# Reassessing the Use of Race Based Correction Factors in Clinical Calculations

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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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Since the completion of the Human Genome Project, clinicians and researchers have predicted a future of “precision medicine” (PM) in which data intensive biological methodologies and predictive analytics could provide personalized treatment approaches to various diseases. In the past two decades, ideals of PM have become apparent in clinical calculations aiming to assess tissue function and/or disease progression to inform treatment options. Correction factors such as age, sex, and body mass index have been added to many calculations to help develop a more targeted treatment approach and time frame of care for affected patients. More controversially, race coefficients have recently been introduced to several clinical models following the publication of correlative studies associating race with biomarker levels indicative of disease.

This paper will explore how the imaginary of race as a corrective factor has been legitimated and the consequences of its use in clinical calculations. Overall, it will be argued that while race has value as a correction factor, the health disparities it introduces validates its reassessment in clinical calculations to optimize PM models. These disparities include negative health outcomes and distrust of treatment strategies and physicians, particularly among minoritized populations. To explore the intent versus impact of correction factors, the use of race in the calculation of estimated glomerular filtration rate (EGFR) will be used as a case study throughout the paper. EGFR is the most widely applied measure of overall kidney function used to determine the urgency of transplantation or dialysis in cases of chronic kidney disease (CKD). A fixed race correction value recognized by most clinicians was added as a factor to EGFR after a 1999 clinical study determined that African Americans had significantly higher natural levels of creatinine, a waste product that indicates renal malfunction (Levey et al., 1999). A thorough review of the stakeholders and policies that elevate race to a common tool of categorization should unveil how PM could be redesigned to better influence healthcare moving forward.

## Legitimation of Race as a Corrective Factor

### *A Push Toward Diversity in Clinical Research*

To realize the vision of race categories in clinical models, the initial push for inclusion at the advent of PM must be understood. It is well established that minoritized racial groups within the US, including African Americans and Hispanics, have been notably underrepresented in genomics research. This has mainly stemmed from a limited engagement in clinical trials due to biomedical mistrust, stigma, and competing demands (Cuccaro et al., 2020). Emphasized by a 2009 study, over 95% of participants in completed worldwide genome wide association studies were of European descent (Need et al., 2009). In the era of PM, this has prevented the identification of gene variants more common to different ancestral populations, limiting the knowledge of biological disease pathways that manifest differently between different genetic lineages.

In order to imagine a new course for PM, several health agencies have encouraged the use of diversity in genomics research. Guidelines released by the National Institutes of Health (NIH) in 2003 titled “NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research” declared that members of minoritized groups must be included in all NIH-funded clinical research without an exceptional rationale (Callier, 2019). In a similar fashion the Food and Drug Administration (FDA) released guidelines in 2005, recently updated in 2016, that recommend “a standardized approach for collecting and reporting race and ethnicity data in submissions for clinical trials for FDA-regulated medical products” (Food and Drug Administration, 2016, p. 5). Examining research around the current EGFR calculation, it is clear [Andrew S.] Levey et al. applied the principle of these guidelines by examining differences in kidney biomarkers specifically by race. Further, the discovery of a significant difference in creatinine concentration between Blacks and all other groups led to the establishment of a binary race coefficient for use in EGFR (Levey et al., 1999). The nature of this corrective value

exemplifies the propagation of diversity stratification into treatment models that are based on race.

***Alliance of Health Actors***

The alliance of clinical researchers and medical associations within the space of PM can also be acknowledged as a legitimator of race based coefficients. In most disease areas, guidelines released by prominent medical associations for diagnosing and managing disease are considered clinical standards of practice by physicians. To generate these suggestions, biomedical researchers who are members of a given association are assembled into study groups to convene findings that can be combined into guidelines. Given they are not officially law and only governed by basic standards issued by the Institute of Medicine (Institute of Medicine, 2011), clinical suggestions are less reviewed and more subject to expert experimental design and opinion (Kane, 1995). Thus, the alliance of health actors (i.e. researchers and medical institutions) allows for the experience and perspective of physician researchers to seep into disease guidelines in a more unregulated way than law.

In addition, the benefits new clinical guidelines provide healthcare professionals and organizations further motivates their publication. As described by Woolf et al., researchers can gain significant credibility within their clinical space by shedding light on current gaps in biomedical evidence. This increases their likelihood to receive financial assistance and promotion from government agencies and clinical foundations for future studies. Similarly, guidelines released under the guise of a medical association can increase political support and funding by demonstrating a commitment to clinical quality and advancement (Woolf et al., 1999).

As demonstrated within the CKD space, the race adjustment value within EGFR proposed in the 1999 experiment was officially advised as the clinical standard with the 2002 publication of “Clinical Practice Guidelines for Chronic Kidney Disease” by the National Kidney Foundation (NKF). It is important to note that Andrew S. Levey led the NKF’s Kidney Disease Outcome Quality Initiative whose chief deliverables were the 2002 guidelines (National Kidney

Foundation, 2002). Due to his influence at the agency, Levey's study was incorporated as a standard of care without review from an external actor. Upon further review, it is evident that Levey's findings could be easily challenged by a non-associated third party. For example, the investigation exclusively included patients with CKD and had a relatively low percentage of Black identifying participants in the cohort (12%) (Levey et al., 1999). A lack of initial objection may also have been due to Levey's prominence as a kidney disease researcher, revolutionizing clinical practice around CKD since the early 1990's. Most notably, Levey developed the first comprehensive EGFR equation by pooling global data of several biomarkers of kidney function, including creatinine, metabolites, and low molecular weight proteins (Alexander Ladenheim et al., 2021). While guidelines aren't a legal requirement to follow, physician trust in the opinion of medical associations and credible researchers is significant, emphasizing the ability of these health actors to sufficiently establish race as a legitimate correction value.

***Historical Undertones: Racialized Views of Genetics***

In a more indirect way, the complex intertwinement of race with genetics throughout the last two centuries must be acknowledged as a force driving the use of the social construct in clinical factors. Race was first introduced into the realm of biology by French naturalist Comte de Buffon as an arbitrary way to classify humans below the taxonomic level of species (R. S. Cooper, 2013). As argued by Comte, race served a scientific purpose by giving meaning to human variation, but not pointing out a specific aspect of that variation (R. Cooper, 1984). However, this entrance of race into clinical ideology allowed for its close association to genetics with the rise of social darwinism in the 1870s and 1880s (Weiler, 2007). During this period, it became widely accepted in the Western world that the laws of natural selection were applicable to human groups as they were to other species of animals and plants. In order to justify racist and discriminatory practices such as segregation and impediment of voting rights, many Western leaders used social darwinism as an avenue to distinguish racial groups according to 'superior' and 'inferior' genetic attributes (R. S. Cooper, 2013). Biologic stratification by race was

reinforced by eugenics, a philosophy largely developed by Sir Francis Galton for improving the human population by increasing the proportion of heritable characteristics socially regarded as desirable. Proponents of eugenics such as the Nazi Party attempted to engage this method by associating race with 'inferior' characteristics and sterilizing those who identified with these minoritized groups (Kevles, 1999). While social darwinism and eugenics have been rejected and detested in the past 50 plus years, they provided an attachment of genetics to racial categories that still permeates clinical ideology in current time.

Policy to disconnect race and genetics in medical school has only recently been attempted with the release of 2020 guidelines by the Association of Medical Colleges (AAMC). In the "AAMC Framework for Addressing and Eliminating Racism at the AAMC, in Academic Medicine, and Beyond", the AAMC recommended a review of race in biology and structural scientific racism as an integral piece of medical school curricula (Association of American Medical Colleges, 2020). Given physician education at its core has not previously attempted to completely clarify race, experts have not avoided its use in clinical calculations considering known correlations with genomic biomarkers. This is exemplified by the perspectives of researchers who established race as a factor in the EGFR equation, especially lead physician Andrew S. Levey. Recently reflecting upon his work, Levey insisted, "We really thought back then in the mid-90's, when we were doing our study, that we were doing a lot of good by recognizing the differences in creatinine between Black [people] and White [people], because we'd have a better estimate" (Ahebee, 2021, p. 1). Undoubtedly, historical associations have entrenched race in the clinical world and legitimated its use as an apparent beneficial adjustment factor.

## Consequences of Race Correction in Clinical Calculations

### *Counterargument: Conservation of Race Coefficients Optimize Treatment*

As argued by the World Health Administration among others, stratification of patients by known factors must be carried out to inform PM clinical calculations given the infeasibility of truly

personalized medicine. Currently, individualized treatment strategies are unrealistic because (i) technology to assess personal genomic features in a limited amount of time at population level is nonexistent and (ii) patient-provider time together is too limited in the clinic to develop a treatment plan precisely adapted to an individual's lifestyle (Erikainen et al., 2019). In clinical models for PM treatment strategies, classification factors common to many equations include, but are not limited to age, sex, body mass index, comorbidities, and race.

Race is often applied given well established correlations with biological markers of disease. As already detailed, Levey et al. have shown a significant increase in normal creatinine levels among Blacks compared to Whites, especially in cohorts of CKD patients (Levey et al., 1999). This is true for numerous other disease areas including the cardiovascular space. A recent investigation found significant racial differences in measures of lipids, adipokines, endothelial function, inflammation, myocyte injury, and neurohormonal stress, which are all predictive markers of cardiovascular disease progression (Hackler et al., 2019).

While correlation doesn't ensure a difference in genetic composition due to an individual's racial makeup, the use of race can be justified when considering the removal of a race factor could decrease the accuracy of clinical calculations even when substituted with other variables. In most circumstances, this is especially true for minoritized groups. When considering the case of EGFR, researchers in a recent investigation studied the impact of replacing the fixed race coefficient with height and weight values on predicting glomerular filtration rates. A substitution of race for height and weight resulted in a systematic underestimation for African American participants. The equation with a race coefficient was also much more accurate for contributors with EGFR values of less than 75 mL/min/1.73 $m^2$, which is indicative of stage 2 or greater CKD (Levey et al., 2020). A removal of race could therefore result in inappropriate treatment of African American CKD patients, including early recommendation of transplant or dialysis and wrongful dosing of drugs for other comorbidities

excreted by the kidneys. Ultimately, these findings suggest race could have relevance in PM treatment models.

***Negative Health Outcomes Among Minoritized Groups***

Although race is useful in clinical calculations to some degree, the negative effects it has on health outcomes and patient-provider relationships are more significant. In regards to patient results, the discrete nature of race adjustment values inherently result in a flawed prediction of disease progression. This is due to the fact that (i) genetic makeup is minimally influenced by race, (ii) genomic variation exists among racial groups and (iii) the boundaries of race are not well defined, with many individuals identifying as multiple races or a race not generally specified in biomedical research (Collins, 2004). These realities don't even consider how the aggregation of patient data into racial categories allows for the overgeneralization of populations in dissimilar social and cultural settings, further leading to predictive ambiguity (Abbott, 2015). A continuous rise in world population will only increase global genetic variation, further reducing the reliability of classifying groups by self-reported or perceived race (George Adigbli, 2020). Thus, it is clear that race factors based on correlational studies propagate error into clinical calculations vital to determining the timing and type of treatment patients require for a particular condition.

The misuse of race most negatively impacts minoritized groups including Hispanic and Black identifying people. This is evident when considering a recent study investigating the predictive accuracy of the race based EGFR equation. In an experiment analyzing CKD patient data sets from 2009, 2012, and 2021, it was determined that the inclusion of a race factor led to a median overestimation in eGFR of 3.7 mL/min/1.73 $m^2$ for Black patients in comparison to their non-Black counterparts (Inker et al., 2021). Given a higher EGFR value indicates better overall kidney function, it is apparent that Black identifying patients are diagnosed and/or treated for CKD at a reduced rate relative to White patients. This is particularly harmful when considering patients declining towards stage 4 (severe) or stage 5 (end stage) CKD that must eventually receive dialysis treatment or a kidney transplant to live. As illustrated by a 2020 study

examining 2225 African Americans with CKD, 33.4% would hypothetically be reclassified to a more severe stage of CKD with the removal of race from the EGFR equation. Specifically, 24.3% and 3.1% of patients would be reassigned to stage 4 and stage 5 CKD, respectively (Salman Ahmed et al., 2020). This lack of urgency at such a critical juncture motivates the reduction or elimination of race from the EGFR equation essential to increasing survival rates among minoritized patients.

Consequences introduced by race correction only perpetuate preexisting health disparities faced by minoritized groups in PM. As mentioned earlier and suggested by a 2019 investigation, greater than 70% of global genomics studies have focused solely on European ancestry populations (Martin et al., 2019). Considering genetic biomarkers from European groups don't consistently predict disease in other populations, it is extremely difficult to optimize treatment among marginalized groups. Along with other inequities including physician bias in health data (Geneviève et al., 2020), the health outcomes of minoritized populations are clearly negatively influenced by PM initiatives.

***Increased Patient-Provider Distrust***

The use of race adjustment values in clinical equations also creates distrust of PM treatment options, which is particularly pronounced among minoritized patients. This ultimately results in a strained relationship with their healthcare provider. To illustrate this reality, one study examined the perspectives of race-based medicine such as CKD strategies among three different racial groups: White, African American, and multiracial. It was found that roughly 40%, 60%, and 90% of White, African American, and multiracial contributors, respectively, reported being "moderately suspicious" or "very suspicious" of raced-based therapeutics (Condit et al., 2003). Evidently, public trust of racially informed treatment is low and significantly reduced in minoritized groups. It is also important to note the high level of skepticism of mixed raced individuals, who are innately obscured by fixed race correction factors.

Further, this seems to in part lead to physician distrust in marginalized populations. A 2003 investigation of US respondents aged 18-75 revealed that non-Hispanic Black participants were 37% less likely to trust their physicians in comparison to non-Hispanic Whites (Boulware et al., 2003). Similarly, Black prostate cancer patients in another study reported a physician trust score 3 points lower than their White counterparts, a statistically significant difference. This is particularly relevant to this analysis considering clinical equations applied to prostate cancer treatment often include race as a predictive factor. Mistrust of medicine and physicians is important when considering their impact on seeking care and access to treatment. In the same prostate cancer patient cohort, it was discovered that Black patients delayed seeking care at a higher rate relative to White participants (Do et al., 2010). Undoubtedly, setbacks in treatment will lead to lower survival rates among patient groups in race based disease areas such as prostate cancer. Thus, patient distrust can be linked to worse health outcomes, increasing the damage of race correction values in clinical care.

Using race as a proxy for biological difference only elevates distrust of clinical experts by minoritized groups already subject to disparities such as physician bias. This is exemplified by a 2016 US study of medical students and residents that determined participants held false beliefs regarding genetic variation between African Americans and Caucasians, which negatively impacted pain assessment and treatment suggestions for people of color (Hoffman et al., 2016). Similarly, another recent investigation uncovered an implicit preference for non-Hispanic Whites over American Indians among US emergency room providers (Puumala et al., 2016). Reassessing race in clinical calculations is therefore necessary to limit further wariness in minoritized populations that could delay treatment and/or result in unequal access to adequate healthcare.

**Discussion: Envisioning a Refined Approach to Clinical Calculations**

While race has been historically linked to genomics and legitimated as a tool of stratification, the inequities it creates in regards to treatment outcomes and patient-provider

relationships decreases its value as a clinical correction factor. As the field of PM progresses, a thorough revision of race in medical calculations is necessary and alternative strategies for informed treatment plans must be developed. This may include the use of only genetic markers correlated to defined biological factors (e.g. age, sex, disease progression) and/or patient discretion towards applying race in clinical calculations. The former is currently being explored in the kidney space with the substitution of race with cytostatin C, a biomarker not correlated with racially linked factors such as diet or muscle mass, in the estimation of EGFR. Cytostatin C is a protein expelled through urine whose high concentration in extracellular fluid indicates renal malfunction (Inker et al., 2021). In the long term, researchers in the kidney space and across the medical landscape will look to develop genomic technologies that can advise treatment in a more individualized manner that rely less on categorical data like race. Going forward, it will be compelling to witness how these advancements shape the future of PM.

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