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Vahid Azimi.
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Guest: Dr. Vahid Azimi from the Alameda Health System's Department of Laboratory Medicine and Pathology in Oakland, CA.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Hemoglobin A_{1c} is frequently measured to screen for diabetes and monitor patients with an established diagnosis because it reflects blood glucose concentrations over a long period of time. A_{1c} is a term familiar to clinical laboratorians and the general public due in large part to its featured role in television commercials for new diabetes drugs. From these ads, we learned that lowering one's A_{1c} decreases the risk of adverse outcomes like retinopathy and kidney disease, and that some people taking these medicines see a drop in their A_{1c} below the desirable threshold of 7%.

The diagnostic threshold of 6.5% and therapeutic target of 7% are now well established in medical guidelines. But what if genetic factors affected A_{1c} independently of glucose? In other words, if genetic variants predisposed an individual to lower A_{1c} values, is it appropriate to apply a standardized cutoff of 7%, or should the cutoff be reduced to minimize that patient's chances of developing diabetes-related complications? A News & Views article appearing in the July 2025 issue of *Clinical Chemistry* highlights a recent publication that identified non-glycemic genetic factors that influence A_{1c} values, proposing a possible role for genetic testing in the personalization of diabetes care.

In this podcast, we are joined by the article's author. Dr. Vahid Azimi is a clinical pathologist and Laboratory Director at Alameda Health System's Department of Laboratory Medicine and Pathology in Oakland, California. His interests focus on promoting equity throughout the laboratory testing process and leveraging lab and clinical data to identify and address care gaps. So, Dr. Azimi, first, what motivated this research into non-glycemic genetic effects on hemoglobin A_{1c} and why is that important for clinical practice?

Vahid Azimi: Yeah. So, hemoglobin A_{1c} is widely used in diagnosing and managing diabetes, but it's pretty easy to forget that it's not just a marker of glucose. It's also influenced by red cell biology. Several studies have shown that genetic variation can actually influence hemoglobin A_{1c} levels independently of blood sugar and that these effects can vary across

populations. This means that two people with the same average glucose can have different hemoglobin A_{1c} levels, which can then affect when they're diagnosed or how aggressively they're treated. The authors of this study wanted to explore whether these genetic effects have real world clinical consequences such as the risk for complications.

To dig into this a bit more, traditional influences on hemoglobin A_{1c} are tied to blood sugar. So, the higher your average glucose, the more glucose attaches to hemoglobin in your red blood cells. But what these studies are starting to show is that some variance can affect how long red blood cells live or how quickly hemoglobin gets glycated independent of glucose levels. So, for example, if you have a shorter red blood cell lifespan due to a genetic variant, then there's less time for glucose to accumulate on hemoglobin. So, your hemoglobin A_{1c} will be lower even if your glucose is elevated.

That means that your hemoglobin A_{1c} doesn't accurately reflect your true glycemic burden. And these are what we call non-glycemic effects, and they can cause a discordance between the measured hemoglobin A_{1c} and actual glucose exposure. And that's really what's motivating this research.

Bob Barrett: Now the study you discussed found that people with low non-glycemic hemoglobin A_{1c} polygenic scores had higher rates of retinopathy even with similar Hb A_{1c} levels. What does that mean in practical terms for diagnosing and managing diabetes?

Vahid Azimi: In practical terms, in some patients, we might actually be underestimating their glycemic burden. So, for example, if someone has a genetic profile that lowers their hemoglobin A_{1c} independently of their glucose levels, they could have harmful levels of hyperglycemia that we're missing because their hemoglobin A_{1c} looks deceptively low. That could potentially delay their diagnosis and treatment, which may partly explain why some individuals develop complications even when they appear to have good control. Practically, from a clinical standpoint, this means that clinicians need to be cautious when a patient's hemoglobin A_{1c} doesn't seem to match the clinical picture.

For example, if someone has symptoms of diabetes or high glucose on other tests, but their hemoglobin A_{1c} is borderline or normal, genetic influences might be part of the explanation. This study also shows that hemoglobin A_{1c} isn't a perfect measure for everyone. In certain patients, we may want to rely more on additional markers like fasting glucose or continuous glucose monitoring to get a fuller picture.

Bob Barrett: This research challenges the idea of using race- or ancestry-based thresholds for hemoglobin A_{1c}. Can you explain why

that is significant and how it relates to broader conversations in laboratory medicine?

Vahid Azimi: It's a great question, and I actually think this is kind of the most interesting part of this study in a lot of ways. There's been an increasing recognition in laboratory medicine that using race as a standard for biology can lead to inequities in care. In this case, although non-glycemic genetic variants are thought to be more common in individuals of African ancestry, the effects of those variants aren't confined to one group. You know, we might think that non-glycemic variants are more common in patients of African ancestry. So, one way to deal with this issue is to apply different thresholds based on ancestry. However, practically speaking, we can't test people's ancestry in the clinic.

So, what people have done in the past, such as with the estimated glomerular filtration rate, was to use race as a proxy for ancestry. But this is problematic for several reasons. One, it led to longer kidney transplant wait times for Black patients. And it also becomes problematic because how do you decide which race to apply to what patients? So, the key point is that genetic effects vary within ancestral groups and not just between them.

So, we can't adjust diagnostic thresholds based on race or ancestry because it would make the problem worse. Ideally, the solution isn't to tailor thresholds by race or ancestry, but rather to develop tools that reflect true biologic variation, ideally at the individual level. Of course, this is easier said than done, but I believe that this is what we should strive for.

Bob Barrett: Doctor, one of the strengths of this study was its use of large diverse databases like the UK Biobank and All of Us. Why is diversity in genetic research so critical, especially in studies like this one?

Vahid Azimi: So, most of our genetic knowledge comes from studies in people of European ancestry, and we risk missing important findings in other populations. This has implications not only for fairness but also for scientific accuracy. For example, if we only use genetic variants that were identified in Europeans, we're going to underperform when applying these tools to other groups. As a result, the tools that we develop, like polygenic risk scores or genetic adjustments for biomarkers, like hemoglobin A_{1c} may work less accurately or be incomplete for underrepresented groups.

This creates the risk of exacerbating disparities rather than addressing them. The All of Us database helps to address this by including participants from historically underrepresented backgrounds. It is really trying to address the most important step in addressing these gaps, which is intentional inclusion,

making sure that genetic studies are designed from the start to include diverse populations. That means expanding recruitment efforts, building trust with historically marginalized communities and ensuring that researchers from those communities are part of the scientific leadership. Increased funding and infrastructure for international collaborations, especially in regions like Africa and Latin America, is also key. Over time, this will help create more equitable and generalizable genetic insights that benefit everyone.

Bob Barrett: Well, finally, Dr. Azimi looking ahead. How do you see this type of research influencing the future of personalized or precision medicine in diabetes care?

Vahid Azimi: I think this is a step toward more individualized care. Right now, we treat hemoglobin A_{1c} targets as a one-size-fits-all, but this research suggests that we may eventually personalize those targets based on a patient's genetic background. That could help us identify patients who need earlier intervention even if their hemoglobin A_{1c} looks normal. That said, we are not quite ready to implement polygenic scoring in the clinic just yet. First, we need larger and more diverse genetic studies to ensure polygenic scores are accurate across populations.

Then those scores have to be clinically validated, showing that they add value beyond current tools, improve patient outcomes, are practical, and cost effective. We also need clear clinical guidelines and educational efforts so that providers understand how to interpret and use this information. Finally, policies must be in place to protect against genetic discrimination and ensure equitable access to these tools.

Bob Barrett: That was Dr. Vahid Azimi from Alameda Health Systems in Oakland, California. He wrote a News & Views article, appearing in the July 2025 issue of *Clinical Chemistry*, describing how genetic variants can affect hemoglobin A_{1c} independently of blood sugar and he's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.