A transparent lens on estimated GFR

Karen Titus

May 2021—Forget about who's buried in Grant's Tomb (though for the record it's Grant, his wife, and their dog). For laboratories, the deceptively simple question now under scrutiny is, What is estimated GFR?

It is indeed an estimate, for starters—an approximation of glomerular filtration rate, which in turn is a physiological parameter that's actually difficult to measure, says Greg Miller, PhD, professor of pathology, co-director of clinical chemistry, and director of pathology information systems, Virginia Commonwealth University. Even so-called measured GFR values are not very precise in individual patients.

It's been carried along by several equations over the decades: Cockcroft-Gault, MDRD, and CKD-EPI, all of which (to the consternation of some) are still in use.

It guides clinical care, including referrals to specialists and placement on kidney transplant lists, as well as dosing of medications such as metformin. Some call it a workhorse.

But estimated GFR (eGFR) has also long been saddled with a race-based component, a coefficient that adjusts for better kidney function for Black patients compared with other patients. As medicine considers its ties to structural racism and related inequities in health care, eGFR is being looked at with fresh eyes.

A National Kidney Foundation–American Society of Nephrology task force, established in summer 2020, recently released its interim report on reassessing the use of race in eGFR (Delgado C, et al. *J Am Soc Nephrol.* Published online ahead of print April 9, 2021. doi:10.1681/ASN.2021010039). In early March, the presidents of both organizations said in a joint statement that race should not be used in eGFR equations (http://bit.ly/NKF-ASN).

In another sign of potential change, a group of physicians has submitted a petition to Labcorp, Quest Diagnostics, and Sonic Healthcare Limited asking them to drop race-based eGFR from their renal function reporting (http://bit.ly/egfr-petition).

To be clear, eGFR itself is not going away. "At the end of the day, glomerular filtration rate is the fundamental indicator of kidney function," says Dr. Miller, a member of the NKF-ASN task force. "An estimate of glomerular filtration rate is very helpful to try to understand if the patient's kidney function is good or not very good or very poor. Doing the estimation has come to be standard of practice and extremely widely used," with more than 90 percent of U.S. labs reporting the value, he estimates. It may not be a thoroughbred, but it belongs in the barn.

So the real question about eGFR is: Can we do this better? It's being asked in many corners of medicine: in laboratories; by medical school students and residents; by nephrologists, family physicians, and other patient-facing clinicians; and by critical race theorists and others devoted to health care equity.

At a number of institutions, change isn't in the air—it's already transpired. A handful of laboratories have dropped the race multiplier or made other adjustments to how they report eGFR, even before the task force delivers its final report, which is expected later this year.

Edwin Lindo (left) and Dr. Geoffrey Baird. At the University of Washington, where the race coefficient is no longer used in eGFR, “There was a lot of support for questioning and for improving our practices,” Dr. Baird says. [Photo: Mike Siegel]

It’s been a team effort. Nephrologists and laboratory colleagues are “natural allies,” says Melanie Hoenig, MD, clinical nephrologist at Beth Israel Deaconess Medical Center and associate professor of medicine at Harvard Medical School. That eased the way for BIDMC to bump the race multiplier more than four years ago. “March 1, 2017,” she recalls. “To my knowledge, we were the first in the nation.”

She also credits medical students at the school, where she directs a required, first-year class called Homeostasis II. Harvard had rolled out a new curriculum the year before, using the flipped classroom model. In that discussion-heavy, lecture-light environment, learning about the race multiplier in eGFR launched a wider exploration. “A student raised his hand and asked, *Why would there be a correction factor for better kidney function for the very individuals at the greatest risk for end-stage kidney disease?”*

Dr. Hoenig had an answer at the ready. The equation was based on studies that observed higher kidney functions in many people who were identified as Black, even with the same creatinine level. The multiplier was used to account for this difference, with the suggestion that it adjusted for the supposedly higher muscle mass in Black people versus white people.

But that’s not where the matter ended. Along with her students (including members of the school’s Racial Justice Coalition), Dr. Hoenig began to look into the matter further, reviewing studies on eGFR, some of which used MDRD (the equation was published in 1999), and others that used CKD-EPI (published in 2009). Ultimately, there seemed to be no compelling reason to use the race multiplier, she says; in fact, there were compelling reasons *not* to use it.

Once the deeper dive began, it didn’t take much to convince others to make the change, Dr. Hoenig says. She and her students met with the head of the clinical laboratory. “He loved eGFR,” she says, “because it was something the lab could provide to clinicians: *We’ll do the math for you*. But he was very moved by our conversations.” Other stops included meetings with the chief of medicine, the clinical laboratory committee, the Nephrology Division, the primary care practice QI folks, and pharmacists (“who told me they were still using Cockcroft-Gault,” she says).

Dr. Hoenig

As they presented the eGFR story to colleagues, she recalls listeners being surprised by two things: No. 1, that estimated GFR was, in fact, an estimate; and No. 2, the flaws of trying to use the social construct of race in a clinical lab report.

“Transplant was also very excited about the change,” Dr. Hoenig says, since it would enable the team to qualify patients sooner for the wait list. “When I presented this to Dr. Martha Pavlakis, the director of our Transplant Institute, she said, ‘We’re starting now—we’re not going to wait for the computer system.’” So they began on Jan. 1, 2017, using the lower number for all patients.

In recent months the University of Washington also dropped the race multiplier.

The move was concomitant with other updates to eGFR, including moving from MDRD to CKD-EPI. “We were maybe even a little late to the game on that,” says Geoffrey Baird, MD, PhD, professor and interim chair, Department of Laboratory Medicine and Pathology.

Dr. Baird and colleagues had been paying attention to the growing literature illuminating the history and consequences of using race to estimate GFR. (For a useful overview on the topic, Drs. Miller and Hoenig recommend: Levey AS, et al. *Clin J Am Soc Nephrol.* 2020;15[8]:1203–1212.) And like Dr. Hoenig, Dr. Baird says he was approached by medical students who were concerned about potential inequities. UW’s Office of Health Care Equity, which includes physicians and a critical race theory scholar, Edwin Lindo, JD, who is the assistant dean for social and health justice, were also in on the conversations.

The path to change was similar at both Beth Israel and UW: Talk to others, and then others, followed by still others. Dr. Baird says he assembled a group that included the chief medical officer and nephrologists. After poring over the literature, they decided to drop the multiplier.

The reasons for doing so piled up quickly:

- concerns about equity.
- potentially misassigning race.
- concern about the accuracy of the original studies.
- doubts about the usefulness of race.

In Dr. Baird’s view, dropping the coefficient meant putting more accurate information into the patient’s record.

He and colleagues also asked basic questions about race: How was race determined for studies used to develop MDRD and CKD-EPI? More fundamentally, how is it determined at all?

Ideally, says Dr. Baird, physicians would use a biologically based determinant, rather than a social construct, to account for the differences seen in eGFR measurements. “If we know someone has biology number one, we would calculate it one way, and if biology number two, calculate it a different way.”

Race has often stood as a proxy for biology, and race-based reference intervals have been standard for decades, notes VCU’s Dr. Miller. He suggests that “ancestry” and “genetic background” would be more useful terms for trying to understand observed differences in patient populations. “Racial construction, most people agree, is more of a social distinction than a biological distinction,” says Dr. Miller, who discussed eGFR’s limitations in a letter to

the editor in *Clinical Chemistry* (2021;67[4]:693–695).

Those who developed the initial eGFR equation suggested the different creatinine measurements they saw in their study could be explained by the supposed difference in muscle mass between Blacks and whites, a premise now widely rejected. “I have yet to see a direct correlation,” Dr. Baird says. “The robust evidence is lacking. And even if it were true across generalities, it’s unclear if it would be true in specific.”

Furthermore, Dr. Baird says, “One would have to actually agree that there is a strong biological underpinning to race.”

There isn’t, says Lindo, the assistant dean for social and health justice who is also acting assistant professor, Department of Family Medicine, and adjunct acting assistant professor, Department of Bioethics and Humanities. One of his roles at UW has been reviewing medical school curriculum to evaluate the use of race to describe biological functions. “We have to be much more precise,” he says. “Using race is, I would argue, intellectually lazy if we don’t define and articulate what we mean when we talk about it.”

When he spoke to his students about race and eGFR, for his elective course at the medical school, “Critical Race Theory in Medicine,” it hit a nerve, he says, and helped lead to the aforementioned discussions. “We were all asking, *Why do we use race?* The answer wasn’t as clear as maybe we were teaching it and applying it in the clinic.”

Lindo credits UW colleagues, particularly those in the laboratory, for their frank discussions about race. The eGFR equations were developed, he says, without considering the effects on Black patients; now that this is being openly discussed, it should lead to a more scientifically sound approach. His laboratory colleagues agreed that race has proved to be a poor proxy in much of biomedical research and that it’s not an effective measurement tool, but many assumed it was the best option. Says Lindo: “It wasn’t until we started digging into it where they said, *Race isn’t as effective as we thought it was.*” A follow-up study of their patient population (which has been submitted for publication) made it clear that the race multiplier could be safely dropped.

Another crucial question was whether the multiplier prevented Black patients from getting care they might have received if they had a “white” eGFR. Fortunately, Lindo says, it didn’t apply to transplant patients at UW Medicine—all patients were already being assigned the lower number, regardless of race.

Even if race were a useful determinant—an “if” that seems to grow larger by the day—how might patients be categorized? (The eGFR equations divide patients into Black and non-Black groups.) And who decides? Wonders Dr. Baird: “Is it the physician? The physician who happens to be the same race or a different race? Is it the check-in person who registers the patient in the medical record? Is it the patient themselves?”

Chimes in Dr. Hoenig: “One example we often come back to is if president Obama came to my clinic, which value does he get? The better kidney function, and I say, ‘See you next year’? Or the less-good kidney function,” which might prompt tighter blood pressure control and earlier follow-up? “Because there are decision points from the estimated GFR that dictate care, this gave us a lot of concern.”

The child-adult transition also draws attention to the multiplier’s drawbacks. Height, not race, is the determining factor for children. “You could be 17½ and six feet tall, and when you turn 18 you could become a white man or a Black man,” Dr. Hoenig says. “There are so many examples of why this whole thing is flawed.”

As Dr. Baird and his colleagues dug into these questions and others, they realized they were trying to see if biology, ancestry, and genetics truly fit together. The eGFR multiplier was using race—ill-defined and problematic as it is—as a correlate of ancestry, which was seen as a correlate of genetics, which stood in for biology. “The chain of custody there is pretty murky,” Dr. Baird says. “There isn’t any conclusive evidence that supports biological differences between racial groups,” assuming those groups can even be defined.

“Now, if we ended up having a genome sequence on patients that we could determine,” says Dr. Baird, “or if we had a high-resolution scan of renal architecture and we could count glomeruli—something that we could actually

assign biology to—that's one thing. But we were using this surrogate—race—that's been tenacious in our mind, our culture, our society. It's incumbent on us to really scrutinize it—are we practicing good medicine?"

"That was the first problem for us," Dr. Baird continues. "Are we using a [multiplier] that is ascribed to a *meaningful* quantity? I told folks over and over again, as we were having these discussions, that it is my desire to not knowingly put incorrect information into the medical record. I'm a laboratorian. I want to put the most accurate laboratory results in there. And if it's a calculation, I want it to be the most accurate one, not one that's misleading."

In the view of Dr. Baird (left), shown here with Lindo at UW, dropping the coefficient meant putting more accurate information into the patient's record. [Photo: Mike Siegel]

A second problem, Dr. Baird says, is a simple, math/chemistry 101 issue. The scatterplots used in eGFR studies appear to show the existence of a mathematical bias when subdividing populations into Black and non-Black groups. But race may not be the correlate. "I haven't seen the ones for Asians, for Latinos, for Native Americans." Moreover, he says, "The correlations look like a cloud of points *around* a line, not a bunch of points that are all clustered *on* a line."

So even if it were possible to somehow identify race and apply it in a meaningful way, Dr. Baird says, "The correlation isn't actually very good. It's just not a very good calculation."

Satisfied with their exhaustive unwinding of the data, Dr. Baird and colleagues felt the next step was manifest: The race coefficient "wasn't clearly helping. It was probably hurting in some edge cases. And there didn't seem to be any clear benefit to the practice. So we decided to stop using it."

The logistics of making the change have been relatively minimal, say those who've updated their approach. It turns out, Dr. Baird says, that some clinicians weren't even using the values derived from the race multiplier. In these cases, "We're just throwing noise into the medical record. What's the point of continuing to put it there?"

And since the laboratory was already making the switch from MDRD, dropping the race multiplier seemed like just another change. "It's sort of like when you're remodeling your home—it's easy to make a major change because you're already ripping down the back of your house," Dr. Baird says, who adds that perhaps the biggest improvement clinically has come from adopting CKD-EPI.

Nor have there been any unintended consequences, he continues. He suspects they may never appear, given the turn-over-every-stone approach. "The group was interested in getting to the bottom of this. It's telling that there

was support at every level—student trainees, nephrology, the folks who were most viscerally invested in creatinine measurements, and the medical leadership level above us all. There was a lot of support for questioning and for improving our practices."

Lindo says while bringing critical race theory to bear on medicine "isn't a process that happens overnight, I will say it happened beautifully fast at UW. Within three meetings, our lab scientists came back and said, *We're going to change this.*"

Similarly, the switch at Beth Israel was "shockingly easy," Dr. Hoenig says. "Yes, I had a million meetings. I went to committee and division meetings to explain the change. That was hard," she says, noting this was well before COVID-19 flattened the world into one giant Zoom gathering. But that was perhaps the hardest part. "Honestly, I think when people discovered eGFR stood for an estimate, they were all too happy to give up race."

Others who've thought deeply about the race multiplier are choosing to hold off on making sweeping changes to eGFR, including Lesley Inker, MD, MS, associate professor of medicine at Tufts University School of Medicine and director of the Kidney and Blood Pressure Center, Tufts Medical Center.

Dr. Inker, a member of the NKF-ASN task force, says her laboratory colleagues "agree with the importance of having a national conversation based on the totality of data, evidence, and considerations, and not having a unilateral move that's quick."

Dr. Inker

"The national conversation has widened, and it's best that well-considered recommendations make the basis for what we do at Tufts, instead of quick changes made without careful consideration of all the issues." She and her colleagues will be guided by the task force's final report, she says.

"I think everybody understands that this is an important change to make," she says. "But they want to make sure it's patient-centric and doesn't harm anybody."

That doesn't mean standing still. "This would be a great time to change to CKD-EPI, which is more accurate," says Dr. Inker, who helped author the equation. She sees no reason to wait. It dismays her that some labs still use MDRD; any discussion about re-examining the race multiplier should be done in the context of finding the best way to estimate kidney function overall.

Likewise, she says, now would be a good time for institutions to boost use of cystatin C, and health care providers should increase their ordering. While assay variation was previously a concern, matters have greatly improved since 2018, Dr. Inker says, crediting the CAP Surveys.

As others have noted, estimated GFR is meant to be a preliminary assessment. It has, however, "taken on a status with respect to classifying patients and qualifying patients to be on a transplant list," Dr. Miller says. He's concerned that eGFR includes too much uncertainty to be used in such weighty decisions. It can offer insight into disease process and the impact of kidney disease on the population level, he says. "But when you start applying it at the individual patient level, it becomes difficult to justify some of the cutpoints that are being used."

It bears repeating: It's an *estimate*. "That sometimes gets forgotten" in clinical practice, Dr. Miller says. "If you calculate a confidence interval for the value, you'll find it's pretty large." If the value doesn't seem consistent with other indicators of kidney function, he suggests, it would be worth a follow-up test, like a cystatin C. It is, however,

a low-volume test at his laboratory. “I can’t tell you why.”

The task force is viewing its work through a wide-angle lens and has “gone through a very methodical process of examining all the issues around race disparity in medicine, particularly in kidney disease,” Dr. Miller says.

As the interim report makes clear, this remains a work in process, a fact some find curious if not frustrating.

Says Dr. Hoenig: “I am disappointed that the interim report is just that—I would have hoped for more definitive response by now.”

Dr. Baird adds, “It doesn’t actually say anything. It is more of a plan to eventually say something.”

Using his own wide-angle lens, Lindo expresses concerns about relying on task forces and national organizations to create more equity in health care. “I think change comes from those closest to the population affected—the labs, the providers, the educators, and students.” He’s watched other laboratories drop the race multiplier and says it’s this type of groundswell that’s pressuring larger groups to act.

Dr. Miller

“I don’t know if I want groups like the NKF to be the ones to lead the work,” Lindo says. “I think we need a fresh critique with innovative ideas, and then it’s received and embraced by the much larger national organizations. I can imagine a task force being created, but if there isn’t, for example, a critical race scholar in these national organizations, are the conversations going to be the same as the ones that got us here?”

Dr. Miller says the group has heard from experts in areas ranging from race and ancestry and equation development to kidney disease and drug dosing, “to try to get a very thorough understanding of the complete picture of the impact of using estimated GFR.”

The members are evaluating more than 20 eGFR equations for potential use, including looking at performance characteristics, feasibility, the representation of racial groups used in developing the equations and validating data sets, and the impact on medical and drug dosing decisions as well as epidemiology.

Removing race doesn’t leave a problem-free equation in its wake. “I think this is one of those situations where there probably is not really a correct answer,” Dr. Miller says. “That’s why we’re looking at so many different aspects—to make sure the recommendation fits various uses of the equation and becomes the most practical solution to a difficult problem.”

Once the race multiplier is dropped, the question becomes, then what?

“This is a big question,” says Dr. Hoenig. “Are you going to have everybody be one number—the Black, or the non-Black, or the lower number? Or are you going to present the two numbers? Or average the two?”

Her institution opted to present both numbers as a range, accompanied by text that briefly explains kidney function. She concedes she’s in a fortunate spot—since they use a home-grown system, “we have a lot of real estate, if you will, in the lab report.”

Among those that use Epic, some simply drop the second number; some Epic reports provide a blood creatinine, an estimated GFR, and then add a line underneath telling them to “multiply by” if the patient is Black. “They don’t do the math for you. So a lot of physicians may just ignore that anyway,” Dr. Hoenig says.

At other institutions, however, Epic programs are linked to patients' registration—patients may identify as Black, white, something else, or prefer not to answer. Epic may pull that information and present the eGFR based on self-reported race, unbeknownst to clinicians, Dr. Hoenig says. "Some think, *We don't even use race*, but it turns out they do. They just didn't know it was happening."

Dr. Hoenig allows room for ambivalence. "We chose both numbers; I'm not sure that was the right decision. It just seemed like the better move." Being able to provide a nuanced report helped. They included language around age-related decline in kidney function, since dropping the Black race coefficient without explanation runs the risk of suggesting kidney disease is present, she says. "You could suddenly label a lot of people with chronic kidney disease."

Though her institution moved early, she says it's reasonable if labs want to wait for the final task force report, since it might bring more consistency to the whole process. On the other hand, "I know a lot of laboratorians who are saying, *Why are we left holding the bag on race?* So many laboratorians want the race thing gone now."

In short, "Either of those stances would be fair," Dr. Hoenig says.

Dr. Baird sounds like he's done thinking about it. "Truth be told, since last March there's been something else occupying the medical system," he says with a laugh. "I'm not going to spend much time perseverating on when other guidelines come out, or when the rest of the systems in the country catch up. I know what we're doing here. It took me a while, but I'm comfortable with it."

Though the ultimate decision doesn't rest with medical students, they've been a key part of the conversations. Dr. Miller has talked with members of VCU's nephrology department, and they, along with the department chair, have met with medical students, residents, and physicians to address "the use of a race term in an estimating equation as potentially introducing disparity in medical treatments."

The concern is legitimate, says Dr. Miller, whose own institution will await the final task force report before making a change. "I think it's very encouraging that medical students are socially responsible in the way they want to practice medicine, and in the way they want to be taught how to practice medicine." He calls their engagement refreshing and adds, "This is a societal issue. Kidney disease is not the only part of medicine where racial disparity has been known to occur."

Certainly not. COVID-19 may be the biggest example, but it's surrounded by others. Race-based benchmarks have even filtered into NFL concussion testing (Possin KL, et al. *JAMA Neurol.* 2021;78[4]:377–378).

As the literature continues to swell with accounts of racial inequities in health care, what role might labs have in solving the problem?

Dr. Baird is unsure. "Many of our problems that have to do with racial and social justice in medicine are probably not related to mathematical biases in lab tests," he says. Rather, he suggests, they're access problems. "It's not that A1c is intrinsically problematic. But if you do not have access to health care for a large swath of your population, that's a bigger problem."

Has the recent SARS-CoV-2 spotlight on labs given them a bullhorn to agitate for broader change? Dr. Baird responds with, "I'd say, 'Yes—*but*.'"

"We could lead this," he says, "but the question is, *How?* It turns out that every 102 years there's probably an opportunity for laboratory testing to be front and center."

It may take another actor—a relatively new presence on the medical stage—to help maintain momentum. Lindo's position as assistant dean for social and health justice is one of only two such posts in the country, Lindo says. "You wouldn't believe the number of emails I get from people seeking guidance, who say, *I don't know how to talk about this with my colleagues.*" Last year he gave 163 talks by Zoom.

The pandemic hasn't made his job any easier, he says, but it has highlighted the racial inequities in medicine. When he talks about it now, "I no longer sound like the person who's presenting in the wrong room," he says with a laugh. He no longer has to explain why he has a position in the Department of Family Medicine. "The pandemic means I no longer have to be shouting from the top of the mountain, saying, 'We have issues.' Now we're talking about how to solve them."

Still, challenges persist. He talks about encounters with those who agree that structural racism exists in medicine, but say that individual racism does not. "That's fascinating," he says. "So who's doing the racism? Desks?"

Others suggest he's looking for racism in places where it doesn't exist. "They say, *Why do you have to be such a nihilist? Do you just walk around and think the world is racist toward you?* And I say, 'I'm not thinking it—it shows me.'"

He uses the personal to pivot back to the larger problem. He and his wife (a surgeon who is Black; Lindo identifies as Latino) are looking to refinance their home. Aware that their racial identities put them at risk for receiving a lower appraisal (http://bit.ly/nyt-appraisal), they've begun contemplating how to avoid the risk, even considering having their white colleagues pose as the owner of the home during the appraisal.

When he shares this story with colleagues, some tell him he and his family should expose the obvious injustice. Lindo is skeptical. "I tell them, 'Let's do a test: How about the next time you refinance, you put pictures of a Black family in *your* home?' It will prove the same point."

"That's the conversation in medicine," Lindo continues. "Where is the burden being placed? On the backs of historically marginalized communities." Even as the best-intentioned providers work to end racial injustice, "There's still collateral damage along the way that we need to contemplate."

The perpetually fresh voices of medical students could remain a force as well.

Dr. Baird recalls when he learned about the race multiplier in residency, "I just thought, *Ah, that's what we do*, and moved on. I just absorbed it." He says it took a wakeup call from students, as well as the events of last year—and perhaps 2021—to start asking his own questions. "I sort of glossed over that in the past," he says, "and I think as a system we didn't give it the due diligence, the questioning, that it could have used."

Like Dr. Baird, Dr. Hoenig says it didn't necessarily occur to her to question the race multiplier. "It was just sort of handed to me: *This is the way we do it.* I had never thought about this before.

"But once you see it, you can't unsee it."

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