Parsing the role of race in Alzheimer's biomarkers

Karen Titus

October 2021—It's not quite six degrees of Kevin Bacon, but the connection between Alzheimer's disease biomarkers and equity in medicine is real (and far more important).

It's a trail researchers have been following for some time, but which has gained more prominence with the recent approval of a new drug for treating the disease (aducanumab) and the acknowledgment of racial disparities in CSF amyloid and tau biomarkers and their associated cutoffs.

Whitney Wharton, PhD, cognitive neuroscientist and associate professor of nursing and medicine, Emory University, has spent decades trying to unsnarl the threads. She recently spoke with CAP TODAY about the work she and colleagues in the field are doing and the impact it could have on clinical laboratories.

As she and others note, African American individuals are at an increased risk of Alzheimer's disease but are underrepresented in most AD biomarker studies. At the same time, more recent studies have found that biomarker levels appear to be different in different racial groups.

In a sense, people like Dr. Wharton are pulling back the curtain on not one but two Wizards of Oz. Patients need to see what biomarkers mean for their health; physicians need to see the patients behind the biomarkers.

Since Dr. Wharton arrived at Emory some seven years ago, her focus on health disparities has been mostly through the lens of race. "That's actually the reason I moved to Atlanta—from Wisconsin, which has a primarily non-Hispanic white population," she says. She's a clinical interventionist who designs lifestyle and pharmaceutical interventions to help prevent AD. Her investigations into the Alzheimer's timeline is based on data showing blood and CSF biomarkers begin to accumulate in patients decades before clinical manifestations of the disease.

"My research is biomarker heavy," says Dr. Wharton, "so in all of the clinical interventions I collect blood, spinal fluid, neuroimaging, and cognitive testing in people who are, as of right now, cognitively normal but at high risk, based on a number of factors," such as gender and race. She does research with the LGBTQ community as well.

She also works closely with people like William Hu, MD, PhD, associate professor and chief of cognitive neurology at Rutgers, who is involved in research to establish fluid biomarkers to reflect the underlying pathology of AD. (See "CSF biomarkers in 'a new era' for Alzheimer's," CAP TODAY, August 2021.)

Dr. Hu was the first to identify apparent differences in tau biomarker levels in African American/Black individuals versus non-Hispanic whites, with tau markers lower, on average, among those in the former group. These findings have since been replicated in patients as young as in their 20s, in studies done by Dr. Wharton and others.

"At first blush that would seem great," says Dr. Wharton. But interventions that target tau might not be appropriate for every patient group, she says, if the disease in those patients is not marked by higher tau levels.

This was the work that led Dr. Hu and Dr. Wharton to contact the national bioethics center at Tuskegee University. Those conversations have helped researchers and physicians take a deeper look at race, equity, and biomarkers.

Dr. Wharton has also looked closely at other, independent biomarkers, primarily related to inflammation (e.g. IL-9). "What we found is that very subtle increases in IL-9 and brain inflammation in general in African Americans might be a bigger culprit and a bigger indicator of Alzheimer's in comparison to tau. And we don't currently have any therapeutics for Alzheimer's disease that target inflammation." No one, perfect biomarker for Alzheimer's disease will cross all categories, including ancestry, sex, age, and disease status, she predicts. Instead, providers need to follow the science, she says. "We need to say, *These seem to be, from the most recent studies, an indicator of brain health for African Americans.* We need to take into account inflammation, like IL-9, as well as beta-amyloid and tau."

While there's nothing new about the need to identify biomarkers and establish cutoffs, Dr. Wharton sees an even older challenge embedded within that work. "Historically, there's been such low representation of people in clinical research. And not just Alzheimer's—childhood leukemia, breast cancer. . . ."

The link between history and biomarkers couldn't be any more direct, in Dr. Wharton's opinion: "We need to have equal representation of people of color in this clinical research, so we can find out what those biomarkers are."

The primary patient cohorts in Atlanta are Black/African American and white. Other regional centers have different populations, of course, and can enroll other groups of patients; Dr. Hu intends to start biomarker studies looking at cohorts of Asian and Asian American patients (as he previously told CAP TODAY). "That will be exceedingly informative," Dr. Wharton says.

Just as informative, she says, are the social determinants of health that may be linked to health disparities in people of color, and which may affect biomarkers.

Her work follows the community-based participatory research model. "That means I work very closely with community members, including Tuskegee," she says, adding that her work is informed and driven by community, local, and national advisory boards. Outreach includes not only patients and their caregivers but also what she calls community gatekeepers, such as those who run health care organizations and those involved in the legal system. These are, in a sense, the earliest preanalytical variables. "We really try to say, *How can we improve the representation of people of color in clinical research?"*

That, in turn, has prompted her to take a closer look at why representation is so low. Historical harms might play a role—the infamous Tuskegee syphilis study, for instance, is routinely trotted out as a barrier.

As Dr. Wharton notes, however, current, real-life issues can prevent people from taking part in research. Lack of trust and trustworthiness are part of the picture as well—disparities that have been further exposed by the pandemic—but so are issues related to transportation and housing, she says.

While her biomarker research is translational, she also uses extensive questionnaires to collect data on access to health care, willingness to participate in clinical research, housing, criminal justice, transportation, and systemic, lifetime racism. The goal is to identify barriers, "and then see how they might influence things like inflammation that we know is a biomarker."

Racism has physiological ramifications, she says. She refers to a tweet sent out this summer by one of her physician colleagues who was racially profiled while shopping and accused of stealing dress shirts, and who noted that the incident was interfering with his sleep and had raised his blood pressure. Asks Dr. Wharton: "What if it's not just that one instance? What if that happens to someone over a lifetime? What does that do to someone's health?"

There's also room to wonder what this means, on a practical level, for clinical laboratories. "Sure," she says. "I understand that. We all get very immersed in our primary and day-to-day work.

"But it is my strong opinion," she continues, "that even if I'm looking at biomarkers, if we're not understanding the mechanism, the root cause, by which these biomarkers influence disease—whether that's kidney function, heart health, Alzheimer's disease—then we're not going to help anybody. I don't always want to just give someone a pill to reduce blood pressure. I want to know why your blood pressure is high. Is that genetic? Is it because you're stressed out all the time? What stresses you out about going to the doctor? Is it because you had to take off work and take two buses to get here? Is it the needles? Is it past atrocities? What is it?" There are, she says, "real clinical implications for all these structural inequities." Not only can they affect mood and cognition, she says, but they are difficult to untangle from conditions such as high blood pressure and diabetes that are independent risk factors for Alzheimer's disease.

None of this is easy work, she says, even among those who are committed to change. Investigators are sometimes not willing to collect data on structural inequities, either because it is a difficult topic for some or because they may

not feel they have the time, given that their jobs are already overstuffed with obligations. Further complicating the disconnect between clinical research and health care and race-related issues is that people of color and others who've been disregarded by health care, such as those who are part of the LGBTQ community, may be hesitant to talk to medical professionals.

When conversation is constrained, it may feel more expedient to follow a speedy, rote script, Dr. Wharton says: *You're in here for blood pressure, so we'll give you a pill to fix your blood pressure.* "Instead of trying to understand what the root cause is and to look at the patient situationally and over a lifespan."

If the culprit is genetic, medication alone might be fine, she acknowledges. "But is there something else we can do besides giving you medication? Can we help assuage other reasons that are contributing to high markers of inflammation?" Biomarkers alone aren't enough for effective interventions, she argues, even if they meet the high bar clinicians typically set: that it has to be actionable. What happens after the results leave the laboratory and clinicians are acting? Can that be better? If not, she says, "you're just kind of throwing buckets of water on a huge health fire."

As a researcher, Dr. Wharton concedes she has more time to figure things out. She makes the most of it, including with her lengthy questionnaires. That, too, has been a revelation.

When she notes, in her grant applications, that subjects will be asked to fill out a 90-minute questionnaire about lifetime and situational stress, an hour-long questionnaire about systemic racism, etc., she's often met with review pushback. "They'll say, *That's just too much of a time burden for participants.*

"But I have never had a participant ever say, *I don't want to answer these questions*," she continues. "In fact, it's just the opposite. I've had participants say, *This did take a lot of time, but thank you for asking.*" It's not a matter of etiquette, she says; rather, patients appreciate being asked about matters that affect their health. And a more detailed, inclusive approach will lead to data that's ultimately more useful, she says. "As a gay woman, I remember the first time I was asked about my sexual orientation in a health care setting," she says. It happened when she was about 30. "I didn't mind answering extra questions because they were taking it into account for my health care. I vividly remember that."

That all makes intellectual sense. What about actually doing the work?

Dr. Wharton is blunt. "It takes a lot of work on the part of researchers to go into communities and make the concerted effort to enroll people of color."
She explains: "We have to prove ourselves trustworthy, and we have to physically go into the communities, and then we have to go back and keep going back." With this comes a change in mindset—researchers can't begin their recruitment efforts in the typical way, with a so-called ask. That simply doesn't work in patient groups that are used to being brushed aside if not blatantly ignored. "We can't go in there and explain to them why they haven't involved themselves in clinical research," she says. "We need to look inward, and say, *Why haven't you been, and what can we, as scientists and clinicians, do better to ensure you're represented?*"

This is a major shift, she says. "The problem is not with people of color, or the LGBTQ community. We in medicine are the problem.

"So we need to fix that," she continues. "It really is just a boots-on-the-ground, grassroots question that takes time and effort. And a lot of listening. So instead of going in and preaching and saying, *This is what's wrong, and this is what we need to do*, and this is what you need to do, we need to say, *How can we help you? What, in your opinion, are the barriers?* And then, *How can we have an honest and open conversation and address those barriers? What can we bring to you that will cut down on your clinic visits? Can we give you transportation? Do we need to pay people more? What do we need to do?"*

This lays the groundwork to identify truly useful biomarkers and cutoffs, she says.

This is also the type of work that led her to meet with Reuben Warren, DDS, DrPH, MPH, the director of the

Tuskegee University National Center for Bioethics in Research and Health Care. In fact, she was helping to lead a participant appreciation event; other speakers included Dr. Hu and Dr. Warren. Several hundred participants attended. ("It was a pretty big deal," Dr. Wharton says.)

The three of them spoke openly about the importance of trust and trustworthiness, she says. They then fielded questions from participants, for nearly three hours. "They got to ask all their questions, and we answered them. We had hard conversations about terminal illness, but also how to prevent disease. It wasn't just, *Thanks for participating,* and no one has any idea what happened in the study.

"We tried to help them understand what an important and vital role they played. Because without them, it doesn't matter how many publications we get, or how many grants are funded," she continues. "If we don't have people willing to donate their time and their body fluids, then we have nothing."

Dr. Wharton has had plenty of surprises throughout this work, including those that have prompted her to reject prevailing beliefs about the impact of the Tuskegee syphilis study.

Ten years ago, she says, "I was in the camp that attributed low numbers of people of color in clinical trials to that study, and to other past research atrocities. And Dr. Hu said, *We actually need to do a study to address this issue, because we don't know if it's accurate or not."*

So they did. And it wasn't—not completely.

"We found that even [among] people who had heard of the Tuskegee syphilis study, a lot of the information they thought they knew was inaccurate," says Dr. Wharton. It may be worth talking about with participants in studies, and always openly, she says. "But it's not the sole barrier to research," despite its continually being cited as such. "For me, that was an aha moment, because we had been saying forever that it was." (The preprint research paper is available at: http://dx.doi.org/10.2139/ssrn.3555860.)

That means medicine has another problem to fix. "An overwhelming majority of clinicians and research scientists are white—myself included," Dr. Wharton says. It's not just a matter of enrolling people of color in clinical trials. "We need more people of color actually doing the research. Being able to go into their own communities and gain trust—that's a whole different conversation. If you don't see yourself in the intervention—if you don't see yourself in the people who are going to help you—what does that mean?"

The flip, and equally important, side is that researchers can fall into the habit of hiding behind diversity. With the best intentions, they set out to include more people of color in their research. "And then they say, Then I need to hire someone specifically to go into that community, because that person shouldn't be me."

Research teams need to be diverse, Dr. Wharton agrees. "But that researcher—be it a person of color, or a member of the LGBTQ community—can't be the *only* representative from your lab going into the community. That is a huge misstep, in my opinion. And it happens all the time."

She recounts a conversation she had with a colleague who spoke glowingly of a new outreach coordinator she'd hired, a Black woman who was well connected with churches and other groups in the Black community. Dr. Wharton asked if the coordinator would be accompanying her colleague to speak to communities.

Recalls Dr. Wharton: "She said, *Oh, I don't go into communities myself. I'm afraid I might say something wrong.* I said, 'Dr. So-and-so, you probably are going to say something wrong. But that's OK, as long as you're honest. And then they will correct you, and you'll move on. But *you* need to go into the communities, because you're the one asking them to come to you as a clinician. They need to hear from the PI why you're doing this. You're the best person to answer those questions. You have to be open and visible. You can't just be the Oz behind the curtain.'"

When she and colleagues apply for NIH grants, they have to disclose they will collect information on racially representative cohorts. The next step, she says, "is actually holding scientists accountable to the numbers they say they're going to include."

As the medical community chips away at entrenched practices, Dr. Wharton sees change coming on another front. Though she doesn't formally teach—"I'm 100 percent researcher"—she does mentor students. The focus is biomarkers—this being, after all, a clinical laboratory. But with a twist. Since students are not fully embedded in the medical field yet, they don't see a tradeoff between looking at biomarkers and looking at the social determinants of health, she says. Rather, they start out willing to encompass complex societal and structural issues into their research.

She finds this fascinating. "Almost all of my students are in or going to attend medical school. They don't see health disparities questions as a time sink or unimportant, even though they want to be biomarker-heavy in their work.

"They don't see a separation," Dr. Wharton says.

Put another way, that's zero degrees—sans Kevin Bacon.

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