinics in neighborhoods that predominantly have minority populations. Such considerations ensure that the medical system is transformed from its problematic past, allowing for more equitable outcomes along racial, ethnic, and socioeconomic boundaries.

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