Hemoglobin A_{1c}—Using Epidemiology to Guide Medical Practice: Kelly West Award Lecture 2020

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The discovery that HbA_{1c} was a valid and reliable measure of average glucose exposure was one of the most important advances in diabetes care. HbA_{1c} was rapidly adopted for monitoring glucose control and is now recommended for the diagnosis of diabetes. HbA_{1c} has several advantages over glucose. Glucose assessment requires fasting, has poor preanalytic stability, and is not standardized; concentrations are acutely altered by a number of factors; and measurement can vary depending on sample type (e.g., plasma or whole blood) and source (e.g., capillary, venous, interstitial). HbA_{1c} does not require fasting, reflects chronic exposure to glucose over the past 2–3 months, and has low within-person variability, and assays are well standardized. One reason HbA_{1c} is widely accepted as a prognostic and diagnostic biomarker is that epidemiologic studies have demonstrated robust links between HbA_{1c} and complications, with stronger associations than those observed for usual measures of glucose. Clinical trials have also demonstrated that lowering HbA_{1c} slows or prevents the development of microvascular disease. As with all laboratory tests, there are some clinical situations in which HbA_{1c} is unreliable (e.g., certain hemoglobin variants, alterations in red blood cell turnover). Recent studies demonstrate that fructosamine and glycated albumin may be substituted as measures of hyperglycemia in these settings. Other approaches to monitoring glucose have recently been introduced, including continuous glucose monitoring, although this technology relies on interstitial glucose and epidemiologic evidence supporting its routine use has not yet been established for most clinical settings. In summary, a large body of epidemiologic evidence has convincingly established HbA_{1c} as a cornerstone of modern diabetes care.

Historical Perspective: Focus on Blood Glucose

Glucose has been central to the diagnosis of diabetes for centuries. The first systematic epidemiologic investigations of glucose in the 1960s demonstrated that a substantial portion of asymptomatic patients with diabetes had a high prevalence of complications at the time of screening (1). At the time, Dr. Kelly West stated, "Well designed long-range prospective studies of subjects who have had various kinds of tests for diabetes will be very helpful in determining the most appropriate criteria for interpreting these tests" (2). Landmark epidemiologic investigations, including the Whitehall study, subsequently established that fasting and 2-h glucose

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levels were associated with retinopathy, albuminuria, and future development of heart disease, stroke, and death (3–5).

A 1965 report by the World Health Organization established an early definition of diabetes in asymptomatic individuals based on elevated 2-h glucose. In the 1970s, optimal definitions were still being debated. In 1979, the National Diabetes Data Group (NGDP)—Dr. West was a member of the workgroup—established a single set of criteria for the diagnosis of diabetes with cut points at 140 mg/dL (7.8 mmol/L) for fasting glucose and 200 mg/dL (11.1 mmol/L) for 2-h glucose (6). These criteria were reevaluated in the mid-1990s, and new criteria were published in 1997 with the fasting glucose threshold for a diagnosis of diabetes lowered to 126 mg/dL (7.0 mmol/L) (7). These diagnostic cut points were largely based on cross-sectional associations of glucose measures with microvascular disease, particularly retinopathy (7).

Taking into account all available evidence, the most useful and appropriate short definition of diabetes mellitus is simple, "too much glucose in the blood."

—Kelly West (1978), in *Epidemiology of Diabetes and Its Vascular Lesions*

HbA_{1c} for Management of Diabetes

Glycated hemoglobins were discovered in the late 1960s (8). In 1968, Dr. Samuel Rahbar conducted hemoglobin electrophoresis in blood samples from 1,200 patients and found that two individuals showed an "abnormal fast moving hemoglobin fraction" and that both of these patients were also found to have diabetes (9). This work subsequently led to the discovery of HbA_{1c} and the observation that HbA_{1c} was elevated in the setting of diabetes (10). Further research established the implications of this finding for the management of diabetes, fundamentally changing diabetes care. Drs. Ronald Koenig, Charles Peterson, and Anthony Cerami demonstrated that the HbA_{1c} molecule could be used to monitor glucose control in patients with diabetes. They showed that HbA_{1c} reflected average exposure to blood glucose over the life span of the erythrocyte and proved that HbA_{1c} was a valid and reliable measure of long-term glucose exposure in humans (10).

Epidemiologic evidence is crucial for the incorporation of a new biomarker into clinical practice. Large epidemiologic studies have demonstrated the association of HbA_{1c} with retinopathy and other diabetes complications (11–14), establishing its value as a prognostic marker. Randomized clinical trials established that interventions that lowered HbA_{1c} slowed or prevented complications in persons with type 1 and type 2 diabetes (15,16). This evidence is the basis for the use of HbA_{1c} treatment targets for diabetes control. Assays became widely available in the 1980s, and HbA_{1c} was rapidly adopted as the standard measure used in clinical practice to monitor glucose control in patients with diabetes.

HbA_{1c} for Diagnosis of Diabetes

Despite the strong epidemiologic evidence for its prognostic utility, it took several more decades before HbA_{1c} was recommended for the diagnosis of diabetes. A major barrier to the adoption of HbA_{1c} as a diagnostic test was a lack of standardization of the HbA_{1c} assays (17). The NGSP (ngsp.org) (formerly, the National Glycohemoglobin Standardization Program) was established in 1996 to implement a system of reference laboratories that would calibrate and standardized HbA_{1c} assessment methods and ensure comparability of results with the reference method established in the Diabetes Control and Complications Trial (DCCT) (15). As a result of the efforts of the NGSP, HbA_{1c} assessment was well standardized by $\sim$2008, removing this barrier to its use as a diagnostic test.

In 2009, an International Expert Committee convened by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation first recommended the use of HbA_{1c} for diagnosis of diabetes. Citing pooled data on the association of HbA_{1c} with prevalent retinopathy, the committee recommended an HbA_{1c} cut point of 6.5% for diagnosis (14). This recommendation was adopted in guidelines issued by the American Diabetes Association, World Health Organization, and other diabetes groups across the globe.

There are a number of advantages of HbA_{1c} for diagnosis of diabetes. First, HbA_{1c} has much lower biological (within-person) variability as compared with fasting glucose or 2-h glucose (18). Second, unlike glucose level, HbA_{1c} is an index of overall glycemic exposure, providing a window into past hyperglycemia over the prior 2–3 months. Third, HbA_{1c} does not need to be measured in the fasting state and HbA_{1c} assessment does not involve burdensome timed sampling like the oral glucose tolerance test, making it a convenient test for patients and providers. Fourth, for HbA_{1c} there are fewer preanalytical factors that can affect laboratory results, and it is relatively unaffected by physical activity, stress, or recent illness, which can alter glucose concentrations. Finally, HbA_{1c} is familiar to patients and providers, as it has been used for monitoring glucose control and guiding and adjusting diabetes treatment for decades.

Diagnostic cut points for diabetes have historically been based on epidemiologic studies demonstrating strong associations of biomarkers of hyperglycemia with prevalent retinopathy (11, 12). Population studies have also established HbA_{1c} as a potent marker of future risk of diabetes and major complications such as heart disease and kidney disease, even among individuals without a history of diabetes (19–21). We undertook one such investigation in a large community-based cohort, the Atherosclerosis Risk in Communities (ARIC) study (22). This work, published in 2010, demonstrated the importance of HbA_{1c} as a marker of future risk for diabetes, cardiovascular disease, and mortality, providing support for its use as a diagnostic test for diabetes.

Use and Interpretation of HbA_{1c} and Fasting Glucose as Diagnostic Tests

Diagnostic cut points for fasting glucose and HbA_{1c} will not always classify the same individuals as having diabetes. The cut point of 6.5% for HbA_{1c} has higher specificity as compared with fasting glucose 126 mg/dL (7.0 mmol/L); many people with elevated levels of fasting glucose will have an HbA_{1c} $<$6.5%. We provide here equivalent values of fasting glucose and HbA_{1c} based on percentile distributions in the U.S. adult population without diabetes (Table 1). An HbA_{1c} value of 6.5% will, on average,

Table 1—Equipercentile values of HbA_{1c} and fasting glucose for U.S. adults age 20 years or older without a history of diagnosed diabetes

Percentile	HbA_{1c} (%)	Fasting glucose (mg/dL)
67rd	5.5	**100**
83rd	**5.7**	106
97th	6.3	**126**
98th	**6.5**	136

Data are participants from the NHANES 1999–2008 fasting subsample with no selfreported doctor-diagnosed diabetes (n = 19,599). Boldface values are American Diabetes Association thresholds for diagnosis of prediabetes and diabetes. To convert glucose to SI units, multiply by 0.0555.

be roughly equivalent to a fasting glucose of 136 mg/dL (7.6 mmol/L) in the general adult population without a history of diabetes.

A simple and efficient approach to the diagnosis of diabetes is to measure fasting glucose and HbA_{1c} in a single blood sample. Until 2019, guidelines recommended that a second test be conducted in a new blood sample to confirm the diagnosis of diabetes. A more streamlined approach is to conduct two different diagnostic tests (e.g., fasting glucose and HbA_{1c}) in the same blood sample: if both tests are elevated, this confirms the diagnosis of diabetes (23,24). With this approach one can avoid the need for repeat bloodwork and potential delays in patient care. In the ARIC study, we examined the risk of a new diabetes diagnosis, kidney disease, cardiovascular disease, and mortality among individuals meeting this single-sample confirmatory definition of undiagnosed diabetes. We found that this definition had high positive predictive value for a future diagnosis of diabetes and identified adults at high risk for microvascular and macrovascular outcomes. This work demonstrated the efficiency and clinical utility of measuring HbA_{1c} and fasting glucose in a single blood sample and prompted changes in diagnostic guidelines in 2019.

In children and adolescents, fasting tests can be unduly burdensome and there has been controversy regarding optimal approaches to screening and diagnosis of diabetes. HbA_{1c} has practical advantages in this population as it does not require fasting and has low within-person variability. We recently demonstrated that HbA_{1c} measurement identifies children and adolescents with a high burden of cardiometabolic risk and is a useful screening test for prediabetes and diabetes for this population (25).

When diabetes diagnostic test results for HbA_{1c} and glucose in the same patient do not agree, health care providers must adjudicate this discordance. Because glucose is one of the most common laboratory tests in the practice of medicine, providers and scientists tend to be inured to its limitations (26–28). When laboratory measurements of glucose and HbA_{1c} are discordant, it is important to consider a potential problem with either test (28) (Table 2). For example, if a low glucose is observed in the setting of a high HbA_{1c} test result, a sample processing problem for glucose might be explored: when samples are not processed promptly, glycolysis will cause low glucose concentrations. Insufficient fasting (i.e., $<$8 h) is a common problem that can cause unexpectedly high glucose. Iron deficiency or other anemias can alter HbA_{1c} and might also be evaluated when glucose and HbA_{1c} test results are discordant.

As with all laboratory tests, HbA_{1c} and glucose results need to be viewed in full context of the patient. Most factors that interfere with laboratory results for HbA_{1c} are uncommon and many will be detected on other routine laboratory tests (e.g., anemia). Modern HbA_{1c} assays are unaffected or relatively unaffected by common hemoglobin variants (HbS, HbC, HbE, HbD), but some methods will give inaccurate results (especially for HbF) (ngsp.org). Hemoglobin variants arose from natural selection, most likely as a protective mechanism against malaria in carriers. The prevalence of abnormal hemoglobin variants globally is ~5% but is higher in certain population subgroups (29). HbS may be as high as 25% in some parts of sub-Saharan Africa (30). The prevalence of HbS is ~8% among Black persons in the U.S. (31,32). Because of potential interference, it is important that health care professionals know which method their laboratory is using. In patients with two alleles of abnormal variants (HbSS, HbCC, or HbSC, for example), the HbA_{1c} test should not be used due to altered erythrocyte turnover.

Controversies in the Interpretation of Racial Differences in HbA_{1c}

There is evidence for a small, but systematic, difference in HbA_{1c} (~0.3%-points) according to race/ethnic ancestry that is independent of glucose (33–35). On the heels of the recommendation for the use of HbA_{1c} for diagnosis of diabetes in 2009, concerns were raised about the interpretation of observed race/ethnicity differences in HbA_{1c}.

Studies documenting race/ethnicity differences in HbA_{1c} have been widely misinterpreted to suggest that HbA_{1c} is a less valid test for certain race/ethnicity minority groups, especially Black adults. Differences in HbA_{1c} have also been used to promote the potentially harmful use of race-specific cut points for screening and diagnosis of diabetes. These claims have been made despite a large and robust literature linking HbA_{1c} with clinical outcomes in diverse populations (20,22,36) and a lack of evidence for racial differences in clinical trials of glucose-lowering interventions (37). Indeed, most studies show a higher risk of diabetes in Black adults and other race/ethnicity minority populations compared with White adults (38,39). There is no evidence for race/ethnicity differences in the correlations of HbA_{1c} with average glucose (assessed by continuous glucose monitoring [CGM]) or fasting glucose (40,41).

Evidence for small, glucose-independent differences in HbA_{1c} is not completely understood but likely arises from genetic variation (42,43). While some genetic variants may be more common in certain race/ethnicity groups, using race/ethnicity as a proxy for genetics or for poorly understood health-related factors is poor medical and scientific practice. Diabetes and its complications disproportionately affect race/ethnicity minority groups in the U.S. and other countries. These disparities primarily stem from a complicated mix of social factors including racism, historical factors (enslavement, segregation), opportunities

Table 2—Considerations related to the use and interpretation of laboratory measurements of glucose and HbA_{1c}

	Glucose	HbA_{1c}
Cost	Inexpensive and available in most laboratories across the world	More expensive relative to glucose and not as widely available globally
Time frame of hyperglycemia	Acute measure	Chronic measure of glucose exposure over the past ~2–3 months
Preanalytic stability	Poor preanalytical stability; plasma must be separated immediately or samples must be kept on ice to prevent glycolysis	Good preanalytical stability
Sample type	Measurement can vary depending on sample type (plasma, serum, whole blood) and source (capillary, venous, arterial)	Requires whole blood sample
Assay standardization	Assay is not standardized	Assay is well standardized
Fasting	Fasting or timed samples required	Nonfasting test; no patient preparation is needed
Within-person variability	High within-person variability	Low within-person variability
Acute factors that can affect levels	Food intake, stress, recent illness, activity	Unaffected by recent food intake, stress, illness, activity
Other patient factors that can affect test results	Diurnal variation, medications, alcohol, smoking, bilirubin	Altered erythrocyte turnover (anemia, iron status, splenectomy, blood loss, transfusion, erythropoietin, etc.), cirrhosis, renal failure, dialysis, pregnancy
Test interferences	Depends on specific assay: sample handling/processing time, hemolysis, severe hypertriglyceridemia, severe hyperbilirubinemia	Depends on specific assay: hemoglobin variants, severe hypertriglyceridemia, severe hyperbilirubinemia

for educational attainment and employment, environmental factors (the built environment, transportation, housing, food availability, pollutants, media exposure), health behaviors (physical activity, diet), and health care (access to care, health literacy, quality of care, communication). Race is a highly imprecise construct. Using race/ethnicity differences to justify differential approaches to diagnosis or treatment can do harm by legitimizing differences in treatment standards based on race/ethnicity rather than relying on objective, biological measures.

Potential Alternatives to HbA_{1c}: Serum Biomarkers of Hyperglycemia

In settings where HbA_{1c} is problematic (e.g., patients with altered red cell turnover or certain hemoglobinopathies), alternatives include fructosamine and albumin, which can be measured in serum or plasma (44). Fructosamine and glycated albumin are both ketoamines, formed by the reaction of glucose with proteins (nonenzymatic glycation). Fructosamine reflects the glycation of total serum proteins, predominately albumin but also globulins and lipoprotein. Glycated albumin is reported specifically as a proportion of total albumin. Serum proteins have a shorter half-life and undergo glycation at a higher rate as compared with hemoglobin. Thus, fructosamine and glycated albumin reflect short-term (2- to 3-week) glycemic control (45).

Fructosamine measurement is available from major laboratories in the U.S. Glycated albumin measurement is newly available in the U.S. (cleared for clinical use by the U.S. Food and Drug Administration in 2020) but has been used in Japan, Korea, China, and some other countries for a number of years. These biomarkers have been proposed for use in monitoring short-term or interim glycemic control as they will respond more quickly to changes in diabetes treatment as compared with HbA_{1c}.

The acceptance of new biomarkers is partly dependent on establishing their associations with clinically relevant outcomes. In our work we have established the prognostic value of fructosamine and glycated albumin measures, demonstrating robust associations with microvascular and macrovascular outcomes, with predictive values similar to HbA_{1c} (46–51). Statements from diabetes and laboratory organizations have suggested that these biomarkers may be useful but have not provided formal guidance on when and how they should be used in clinical practice (52). The results of our studies—particularly evidence of similar prediction relative to that of HbA_{1c}—suggest that fructosamine and glycated albumin may be useful as substitutes for HbA_{1c} or as complements for monitoring short-term glucose control.

Cut points are necessary for disease diagnosis, treatment monitoring and decision-making, and health care payment. Because there is no consensus on clinical cut points for fructosamine or glycated albumin, one approach is to use values that are roughly equivalent to those used for HbA_{1c} and fasting glucose. For example, our data from the ARIC study suggest that an HbA_{1c} of 7% is roughly equivalent to a fructosamine value of 280 μmol/L and a glycated albumin value of 17% (48) (Table 3).

HbA_{1c} for Population Surveillance: Accurately Estimating the Burden and Control of Diabetes

The widespread availability of HbA_{1c} testing has had a major effect on public health and diabetes surveillance. HbA_{1c} is routinely measured in large

Table 3—Equipercentile values of HbA_{1c}, fructosamine, and glycated albumin for adults with and without diabetes—the ARIC study*

Percentile	HbA_{1c} (%)	Fructosamine (μmol/L)	Glycated albumin (%)
No diabetes			
77th	5.7	241	14
97th	6.5	270	16
Diabetes			
71st	7	280	17
84th	8	320	20
91st	9	375	24

*Adults age 47–70 years without diabetes (n = 11,663) and with a diagnosis of diabetes but not currently taking glucose-lowering medication (n = 313).

epidemiologic studies and national surveys. These data are used to estimate the burden of prediabetes and diabetes in the population and to evaluate trends in glucose control among patients with diabetes. National data on HbA_{1c}, such as those from the National Health and Nutrition Examination Survey (NHANES), allow us to monitor the population-level impact of diabetes, guiding allocation of public health resources.

We have used data from NHANES to evaluate trends in the prevalence of undiagnosed and diagnosed diabetes (53) and to document trends in diabetes control in U.S. adults (54,55). Modern point-of-care technology that can accurately and rapidly measure HbA_{1c} in a finger stick further opens up the opportunity for more wide-scale population screening and epidemiologic surveillance without the need for fasting or venous samples. In high-income countries, data on trends in undiagnosed diabetes and prediabetes are based on laboratory testing done as part of resource-intensive epidemiologic studies. Few data are available in the rest of the world.

Point-of-care HbA_{1c} testing is widely used, but there is substantial variability across devices, with some showing very poor performance and high bias (56). For this reason, HbA_{1c} point-of-care devices are not recommended for the diagnosis of diabetes. If methodological and standardization barriers can be overcome, it is possible that well-calibrated point-of-care HbA_{1c} testing could be used effectively in epidemiologic research, potentially offering an affordable alternative that could be implemented in low- and middle-income countries to fill a gap in global diabetes surveillance.

CGM and HbA_{1c}: Better Together

HbA_{1c} is invaluable for diagnosis and management of diabetes, but it does not provide information on hypoglycemic episodes or glucose variability. CGM is a novel technology that provides detailed information on glucose patterns and can detect hypoglycemia and short-term glucose variability. Recent studies have demonstrated the utility of CGM in the management of type 1 diabetes (57,58), and guidelines recommend the use of CGM technology for people with diabetes (of any type) who are on intensive insulin therapy (59).

CGM can add nuance to HbA_{1c}. However, there are a number of downsides to CGM that pose barriers to its widespread adoption for monitoring glucose control (Table 4). One issue in its interpretation is that CGM technology measures subcutaneous interstitial glucose. Interstitial glucose is determined by glucose diffusion from the plasma into the interstitial space and will be affected by blood flow and other factors (60). CGM devices have poor accuracy at the low (hypoglycemic) range (60–63), and CGM sensors from different manufacturers demonstrate discordance with each other (65–67). CGM technology generates huge amounts of data, with up to ∼1,000 to ∼5,000 measurements of glucose in one patient, typically over a 14-day period. For simplification of this information, summaries of these data are provided to patients including mean glucose, the coefficient of variation, and percentage time spent "in range" (typically 70–180 mg/dL). Even when this information is simplified, the amount of information can be overwhelming to patients and providers. It remains unclear how to use CGM data to optimize care, especially for patients who are not on insulin therapy.

To provide a summary measure of glucose control from CGM, some have suggested using an estimated HbA_{1c}, termed the "glucose management indicator" (GMI). However, this measure is unlikely to replace HbA_{1c}. The GMI is based on interstitial glucose measurements, is not standardized or validated, and will not necessarily align with laboratory HbA_{1c}. Studies have not yet demonstrated a clinical benefit of providing estimated GMI values to patients, and distinguishing "expected" from "unexpected" discordance between GMI and HbA_{1c} may be difficult for patients and health care providers.

Rigorous epidemiologic studies are needed to evaluate CGM as a useful adjunct measure to HbA_{1c}. The literature on CGM primarily comes from studies of populations with type 1 diabetes, often predominately White and educated patient populations being treated at academic medical centers. There are few large studies in diverse populations of adults with type 2 diabetes and sparse epidemiologic data linking CGM use and its metrics to long-term outcomes. Moving forward, we need rigorous studies in diverse populations that address how to use CGM and HbA_{1c} in a complementary manner to improve health outcomes for patients with diabetes.

Conclusions

For almost three decades, HbA_{1c} testing has been a cornerstone of modern diabetes care, providing patients and their doctors with a simple and reliable test that allows for the assessment of 2- to 3-month average glucose control in a single blood sample. HbA_{1c} testing can be done without fasting and gives an accurate picture of chronic glucose exposure in adults with and without diabetes. Unlike many other laboratory tests, HbA_{1c} is not acutely altered by common physiological factors and is stable over time (minimal within-person variability). These properties have made HbA_{1c} one of the most valuable blood tests in the practice of medicine.

Epidemiologic studies have demonstrated that HbA_{1c} is a strong marker of risk. HbA_{1c} is an important screening and diagnostic test that can identify people at high risk for complications,

Table 4—Considerations in use and interpretation of CGM systems

• Interstitial glucose levels are determined by glucose diffusion from plasma and will be affected by uptake by subcutaneous tissue, blood flow, permeability, and metabolic factors
• CGM readings will lag behind other glucose measurements (plasma, serum, capillary)
• CGM values will not necessarily align with finger-stick (capillary) glucose levels, which can be confusing to patients
• CGM sensor characteristics (placement, pressure, bleeding, inflammation) can affect glucose levels
• CGM readings are influenced by the calibration of the device
• Different sensors will give different results—often very different results
• Accuracy (vs. venous glucose) is poor in the low glucose (hypoglycemic) range
• Trends in CGM values are typically thought to be more informative than absolute levels
• CGM sensors generate huge amounts of data; it is not always clear how to optimize the use of the data for patients and health care providers
• Expensive, and coverage by health plans is currently limited
• Acetaminophen, aspirin, and vitamin C interfere with some devices. Other drug interferences are possible
• Adoption in hospitalized patients has been slow due to concerns about accuracy related to concomitant medication use or theoretical alterations in correlation between interstitial and blood glucose caused by serious illness
• Relatively few studies linking CGM to long-term clinical (hard) outcomes
• Sparse data for diverse populations (underrepresented groups, older adults) and people with type 2 diabetes

and when HbA_{1c} is measured in large surveys it can be used to monitor population trends. For individuals with diabetes, HbA_{1c} is fundamental to care.

Fructosamine and glycated albumin measures may be appropriate alternatives to HbA_{1c} in circumstances where the interpretation of HbA_{1c} is unreliable, such as in patients with anemia or certain hemoglobin variants, or for measurement of short-term (2–3 weeks) glycemic control.

CGM is a promising new technology that may add information complementary to that provided by HbA_{1c}. Research into the use of CGM in the setting of type 2 diabetes care is a high priority to address how to optimize the use of this technology to improve the health of patients. To quote the final words in Kelly West's seminal book (68) on the epidemiology of diabetes: "Better data are needed."

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References

1. Keen H. The presymptomatic diagnosis of diabetes. Proc R Soc Med 1966;59:1169–1174
2. West KM. Laboratory diagnosis of diabetes. A reappraisal. Arch Intern Med 1966;117:187–191
3. Keen H, Rose G, Pyke DA, Boyns D, Chlouverakis C. Blood-sugar and arterial disease. Lancet 1965;2:505–508
4. West KM, Erdreich LJ, Stober JA. A detailed study of risk factors for retinopathy and nephropathy in diabetes. Diabetes 1980;29:501–508
5. Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H. Mortality from coronary heart disease and stroke in relation to degree of glycaemia: the Whitehall study. Br Med J (Clin Res Ed) 1983;287:867–870
6. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28:1039–1057
7. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of The Expert Committee on the Diagnosis and Classi-fication of Diabetes Mellitus. Diabetes Care 1997;20:1183–1197
8. Holmquist WR, Schroeder WA. A new N-terminal blocking group involving a Schiff base in hemoglobin AIc. Biochemistry 1966;5:2489–2503
9. Rahbar S. An abnormal hemoglobin in red cells of diabetics. Clin Chim Acta 1968;22:296–298
10. Koenig RJ, Peterson CM, Jones RL, Saudek C, Lehrman M, Cerami A. Correlation of glucose regulation and hemoglobin AIc in diabetes mellitus. N Engl J Med 1976;295:417–420
11. McCance DR, Hanson RL, Charles MA, et al. Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ 1994;308:1323–1328
12. Davidson MB, Schriger DL, Peters AL, Lorber B. Relationship between fasting plasma glucose and glycosylated hemoglobin: potential for false-positive diagnoses of type 2 diabetes using new diagnostic criteria. JAMA 1999;281:1203–1210
13. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141:421–431
14. The International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–1334
15. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
16. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
17. John WG, Mosca A, Weykamp C, Goodall I. HbA1c standardisation: history, science and politics. Clin Biochem Rev 2007;28:163–168
18. Selvin E, Crainiceanu CM, Brancati FL, Coresh J. Short-term variability in measures of glycemia and implications for the classification of diabetes. Arch Intern Med 2007;167:1545–1551

19. Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of european prospective investigation of cancer and nutrition (EPIC-Norfolk). BMJ 2001;322:15–18
20. Cavero-Redondo I, Peleteiro B, Álvarez-Bueno C, Rodriguez-Artalejo F, Martínez-Vizcaíno V. Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis. BMJ Open 2017;7:e015949
21. Selvin E, Ning Y, Steffes MW, et al. Glycated hemoglobin and the risk of kidney disease and retinopathy in adults with and without diabetes. Diabetes 2011;60:298–305
22. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800–811
23. American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Care in Diabetes—2019*. Diabetes Care 2019;42 (Suppl. 1):S13–S28
24. Selvin E, Wang D, Matsushita K, Grams ME, Coresh J. Prognostic implications of single-sample confirmatory testing for undiagnosed diabetes: a prospective cohort study. Ann Intern Med 2018;169:156–164
25. Wallace AS, Wang D, Shin JI, Selvin E. Screening and diagnosis of prediabetes and diabetes in us children and adolescents. Pediatrics 2020;146:e20200265
26. Gambino R. Glucose: a simple molecule that is not simple to quantify. Clin Chem 2007;53:2040–2041
27. Davidson MB. Diagnosing diabetes with glucose criteria: worshiping a false God. Diabetes Care 2011;34:524–526
28. Sacks DB. A1C versus glucose testing: a comparison. Diabetes Care 2011;34:518–523
29. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ 2008;86:480–487
30. Williams TN, Weatherall DJ. World distribution, population genetics, and health burden of the hemoglobinopathies. Cold Spring Harb Perspect Med 2012;2:a011692
31. Naik RP, Derebail VK, Grams ME, et al. Association of sickle cell trait with chronic kidney disease and albuminuria in African Americans. JAMA 2014;312:2115–2125
32. Schneider RG, Hightower B, Hosty TS, et al. Abnormal hemoglobins in a quarter million people. Blood 1976;48:629–637
33. Selvin E. Are there clinical implications of racial differences in HbA_{1c}? A difference, to be a difference, must make a difference. Diabetes Care 2016;39:1462–1467
34. Saaddine JB, Fagot-Campagna A, Rolka D, et al. Distribution of HbA_{1c} levels for children and young adults in the U.S.: Third National Health and Nutrition Examination Survey. Diabetes Care 2002;25:1326–1330
35. Selvin E, Steffes MW, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL. Racial differences in glycemic markers: a cross-sectional analysis of community-based data. Ann Intern Med 2011;154:303–309
36. Sakurai M, Saitoh S, Miura K, et al.; NIPPON DATA90 Research Group. HbA1c and the risks for all-cause and cardiovascular mortality in the general Japanese population: NIPPON DATA90. Diabetes Care 2013;36:3759–3765
37. Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
38. Brancati FL, Kao WHL, Folsom AR, Watson RL, Szklo M. Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities study. JAMA 2000;283:2253–2259
39. Bancks MP, Kershaw K, Carson AP, Gordon-Larsen P, Schreiner PJ, Carnethon MR. Association of modifiable risk factors in young adulthood with racial disparity in incident type 2 diabetes during middle adulthood. JAMA 2017; 318:2457–2465
40. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D; A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008;31:1473–1478
41. Selvin E, Sacks DB. Variability in the relationship of hemoglobin a1c and average glucose concentrations: how much does race matter? Ann Intern Med 2017;167:131–132
42. Jun G, Sedlazeck FJ, Chen H, et al. Identification of novel structural variations affecting common and complex disease risks with $>$16,000 whole genome sequences from ARIC and HCHS/SOL. Presented at the 68th Annual Meeting of The American Society of Human Genetics, 16–20 October 2018 (abstract/poster 3186w). Accessed 5 August 2021. Available from https://www.ashg.org/wp-content/uploads/2019/10/2018-poster-abstracts.pdf
43. Sarnowski C, Leong A, Raffield LM, et al.; TOPMed Diabetes Working Group; TOPMed Hematology Working Group; TOPMed Hemostasis Working Group; National Heart, Lung, and Blood Institute TOPMed Consortium. Impact of rare and common genetic variants on diabetes diagnosis by hemoglobin A1c in multi-ancestry cohorts: the Trans-Omics for Precision Medicine program. Am J Hum Genet 2019;105:706–718
44. Parrinello CM, Selvin E. Beyond HbA1c and glucose: the role of nontraditional glycemic markers in diabetes diagnosis, prognosis, and management. Curr Diab Rep 2014;14:548
45. Armbruster DA. Fructosamine: structure, analysis, and clinical usefulness. Clin Chem 1987; 33:2153–2163
46. Selvin E, Rawlings AM, Grams M, et al. Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. Lancet Diabetes Endocrinol 2014;2:279–288
47. Selvin E, Rawlings AM, Lutsey PL, et al. Fructosamine and glycated albumin and the risk of cardiovascular outcomes and death. Circulation 2015;132:269–277
48. Selvin E, Warren B, He X, Sacks DB, Saenger AK. Establishment of community-based reference intervals for fructosamine, glycated albumin, and 1,5-anhydroglucitol. Clin Chem 2018;64: 843–850
49. Shafi T, Sozio SM, Plantinga LC, et al. Serum fructosamine and glycated albumin and risk of mortality and clinical outcomes in hemodialysis patients. Diabetes Care 2013;36:1522–1533
50. Juraschek SP, Steffes MW, Miller ER 3rd, Selvin E. Alternative markers of hyperglycemia and risk of diabetes. Diabetes Care 2012;35: 2265–2270
51. Juraschek SP, Steffes MW, Selvin E. Associations of alternative markers of glycemia with hemoglobin A(1c) and fasting glucose. Clin Chem 2012;58:1648–1655
52. Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan DM; American Diabetes Association. Tests of glycemia in diabetes. Diabetes Care 2003;26(Suppl. 1):S106–S108
53. Selvin E, Wang D, Lee AK, Bergenstal RM, Coresh J. Identifying trends in undiagnosed diabetes in u.S. Adults by using a confirmatory definition: a cross-sectional study. Ann Intern Med 2017;167:769–776
54. Selvin E, Parrinello CM, Sacks DB, Coresh J. Trends in prevalence and control of diabetes in the United States, 1988-1994 and 1999-2010. Ann Intern Med 2014;160:517–525
55. Fang M, Wang D, Coresh J, Selvin E. Trends in diabetes treatment and control in U.S. adults 1999-2018. N Engl J Med 2021;384:2219–2228
56. Lenters-Westra E, English E. Evaluation of four hba1c point-of-care devices using international quality targets: are they fit for the purpose? J Diabetes Sci Technol 2018;12:762–770
57. Pratley RE, Kanapka LG, Rickels MR, et al.; Wireless Innovation for Seniors With Diabetes Mellitus (WISDM) Study Group. Effect of continuous glucose monitoring on hypoglycemia in older adults with type 1 diabetes: a randomized clinical trial. JAMA 2020;323:2397–2406
58. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group; Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464–1476
59. American Diabetes Association. 7. Diabetes technology: *Standards of Care in Diabetes—2021*. Diabetes Care 2021;44(Suppl. 1):S85–S99
60. Cengiz E, Tamborlane WV. A tale of two compartments: interstitial versus blood glucose monitoring. Diabetes Technol Ther 2009;11 (Suppl. 1):S11–S16
61. Lindner N, Kuwabara A, Holt T. Non-invasive and minimally invasive glucose monitoring devices: a systematic review and meta-analysis on diagnostic accuracy of hypoglycaemia detection. Syst Rev 2021;10:145
62. FDA executive summary: Dexcom G5 Mobile Continuous Glucose Monitoring System, 2016. Accessed 5 August 2021. Available from https://www.fda.gov/media/98967/download
63. FDA summary of safety and effectiveness data: Freestyle Libre 14 Day Flash Glucose Monitoring System, 2018. Accessed 5 August 2021. Available from https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160030S017B.pdf
64. Farrell CM, McNeilly AD, Hapca SM, McCrimmon RJ. Real-time continuous glucose monitoring during a hyperinsulinemic-hypoglycemic clamp significantly underestimates the

degree of hypoglycemia. Diabetes Care 2020;43: e142–e143
65. Freckmann G, Pleus S, Schauer S, et al. Choice of continuous glucose monitoring systems may affect metrics: clinically relevant differences in times in ranges. Exp Clin Endocrinol Diabetes. 28 January 2021 [Epub ahead of print]. DOI: 10.1055/a-1347-2550. PMID: 33511578
66. Howard R, Guo J, Hall KD. Imprecision nutrition? Different simultaneous continuous glucose monitors provide discordant meal rankings for incremental postprandial glucose in subjects without diabetes. Am J Clin Nutr 2020;112:1114–1119
67. Jafri RZ, Balliro CA, El-Khatib F, et al. A three-way accuracy comparison of the dexcom g5, abbott freestyle libre pro, and senseonics eversense continuous glucose monitoring devices in a home-use study of subjects with type 1 diabetes. Diabetes Technol Ther 2020;22: 846–852
68. West KM. *Epidemiology of Diabetes and Its Vascular Lesions*. New York, Elsevier 1978