

## "Race-based medicine" using the example of GFR calculation

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### 1 What is the problem?

Modern medicine should be as evidence-based and reliable as possible. To make this possible, doctors use various scores and laboratory parameters that are as valid, time-saving and cost-effective as possible. However, people are individual, so this is not always possible without further ado. Based on this assumption, factors are taken into account in various medical formulas so that the state of health can be reflected as accurately as possible. In addition to various laboratory parameters, gender, age and also ethnicity in the sense of skin colour are taken into account when determining kidney function. A better-known example of the significance of skin colour in medicine is pulse oximetry. In the case of black people, hypoxaemia is often overlooked, which has been described many times during the Covid pandemic (Ärzteblatt, 2022). As a result, a critical illness in Black people is not properly recognised and necessary measures cannot be taken. The cause of the increased lethality of Covid infection in Black people during the Covid pandemic is the result of many different factors (Washington, 2021), but poorer medical care due to unrecognised hypoxaemia, among other things, is a facilitating, potentially fatal factor.

#### 1.1 What is the eGFR?

The kidney is responsible for the filtration and excretion of urinary substances in the urine. Its function is assessed on the basis of the glomerular filtration rate (GFR) and describes the amount of plasma that is filtered per minute. However, the GFR cannot be measured directly and is therefore calculated and estimated in medical practice using other parameters; this is referred to as the eGFR ("estimated GFR") (Amboss, 2023). The creatinine level in the blood often serves as the basis for determining the eGFR. Creatinine is a breakdown product of the body's muscles and is found in the blood of all people. The creatinine level is influenced by many factors, including your own muscle mass, diet and kidney function. Various studies have shown that serum creatinine is higher on average in people who self-identify as Black in the USA, so that a "race factor" has been included in the most common eGFR methods (MDRD ("Modification of Diet in Renal Disease") and CKD EPI ("Chronic Kidney Disease Epidemiology Collaboration")) (National Kidney Foundation, 2023). The "race factor" corrects the eGFR so that, depending on the method used, the eGFR for people who identify as Black in the USA is 16-18% higher than for people who do not. It should be noted that a higher GFR means better kidney function. (see Figure 1) (Prabhdeep Uppal et al., 2022).

STAGES OF CHRONIC KIDNEY DISEASE		GFR*	% OF KIDNEY FUNCTIONS
Stage 1	Kidney damage with <b>normal</b> kidney function	90 or higher	90-100%
Stage 2	Kidney damage with <b>mild loss</b> of kidney function	89 to 60	89-60%
Stage 3a	<b>Mild to moderate</b> loss of kidney function	59 to 45	59-45%
Stage 3b	<b>Moderate to severe</b> loss of kidney function	44 to 30	44-30%
Stage 4	<b>Severe</b> loss of kidney function	29 to 15	29-15%
Stage 5	Kidney failure	Less than 15	Less than 15%

\* Your GFR number tells you how much kidney function you have. As kidney disease gets worse, the GFR number goes down.

Figure 1: Stages of chronic kidney disease from (Prabhdeep Uppal et al., 2022).

"The Case Against Race-Based GFR", Delaware Journal of Public Health.

## 1.2 What is criticised about the "race factor" and the creatinine-based GFR calculation?

However, the "race factor" is now the basis of many discussions. It is criticised that "race" is a social construct and cannot be defined on the basis of specific genetic clusters. It is primarily a self-attribution that does not fairly reflect the diversity of ethnic groups (Prabhdeep Uppal et al., 2022), (National Kidney Foundation, 2023).

It has also been criticised that the incidences of higher creatinine levels in subjects who identified as Black people in the USA were used to infer that Black people in the USA have a higher average muscle mass and that other factors that explain higher creatinine levels were not taken into account (Prabhdeep Uppal et al., 2022). However, more recent studies suggest that there is a significant association between African descent and serum creatinine levels in the USA, independent of factors such as age, gender and body weight (Chi-yuan Hsu et al., 2021), (Williams, 2023). Significantly higher serum creatinine levels were also shown for Black people in the UK compared to non-Black people.

The race factor mainly excludes factors such as diet, social effects and racism and neglects the fact that the risk of progression to chronic kidney disease (CKD) and the prevalence of end-stage CKD is increased among Black people in the USA despite higher average eGFR values (Williams, 2023).

Until a few years ago, there was no data on the normative values related to kidney function in the African population. For this reason, data from black people in the USA was generally used, even though lifestyle habits between the USA and sub-Saharan Africa differ massively in some cases (Yayo et al., 2018). However, a multinational study in South Africa, Malawi and Uganda has now shown that creatinine-based eGFR significantly underestimated renal function compared to mGFR (iohexol-based measurement method) and even increased with lower mGFR rates. With the addition of the race coefficient, the deviation became even greater. Even the race-neutral CKD-EPI formula (2021) did not show sufficient accuracy (Fabian et al., 2022).

To understand the importance of African research for Africa, it is important to know the history of medical education in Africa. The beginning of modern medical education in Africa can be traced back to the establishment of medical schools by the European colonial powers in the first half of the 20th century. Due to independence movements, political instability, wars and corruption, medical education in parts of sub-Saharan Africa in the second half of the 20th century could not develop at the same pace as it was possible in other regions of the world. For medical professionals, emigration was often the goal (Monekosso, 2014). Increasing political stability has led to a significant increase in medical training in recent years, but this varies greatly from region to region, so in 2021 there were still some countries with no medical faculty or only one (Monekosso, 2014), (Kigotho, 2021). A US study also showed that the Covid-19 pandemic has worsened medical education in parts of Africa and that the shortage of medical professionals could be exacerbated by the pandemic in some parts of the continent (Bernhard et al., 2021). From a historical perspective, medical education in the global African South is therefore closely linked to the global North. Due to persistent structural difficulties in many African regions, the possibilities for comprehensive regional research are limited. Research findings from the global North are therefore often used as the basis for medical treatment, even if the evidence for the local population in Africa is lacking.

### 1.3 What problems arise from the current GFR determination?

The current methods of creatinine-based eGFR determination do not correctly represent kidney function for all people. Incorrect eGFR values, in particular overestimation of GFR and thus overestimation of kidney function, result in individual problems in medical practice: reduced kidney function and thus chronic kidney disease (CKD) is recognised with a delay. Medication is subsequently overdosed and the initiation of therapy is delayed, with sometimes dramatic consequences for the individual. In the final stage of CKD, the indication for a kidney transplant is delayed and the waiting time for a kidney transplant is extended (Prabhdeep Uppal et al., 2022), (National Kidney Foundation, 2023). It is assumed that without the race coefficient, up to 16% more cases of CKD would be diagnosed in Black people in the USA and up to 43% of Black people in the USA with CKD could be assigned to a higher CKD class (Ahmed et al., 2021).

The race correction is particularly discriminatory in that the actual kidney function (mGFR) at eGFR is different for clinically identical people of the same age, gender and serum creatinine level depending on their assignment to Black and non-Black people and thus ultimately does not result in the same treatment (Williams, 2023).

## 2 What needs to change?

The aim of evidence-based medicine is patient-centred medicine based on scientific knowledge. Accordingly, two comparable people should be offered the same treatment as long as they fulfil the same basic requirements. With the currently common method of determining eGFR based on serum creatinine, this is not the case for black people in particular.

Therefore, the problem of the race factor in the calculation of the GFR is often discussed. A race-independent GFR is often called for (Levey et al., 2020), (Prabhdeep Uppal et al., 2022). At the same time, however, it is also described that renal function cannot be correctly estimated even without race coefficient (Chi-yuan Hsu et al., 2021).

In the USA, a task force of the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) has therefore been set up. Since 2021, they have recommended the determination of eGFR for all adults using the CKD-EPI 2021 formula, regardless of race. In addition, GFR determination based on cystatin C should be carried out across the board, especially in adults at risk of CKD. (Delgado et al., 2021), (Inker et al., 2021). While serum creatinine levels were shown to be significantly different for Black and non-Black people, no significant differences were shown for cystatin C, a biomarker that can also be used to determine eGFR (Chi-yuan Hsu et al., 2021), (Ahmed et al., 2021). In addition, a new eGFR formula was determined that uses both creatinine and cystatin C as race-independent biomarkers and is more accurate than eGFR from either biomarker alone. In addition, the Task Force calls for further research to identify more accurate, bias-free and specific methods for GFR determination (Delgado et al., 2021), (Inker et al., 2021).

However, the issue of eGFR inaccuracies is a problem that extends beyond the borders of the US. For people in sub-Saharan Africa, the eGFR cannot be accurately determined using current methods, which means that the actual kidney function cannot be mapped. Cystatin C-based eGFR formulas appear to be superior to creatinine-based methods in sub-Saharan Africa, but are too cost-intensive for practical use and are therefore currently not a realistic alternative (Niang and Luyckx, 2022).

To summarise, with the currently established methods it is not possible to offer all people the same medical care based on the kidney function determined. Further research is necessary in order to offer everyone the best possible treatment. The establishment of testing methods that are cost-effective and time-efficient and that correctly map kidney function are important beyond the USA. This is because the currently established procedures underdiagnose individual groups, particularly black people in the USA and the global South, with regard to CKD. These people are thus denied prognosis-critical therapies.

### 3 How can things change?

The aim should be to establish procedures that reliably and cost-effectively map kidney function, regardless of gender, weight and ethnicity. To date, GFR determination based on serum creatinine is the standard; alternative methods that use cystatin C as a basis are currently not possible across the board due to the high cost factor. The establishment of a race-free GFR determination based on serum creatinine (CKD-EPI 2021) has already been implemented, but is still associated with imprecision and is therefore not a conclusively satisfactory solution.

It is therefore important that doctors currently practising in both the global North and the global South become aware that there is a certain degree of inaccuracy with the established methods and that kidney function may be overestimated, especially in black people. For this group of people in particular, if there is a relevant consequence for action, kidney function should be assessed using alternative methods, e.g. using cystatin C, even if this results in higher costs.

Furthermore, it is also necessary to continue research and collect data in the Global South because, as has already been shown, kidney function cannot be correctly determined in the Global South using the methods commonly used in the Global North. Raising awareness of this is also of great

importance. Improving the structural framework conditions for African research in Africa is necessary for better care for the people of the global South.

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### **Abbreviations:**

ASN - American Society of Nephrology

CKD - Chronische Nierenerkrankung

CKD EPI - Chronic Kidney Disease Epidemiology Collaboration

eGFR - Estimated GFR

GFR - Glomeruläre Filtrationsrate

MDRD - Modification of Diet in Renal Disease

mGFR - Measured GFR

NKF - National Kidney Foundation