Assessing metabolic health: where HbA1c falls short, and how it compares to fasting glucose, CGM, and OGTT

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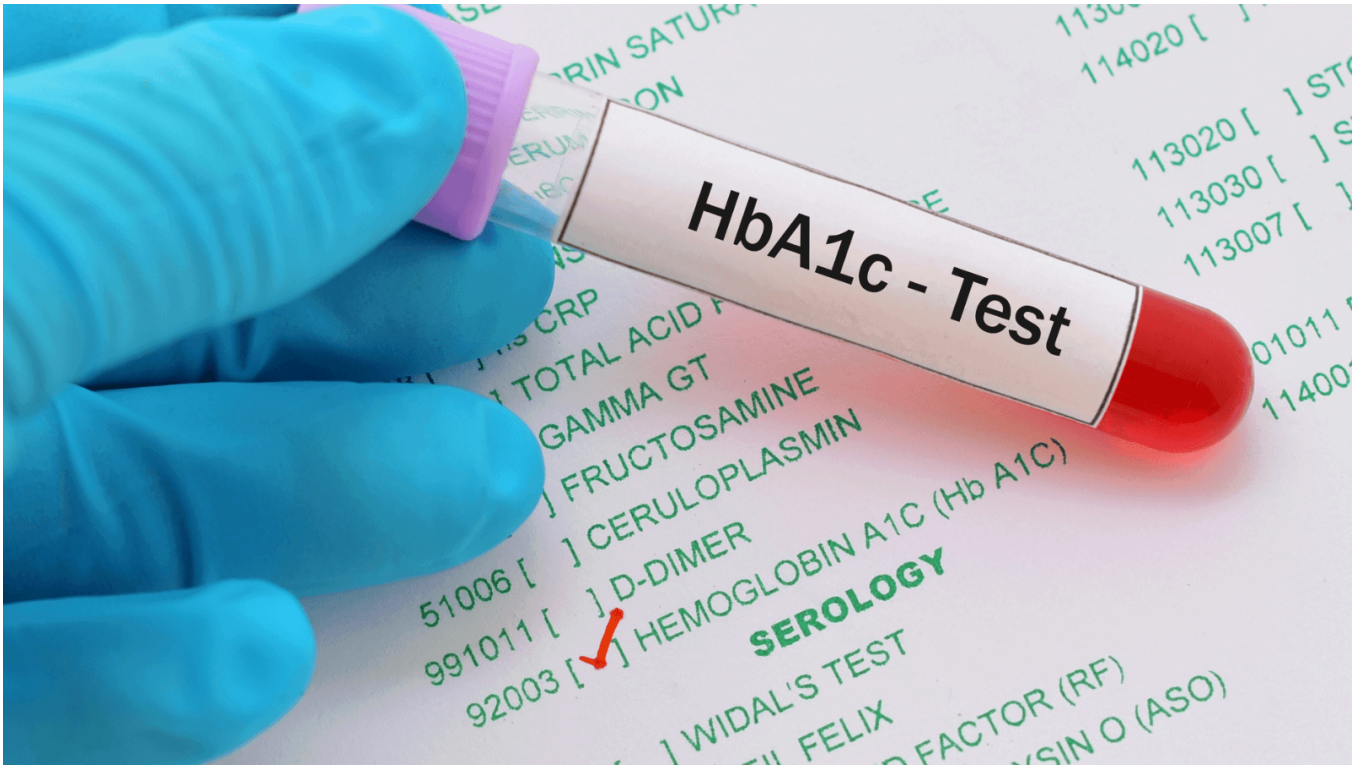

The onset of type II diabetes (T2D) is slow and often asymptomatic until it has reached an advanced stage, by which point years of damage have likely already been done. Rather than wait for the onset of symptoms, T2D can be detected at earlier stages using metrics related to the disease's most damaging characteristic, the impairment of glycemic control. Specifically, current clinical diagnostics rely on measurements of fasting plasma glucose, plasma glucose levels in response to an oral glucose tolerance test (OGTT), and, most recently, hemoglobin A1c, or HbA1c (and by "most recently" I mean over the past fifteen years). But while these tests are the most commonly used, are they all equally sufficient for detecting early stages of metabolic disease? Where does each succeed, and where does each fall short?

Diabetes development and progression

One of the early hallmarks of metabolic disease is insulin resistance (IR) and loss of glycemic control, which can precede T2D by 10 to 15 years.[1] Blood glucose levels are normally tightly controlled by the liver, although they can (and should) fluctuate with energy intake. When you eat a meal and have a temporary postprandial increase in circulating glucose, pancreatic beta cells release the hormone insulin to signal muscle and adipose cells to increase their glucose uptake from the blood and thus lower circulating glucose levels. In a metabolically healthy person, a dose-dependent amount of insulin is secreted, meaning that a higher elevation in blood glucose will stimulate a higher secretion of insulin.[2]

However, over time, *chronic* caloric intake above energy balance causes fat deposition, and fat storage within skeletal muscle impairs the uptake of glucose via the GLUT4 transporter. When glucose uptake is reduced in this way, the pancreas must secrete higher and higher levels of insulin to dispose of the excess glucose. Eventually, the stress placed on the beta cells to produce ever-higher insulin levels causes "beta-cell fatigue," a phenomenon whereby histologically normal beta cells fail to produce enough insulin to regulate blood glucose, resulting in T2D. However, the slow progression of metabolic dysfunction makes IR amenable to detection within a window in which both IR and even early-stage diabetes are quite reversible with lifestyle interventions. Early management is also critical to prevent the debilitating effects of *advanced* T2D, such as diabetic neuropathy, diabetic retinopathy, and vascular damage.

Historical methods for diagnosing diabetes

The perceivable symptoms of diabetes, such as frequent urination and excessive thirst, have been observed in humans for thousands of years. One of the first methods of "diagnosing" this condition was through the detection of sugar in a patient's urine. This was done by testing whether ants were attracted to a patient's urine (due to the presence of sugar) or by having the physician taste the urine for sweetness.

Luckily for modern physicians, in the early 1900s, methods to measure plasma glucose were developed, and both fasting and post-glucose loading became methods for diagnosing diabetes. For most of the 20th century, there was no clear consensus as to precise plasma glucose thresholds for T2D diagnosis or specific protocols for OGTT (e.g., glucose load, measurement timing), though these diagnostic methods were eventually standardized in 1979 – at which point, the 2-hour, 75-g glucose load protocol for OGTT was established, and a fasting plasma glucose (FPG) of ≥140 mg/dl was set as a threshold for T2D diagnosis.[3] In 1997, the fasting plasma glucose (FPG) criteria for T2D diagnosis were revised again to yield the standards that are still in place today, by which T2D is diagnosed by an FPG of ≥126 mg/dl or plasma glucose of ≥200 mg/dl two hours after consuming a 75-g glucose drink in an OGTT. Even though these criteria are more reflective of insulin resistance, currently, most if not all diagnoses of T2D are now made using HbA1c.

Hemoglobin A1c was discovered in the late 1960s, but HbA1c was not recommended for use in diagnosing T2D until 2009 due to the prior lack of standardization in laboratory measurements. However, since that time the convenience of HbA1c has led to an overwhelming reliance on this test, diagnosed by an HbA1c of 6.5% or higher.

The original metrics

As I just mentioned, the thresholds for T2D are somewhat arbitrary and have been changed based on trends from population data. Generally speaking, they are intended to mark a point above which the risk for diabetic retinopathy – which can cause vision loss and blindness – increases linearly with increasing FPG.[4] Even for the original two tests (FPG and OGTT),

making a T2D diagnosis currently only requires that *either* FPG or OGTT meets a diagnostic threshold – only one, not both, is needed, even though the pathophysiology behind the two results occurs for different reasons

When glucose is ingested, insulin is released in a biphasic manner. The first phase is short, on the order of ten minutes, and the primary goal of this phase is to suppress the endogenous glucose production by the liver. The second phase lasts much longer, on the order of two to three hours, to facilitate glucose uptake by primarily skeletal muscle and to a lesser extent adipose tissue. Elevated FPG indicates an impaired insulin response by the liver, meaning that the liver doesn't stop glucose production in response to an insulin bolus. An insulin-resistant liver also increases its basal glucose production rate, which is thought to cause a higher resting FPG.[5] However, many IR patterns observed during an OGTT start with a normal FPG. These dysregulated patterns (discussed in depth in AMA 51) are due to IR in skeletal muscle during the second phase of insulin release. As metabolic dysfunction progresses, both of these metrics will eventually cross the threshold of a diagnosis, but that doesn't mean damage from higher glucose levels isn't accumulating in the meantime. For individuals who have other indications of metabolic syndrome, an OGTT is a more comprehensive (and underutilized) measurement than FPG alone for detecting impaired glucose tolerance.

The addition of hemoglobin A1c

Over the last fifteen years or so, HbA1c (also called glycated hemoglobin) has also gained acceptance as a diagnostic measure for T2D, largely because it is a better test than FPG and a much easier test to administer than OGTT. When present in the bloodstream, glucose will spontaneously bond with hemoglobin, the protein responsible for oxygen transport that gives red blood cells (RBCs) their characteristic color, and the higher the concentration of glucose in the blood, the more this spontaneous reaction occurs. HbA1c, which expresses the percentage of total hemoglobin that is bound to glucose, thus reflects average circulating glucose levels. Typically, an individual is classified as "normal" if this percentage is under 5.7%, which, under the big assumption that everyone's red blood cells have a three-month lifespan, should correspond to an average blood glucose of 117 mg/dL. At least, in theory – we'll return to this shortly.

Once hemoglobin is glycated, it remains that way for the rest of the lifespan of the RBC, so HbA1c has the advantage of being a slow-changing measurement – it isn't susceptible to the large daily fluctuations that occur in blood glucose concentrations as a result of meals, exercise, or other factors. Additionally, unlike FPG and OGTTs, HbA1c requires neither fasting nor the two-hour protocol of an OGTT, making HbA1c more convenient and thus a more commonly used test. But while convenient, it is misguided to rely on HbA1c alone, especially without an understanding of its limitations and potential to miss an early window for intervention.

Limitations of HbA1c for measuring average blood glucose

Because hemoglobin glycation is sustained throughout the lifespan of the RBC, HbA1c depends not only on average blood glucose concentrations but also on the RBC lifespan, which averages about three months. Assuming normal RBC turnover, HbA1c thus represents the average blood glucose concentration over the previous three months. However, several variables can cause one to have RBC turnover rates which deviate significantly from this 3-month average. For instance, if an individual is iron deficient, anemic, or has had their spleen removed, they will have reduced RBC clearance and a longer RBC lifespan, thus artificially increasing HbA1c. Indeed, in patients with untreated iron-, vitamin B12-, or folate-deficiency anemia, iron or B-vitamin supplementation alone can reduce HbA1c by 0.3-1.0% with no other intervention (e.g., a drop from say, an HbA1c of 6% to an HbA1c of 5%), demonstrating how dramatically this metric can be affected by factors other than blood glucose.[6]

The reverse is also possible; people with conditions such as chronic kidney disease, splenomegaly (an enlarged spleen), and sickle cell anemia have increased RBC turnover and a shorter average RBC lifespan, which leads to an artificially low HbA1c. In addition to variation in RBC lifespan, HbA1c can also be influenced by conditions that affect hemoglobin concentration and RBC size, as well as genetic hemoglobin variants. Altogether, this means that although the convenience of HbA1c makes it a useful tool for measuring relative changes in an individual, the susceptibility of this metric to variables other than blood glucose means that, in many individuals, it is an unreliable test for those who are at or near the HbA1c thresholds for prediabetes and T2D.

For example, I have a patient whose HbA1c and FPG were both classified as normal at 5.6% and 84 mg/dl, respectively. However, their high fasting insulin – at 36 μU/ml – raised a red flag, as the normal range is 5-15 μU/ml. Not surprisingly, in response to an OGTT, their blood glucose spiked to over 200 mg/dL at 30 minutes and remained elevated (at 168 mg/dL) at one hour, and insulin sharply increased in response to the glucose load and continued to rise over the next 90 minutes. Yet despite these very clear indications of glucose dysregulation and hyperinsulinemia, this person would still not be classified as prediabetic in light of their HbA1c and FPG metrics (their blood glucose recovered to around 100 mg/dL by the end of the 90-minute test period). This is exactly the person who would benefit from lifestyle interventions that can increase insulin sensitivity (e.g., improving sleep, increasing exercise volume, reducing added sugars in an energy-balanced diet – all covered more extensively in AMA 51), yet this person would get overlooked by static measurements of FPG and HbA1c.

On the other end of the spectrum, I have a patient who initially seemed to be prediabetic based on an HbA1c of 6.1%, which should correspond to an average blood glucose of 128 mg/dL. Yet this person's continuous glucose monitoring (CGM) reported an average blood glucose of 94±13 mg/dl over 30 days, which should correspond to an HbA1c of just 4.9% – an indication that there was likely a cause other than glucose levels leading to a high HbA1c. These types of false positives or false negatives in prediabetic diagnoses are why we need to use better (if at times less convenient) testing methods.

OGTT and the importance of measuring insulin and glucose

As mentioned above, HbA1c has largely replaced OGTT for diabetes diagnoses primarily because it is simply an easier test to perform, but despite being far more time-intensive than either FPG or HbA1c, OGTT is a superior tool for assessing metabolic health. Although used less and less frequently, OGTT is the first test that can pick up dysregulated insulin responses – the so-called canary in the coal mine of postprandial hyperinsulinemia, and the addition of insulin measurements to an OGTT elucidates patterns of glycemic response that can diagnose metabolic dysregulation at a much earlier stage. However, OGTTs require fasting for at least 8 (and ideally up to 12) hours, followed by consumption of a pure glucose drink and 3-5 subsequent blood draws at 30-minute intervals over two hours, during which the patient needs to remain sedentary. (In a metabolically healthy person, fasting glucose will start at <100 mg/dL, rise to a maximum of about 140 mg/dL, and then return to approximately 100 mg/dL by the 2-hour mark.) Still, despite the inconveniences, an OGTT that measures blood glucose *and* insulin is one of the best ways to measure a person's response to a specified glucose load.

In addition to its use in detecting early metabolic disease, an OGTT can be used to determine if current treatments are effective. For example, a new patient who came into our practice had been taking metformin for years after being diagnosed with prediabetes nearly a decade ago. By static metrics, it would seem that this patient's glycemia was well controlled with metformin. This patient's fasting glucose was 71 mg/dl and their fasting insulin was 3 µIU/ml, both in the metabolically healthy range, and their HbA1c was 5.9%, which would classify them as prediabetic – an improvement from the HbA1c of 6.5% that led to their T2D diagnosis years ago. But when we turn to *dynamic* metrics like OGTT and CGM, this patient's metabolic dysfunction was worse than was predicted by their blood-based biomarkers.

During an OGTT, at the 30-minute mark after consuming the glucose drink, this patient's plasma glucose level was 199 mg/dl, and at 60 minutes it rose to 379 mg/dl, well over the 140 mg/dl ideal. Their blood glucose remained high at 348 mg/dl at 90 minutes, qualifying this patient as still diabetic. Additionally, the patient's insulin levels did not increase appropriately for the rise in circulating glucose, indicating significant IR and beta cell dysfunction. Furthermore, when corroborated with this patient's CGM data from the past 90 days, their average glucose level was 120 mg/dl, equivalent to an imputed HbA1c of 6.2% – higher than the measured HbA1c.

If relying on static, blood-based biomarkers alone, it is unlikely that this patient's treatment would have been altered, but in light of data from these additional metrics, this patient was subsequently counseled to start a low carbohydrate diet and increase their exercise volume to improve insulin sensitivity. If these lifestyle changes do not improve this patient's glycemic excursions, they will likely need a second medication on top of continuing metformin.

Still, the static metrics aren't completely without merit. For instance, even though HbA1c on its own was not useful for indicating the extent of this patient's metabolic dysfunction, it can be informative if tracked over time, with some caveats. In future blood draws, if HbA1c goes significantly down, by a percentage point or more, it indicates metabolic improvements, whereas if it stays the same or goes up, it's a simpler way to know that this patient may need

even more aggressive interventions. For smaller tracked changes to have value, over time the error between HbA1c and average glucose must remain the same, something that is very difficult to confirm given that the error could be caused by the myriad of factors discussed above.

CGM provides real-time, longitudinal metabolic data

CGM is one form of measuring glycemic control that is superior to HbA1c if calibrated correctly (a big, but achievable, "if"). A CGM device records glucose levels in interstitial fluid in real-time, which provides information on the extremes of a patient's glycemic excursions, average glucose levels, and glucose fluctuation around the mean (the standard deviation) – metrics that HbA1c and FPG do not capture. A recent study used CGM devices in nondiabetic adults (HbA1c < 6.5%) for an average of seven days and found that each individual's FPG levels varied by about 7.5 mg/dL. Of the more than 5,000 participants who would have been classified as nondiabetic by their FPG on day one, using average FPG *over the week* reclassified 40% of these participants as prediabetic and 3% as diabetic, indicating that the day-to-day variability of FPG can be another reason for a delayed or missed diagnosis.[7] Furthermore, long-term average blood glucose from a CGM device can be used to *impute* a person's HbA1c, which can indicate how much discrepancy there is between the two measurements.

Even before you can assess long-term patterns, a CGM can give you insight into how certain foods and habits affect your blood sugar. The added factor of accountability often helps individuals to modify their eating habits, especially if CGM data is being monitored by someone else such as a physician or caretaker. Some of the downsides of CGMs include the cost of the sensors, the aforementioned need to calibrate the device with a finger stick, skin irritation from the sensor, and potential information overload. For instance, I've often had patients mention that they've noticed CGM spikes when eating fruit, leading them to question whether this means they shouldn't eat fruit at all. In response, I would first note that not all fruit is equal, but also that it's important to avoid *overinterpreting* CGM data and their value. In other words, a spike in glucose, in isolation, tells you very little, unless it is very high (e.g., over 160 or 180 mg/dL).

Over-the-counter CGMs

Until recently, a prescription from a medical care professional was required to get a CGM, but in March 2024, the FDA cleared the first over-the-counter CGM in the U.S. (Dexcom Stelo). While these over-the-counter (OTC) devices will potentially make a tool like this more accessible (as of publishing, the U.S. price has not yet been announced), the prescription and OTC versions differ in some respects – most notably, in the time between measurements and in the devices' lifespans. The equivalent prescription CGM sensor (Dexcom G7) has a lifespan of 10 days before a new sensor must be inserted, whereas the new OTC version will have a lifespan of 15 days per sensor. Although it lasts longer than its prescription counterpart, the OTC CGM will only record glucose levels at 15-minute intervals, compared to every 5 minutes with the G7 device.

Shortly after the Dexcom Stelo was approved, the FDA also approved Abbot's Lingo and Libre Rio, two more OTC CGM devices. The Lingo is already available in the United Kingdom and is going to be available this summer, marketed for people without diabetes looking to make lifestyle changes because it has a truncated glucose measurement range of 55 to 200 mg/dL. It has a similar lifespan (14 days) to prescription versions and will measure minute-by-minute but without alarms for either low or high glucose levels. Less is known about the Libre Rio, but it is speculated to be more like the Dexcom Stelo in that it is intended for people with T2D who are not insulin dependent. It has the same metrics as the equivalent prescription device, including minute-by-minute readouts and a glucose measurement range of 40-400 mg/dL. However, like the Lingo, the Libre Rio does not have alarms for low or high glucose levels or the ability to integrate with automated insulin delivery devices.

The lack of alarms and inability to integrate with insulin delivery are the main reasons why OTC CGMs are intended for people with or without T2D who do *not* use insulin and want to understand how their eating habits affect their blood glucose. (This is the FDA's way of ensuring that if someone is going to use a CGM to dose insulin, it must be provided through a prescription.) In contrast, people with diabetes who *do* rely on insulin should not use either the Dexcom OTC CGM, as 15 minutes is too long an interval between measurements, or the Abbott Lindo, as the glucose measurement range is too limited. These device designs are likely to discourage insulin-dependent people from using these devices, especially if there is a significant price difference between the prescription and OTC versions. Furthermore, the Dexcom Stelo has lower precision than its prescription equivalent– which, for all CGM devices, is estimated by average mean absolute relative difference (MARD), the average difference between matched CGM and blood glucose readings.[8] The less precise OTC Dexcom Stelo has a MARD of 9.2%, compared to the 8.2% MARD of the Dexcom G7. Another reason to make an OTC CGM incompatible with insulin use is to ensure that these patients receive physician counseling about sensor placement, false readings of elevated glucose from drugs or supplements, and how to use CGM readings to determine the timing and dosage of insulin around meals. The precision of a CGM sensor is sensor location-dependent: upper arm placement results in the reported precision, whereas placement on the abdomen reduces MARD by about 1%.[9]

All measurements have limitations

Each method of measuring glycemic control has its limitations, which is why it is necessary to use a *combination* of methods for evaluating and monitoring metabolic health. Even though an OGTT is the gold standard for assessing response to a glucose load, it only measures glycemic control at an isolated time point. The results of an OGTT thus need complementary long-term glycemic monitoring, ideally using a CGM. In the absence of a CGM, tracking a biomarker like HbA1c would also provide an estimate of relative change in plasma glucose in three-month intervals.

The bottom line

Decades before the frank manifestations of T2D appear, the physiologic underpinnings of dysregulated glycemic control are laying the foundation for a disease that shaves years off of life, both through its own direct effects and through the increase in risk it confers for other deadly chronic diseases. It is therefore unacceptable that a person be given such a diagnosis years after the cascade of events described above. Caught early, this process is fully reversible, underscoring the vital importance of using the best available metrics to facilitate the earliest possible detection of metabolic dysregulation.

The thresholds for static measurements of FPG and HbA1c are intended to facilitate diagnosing prediabetes and T2D before uncontrolled blood sugar causes significant damage. However, despite the convenience, we should shy away from using HbA1c as the *exclusive* method of determining the early phases of metabolic disease. Furthermore, patients with known risk factors of metabolic syndrome should be screened with an OGTT, even if FPG is normal since the signs of hyperinsulinemia and IR can appear in response to a glucose load well before changes are seen in measurements from a single blood draw. Although less convenient (and likely a higher upfront cost), both CGM devices and OGTT are far better at detecting early stages of glycemic dysregulation. The most comprehensive detection and monitoring of metabolic health will use multiple metrics that complement one another and thus facilitate interventions that prevent disease progression before there are serious health consequences.

Disclosure: From September 2020 through August 2021 I consulted for Dexcom in the development of sensors for non-glucose analytes.

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References

1. Freeman AM, Acevedo LA, Pennings N. Insulin Resistance. In: *StatPearls*. StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/pubmed/29939616

2. Gerber KM, Whitticar NB, Rochester DR, Corbin KL, Koch WJ, Nunemaker CS. The Capacity to Secrete Insulin Is Dose-Dependent to Extremely High Glucose Concentrations: A Key Role for Adenylyl Cyclase. *Metabolites*. 2021;11(6). doi:10.3390/metabo11060401

3. Bartoli E, Fra GP, Carnevale Schianca GP. The oral glucose tolerance test (OGTT) revisited. *Eur J Intern Med*. 2011;22(1):8-12. doi:10.1016/j.ejim.2010.07.008

4. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care*. 2009;32(7):1327-1334. doi:10.2337/dc09-9033

5. Solis-Herrera C, Triplitt C, Cersosimo E, DeFronzo RA. Pathogenesis of Type 2 Diabetes Mellitus. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. *Endotext*. MDText.com, Inc.; 2021. https://www.ncbi.nlm.nih.gov/pubmed/25905339

6. Pilla R, Palleti SK, Rayana R, Skss SR, Abdul Razzack A, Kalla S. Glycated Haemoglobin (HbA1c) Variations in Nondiabetics With Nutritional Anemia. *Cureus*. 2020;12(11):e11479. doi:10.7759/cureus.11479

7. Shilo S, Keshet A, Rossman H, et al. Continuous glucose monitoring and intrapersonal variability in fasting glucose. *Nat Med*. 2024;30(5):1424-1431. doi:10.1038/s41591-024-02908-9

8. Freckmann G, Pleus S, Grady M, Setford S, Levy B. Measures of Accuracy for Continuous Glucose Monitoring and Blood Glucose Monitoring Devices. *J Diabetes Sci Technol*. 2019;13(3):575-583. doi:10.1177/19322968188120629. Garg SK, Kipnes M, Castorino K, et al. Accuracy and Safety of Dexcom G7 Continuous Glucose Monitoring in Adults with Diabetes. *Diabetes Technol Ther*. 2022;24(6):373-380. doi:10.1089/dia.2022.0011

9. Garg SK, Kipnes M, Castorino K, et al. Accuracy and Safety of Dexcom G7 Continuous Glucose Monitoring in Adults with Diabetes. *Diabetes Technol Ther*. 2022;24(6):373-380. doi:10.1089/dia.2022.0011