In the US, diabetes occurs more often in Black, Hispanic, and Native American people than in White people, according to the US Centers for Disease Control and Prevention. For Judith Simcox, a biochemist at the University of Wisconsin–Madison, this is more than a statistic: the data points represent her friends and family on the Crow Indian Reservation in Montana, where she grew up.

Simcox has long wondered why this difference occurred. Until 2019, her research had focused on the mind-boggling diversity of lipids in mice and used mass spectrometry to identify various fats and their functions. She switched to studying lipids in humans shortly after she moved to Madison that year to set up her new lab. There, colleagues working on a study of aging known as Midlife in the United States (MIDUS) needed help validating lipidomic data they had just received on some human serum samples. But just as Simcox and her team were to begin their analyses, the pandemic shut their lab down.

Without access to the lab bench, they delved into the data available. They built a machine learning algorithm to spot which lipids in the MIDUS data set were correlated with disease. And they began to probe biomarkers of metabolic syndrome, a condition that often precedes a person developing heart disease or diabetes.

In the clinic, doctors usually gauge a person’s risk of having the condition by running blood tests for molecules that reveal levels of circulating triglycerides and low-density lipoproteins and for low response to the hormone insulin, also known as insulin resistance. But researchers have known for decades that these common biomarkers of the condition don’t correlate with actual health in women, Black and Native American populations, and other people of color around the world. For example, researchers have found that Black people in the US have lower triglyceride levels, which might indicate that they’re at low risk of heart disease. Yet overall, Black populations in the US experience higher rates of heart disease than White people.

To Simcox, that contradiction hints at a problem: “The data tell us that the markers we’re using to assess health are poor markers,” she says.

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Now, she and other researchers are seeking newer measures—ones that not only better predict disease in everyone, including people of color, but are also easier to deploy in a wide range of settings. While some researchers, such as Simcox, have focused on molecules circulating in the bloodstream, others are developing risk measures based on testing for certain genes responsible for lipid metabolism. Measuring the molecules in the blood or testing for the genes would help diagnose disease sooner, which could help close a gap in care for people whom researchers have long excluded from studies. “People don’t realize that all of these biomarkers of metabolic syndrome were developed in studies of male populations of Western European descent,” Simcox says.

Overlooked Populations
Clinicians use a few standard measures to assess whether a person has metabolic syndrome. Those include an elevated waist circumference, high blood pressure, elevated fasting blood sugar, elevated triglyceride levels, and low high-density lipoprotein (HDL) cholesterol. A person with any three out of the five criteria has double the risk of heart disease and a fivefold risk of diabetes than a person without these traits.

Metabolic syndrome
People who meet three out of five criteria for metabolic syndrome have a high risk of cardiovascular disease and type 2 diabetes.

- Elevated waist circumference (≥88 cm for women and ≥102 cm for men, or ≥35 in and ≥40 in, respectively)
- Elevated triglycerides (≥150 mg/dL)\(^a\)
- Low high-density lipoprotein cholesterol (<50 mg/dL for women and <40 mg/dL for men)\(^a\)
- Elevated blood pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg, or both)\(^a\)
- Elevated fasting blood glucose (≥100 mg/dL)\(^a\)

Source: Prev. Chronic Dis. 2017, DOI: 10.5888/pcd14.160287.
\(^a\) Drug treatment for the condition also meets the criterion.

People who meet three out of five criteria for metabolic syndrome have a high risk of cardiovascular disease and type 2 diabetes. Credit: Prev. Chronic Dis. 2017, DOI: 10.5888/pcd14.160287.

But these biomarkers change depending on a person’s diet, exercise habits, and many other cultural, socioeconomic, and environmental factors. If participants in a study don’t represent this diversity of life experiences, then biomarkers developed in that study might not apply universally, says endocrinologist Anne Sumner of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Sumner points to the long-running Framingham Heart Study, which has tracked a cohort of people in the town of Framingham, Massachusetts, since 1948 to understand risk factors for heart disease. The study has helped researchers identify the importance of blood pressure and lipid levels in assessing a person’s risk of heart disease. But only 4% of the original participants did not have European ancestry.

As researchers began to study people from more diverse backgrounds, they found that the results of the Framingham study didn’t always apply to these other groups. “We have all these ethnicities that weren’t part of the sample sets, but the data [from those samples] get extrapolated to other communities,” says research chemist Christina Jones, who leads quality-control programs for metabolomics at the US National Institute of Standards and Technology. “So the biomarkers don’t hold up as well, and the prediction isn’t as great.”

In studies using data from the National Health and Nutrition Examination Survey, Sumner and others have found that HDL, commonly known as “good” cholesterol, tends to be consistently higher and triglyceride levels lower in Black people than in White people. In a 2019 study in the US, researchers found that East and South Asians had greater insulin resistance than non-Hispanic White and Black people. Higher triglyceride concentrations were linked to greater insulin resistance, regardless of race and ethnicity.

But at all levels of insulin sensitivity, Black people had the lowest triglyceride levels. “If you see [a person has] high triglycerides and low HDL, that triggers in your mind the thought that they might be at risk for diabetes and cardiovascular disease,” says Stanford University researcher Joshua Knowles, who coauthored the 2019 study. “But in a Black individual, you might be fooled because their triglyceride levels are not as high. That could lead to potential underestimation of the risk.”

Researchers dubbed this problem the “triglyceride paradox”: Black populations have levels of biomarkers assumed to indicate good health, despite higher rates of disease. Differences in diet, low socioeconomic status, and experiences of racism all contribute to greater levels of disease. But these differences would not explain why levels of biomarkers like HDL and triglycerides actually appear to be better if you look at rates of diabetes in Black populations, says genomic researcher Amy Bentley of the National Human Genome Research Institute.

Capturing Diversity
One temporary strategy to improve existing biomarkers’ ability to predict disease risk has been to establish different
cutoff points for people of different races. But this stopgap solution is flawed, because it reduces a vast range of social, environmental, and cultural influences to race. Not only can this approach worsen health disparities by delaying necessary diagnoses and treatments, it also reinforces the false notion that race is biological. “When we talk about race, we’re not getting at what is biologically meaningful,” Bentley says. “Whether someone self-identifies as African American is not what is driving the difference in risk here.”

Discrimination and racism result in different rates of disease through a range of mechanisms. Existing tests don’t represent those mechanisms or global differences in metabolism, environmental factors, living conditions, and more. Without accurate data on these factors, it’s tough to predict disease risk for everyone using current tests. “For so many people of African, South Asian, and other ancestries, we don’t have all of the variation described yet,” Bentley says.

Studies of genetic disease markers have shown how describing this variation can help improve clinical prediction of risk. In 2021, researchers sought markers of cholesterol metabolism by examining genes that govern lipid levels. Of the 1.65 million people in the sample, 21% had non-European ancestries. Including this population made the team’s genetic risk score more predictive than it was when additional European samples were included instead. “Even with only a small fraction of non-European samples, we saw a dramatic improvement in the performance of our risk score to predict lipid metabolism and, presumably, coronary disease,” says cardiologist Themistocles “Tim” Assimes of Stanford University, who coauthored the study.

Representation in large-scale studies is important not only because it yields more useful results overall but also because it can help spot biomarkers relevant for specific subgroups of people, Bentley says. For instance, including too few people of African ancestry in a larger cohort of people of European ancestry may make certain risk factors seem statistically insignificant, she points out. “It’s not just about inclusion,” she says. “You have to think about how you’re including different groups to make sure that we’re allowing for novel discoveries.”

Doing so helped researchers to identify a more effective biomarker for diabetes. Typically, clinicians measure blood levels of glycated hemoglobin (HbA1c) as a proxy for average blood sugar levels over time and use it to estimate diabetes risk. But it more accurately predicts risk in higher-weight individuals than those who are not higher weight, Sumner says.

In 2016, NIDDK’s Sumner and her colleagues tested HbA1c in a group of healthy African immigrants to the US and found that when used on its own, HbA1c correlated with abnormal glucose levels in only about half the participants. Other molecules, such as glycated albumin—another biomarker for abnormal blood sugar previously studied in Asian populations—also correlated with disease risk in only about half the group. But the combination of both markers—HbA1c and glycated albumin—effectively predicted risk for about 80% of the study participants. Unlike HbA1c, glycated albumin was discovered only because of studies conducted in Japan and China among people of average body weight, who are often considered to be at low risk of diabetes.

If researchers had focused only on people of higher weight, they might have overlooked glycated albumin as a potentially useful biomarker, Sumner says. In more recent studies, she and her colleagues have found that combining both markers may bypass the need to consider a person’s weight when evaluating the risk of developing diabetes. Eventually, “what there might come to be is a panel of tests that would incorporate the different features from different populations,” Sumner says.
Simcox agrees: "If we took true representation of people from all over the world and through different populations, I think that the current markers probably wouldn’t hold up," she says.

**Better Blood Tests**

Diversifying the identities of study participants is important. But also important are the identities of researchers because they frame the questions posed of data. In 2020, students on Simcox's team began to probe MIDUS and other existing data sets for insights into the different lipids correlated with disease. Camille King, an undergraduate at Hampton University who was doing a virtual summer internship in Simcox's lab, looked at whether there were differences in the age at which Black and White women developed heart disease and whether socioeconomic factors correlated with differences in circulating lipids. The team identified 529 lipid molecules correlated with hypertension in White participants and approximately 137 in Black participants. The work is now undergoing peer review.

The researchers are also extending their studies to Menominee populations in Wisconsin. Adding data on lipid molecules from a new population could increase the ability of the team’s current lipid biomarkers to predict risk of disease, says Stanford’s Knowles.

The work is especially meaningful to students like King, who is Black, and Autumn Rain Chevalier, who is a member of the Menominee Indian Tribe and leads the work with that population. King, now a graduate student at Meharry Medical College, lost her grandmother to congestive heart failure during her internship. She recalls the surprise in her father’s voice when she told him about her research project. He asked her to share her conference presentation on the topic. “I always know that when he asks me to send him something, he’s deep in thought about it,” King says. “He might not say too much, but I know it’s something that’s turning his wheels.”

It may take years for the lipids Simcox and her team are identifying to make their way onto routinely-used clinical tests. But to Chevalier, simply looking for these biomarkers and engaging communities in the process is a much-needed first step. “As Native people, we’re often forgotten, even in the data,” she says. “It’s really important that this work benefits my community, my future kids. That means more than just answering a research question.”

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