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Point-of-Care HbA_{1c} in Clinical Practice: Caveats and Considerations for Optimal Use

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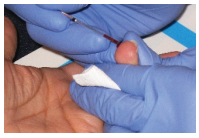

POC A1C Testing Compared With Laboratory Assay:

ADVANTAGES	DISADVANTAGES
• Rapid – result available when patient is seen	• Waived – no proficiency testing/evaluation of performance
• Single visit – test done where patient receives care	• Less accurate than laboratory testing
• Convenient – finger stick specimen	• Testing costs higher than those for laboratory measurement
• Waived in U.S. – trained laboratory personnel not required	• Interference by Hb variants
• Potential for broader reach to low-access populations	• Accuracy concerns and lack of data – not recommended for diagnosis of diabetes
• Glycemic outcomes on average = those with use of laboratory testing	

The A1C test provides considerable value in screening and diagnosing diabetes. POC A1C testing is convenient and may better reach patients in resource-poor settings. However, clinicians should be aware of caveats to the use of POC A1C testing and take steps to minimize harm and maximize the benefits of this modality.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  We undertook the study to evaluate use of point-of-care (POC) A1C measurement in clinical practice.
- **What is the specific question(s) we wanted to answer?**
  How is POC A1C testing used in clinical situations, and what are the advantages and disadvantages of POC A1C?
- **What did we find?**
  POC A1C testing is convenient and yields glycemic control results similar to those seen with laboratory A1C assays in individuals with diabetes. However, POC A1C testing is limited by bias and lack of accuracy, precluding its use for diabetes diagnosis.
- **What are the implications of our findings?**
  For management of patients with diabetes, clinicians should be aware of limitations of POC A1C testing and take steps to minimize harm and maximize the benefits.

REVIEW

Point-of-Care HbA_{1c} in Clinical Practice: Caveats and Considerations for Optimal Use

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Hemoglobin A_{1c} (A1C) is widely used for the diagnosis and management of diabetes. Accurate measurement of A1C is necessary for optimal clinical value. Assay standardization has markedly improved the accuracy and consistency of A1C testing. Devices to measure A1C at point of care (POC) are commercially available, allowing rapid results when the patient is seen. In this review, we describe how standardization of A1C testing was achieved, leading to high-quality results in clinical laboratories. We address the use of POC A1C testing in clinical situations and summarize the advantages and disadvantages of POC A1C testing. We emphasize the importance of considering the limitations of these devices and following correct testing procedures to ensure that accurate A1C results are obtained for optimal care of patients.

Three different hemoglobins, namely, HbA (~97% of the total), HbA2 (~2.5%), and HbF (~0.5%), make up normal adult hemoglobin. HbA comprises four polypeptides, two α-chains and two β-chains. The nonenzymatic—and irreversible—attachment of glucose to the N-terminal valine of the β-chain of hemoglobin is termed hemoglobin A_{1c} (A1C). In addition to the N-terminal valine, glycation also occurs at several lysine residues on the α-chain or β-chain (1). Total glycated hemoglobin is the term used to encompass all these forms of glycated hemoglobin. Since red blood cells have a life span of ~120 days, A1C reflects the weighted (more recent glycemia contributing more than earlier glycemia) average blood glucose concentration over the prior 8–12 weeks (2).

CLINICAL AND POPULATION HEALTH USE OF A1C

The clinical importance of A1C became evident in 1993 when the results of the Diabetes Control and Complications Trial (DCCT) demonstrated that people with type 1 diabetes randomized to the intensive glycemic control group had delayed onset and reduced rate of progression of microvascular complications compared with those randomized to the standard glycemic control group (3). There was a clear separation in mean A1C between groups (7.2% and 9.1%, respectively) over the 6.5 years of study follow-up. Similarly, the UK Prospective Diabetes Study (UKPDS) documented that lowering A1C in patients with type 2 diabetes significantly reduced the risk of microvascular complications of diabetes (4). Longer follow-up of participants in both trials revealed that the risk of myocardial infarction, a macrovascular complication, was lower in the intensive glycemic control treatment group in both the DCCT (5) and UKPDS (6).

A1C plays a fundamental role in diabetes (Table 1). Numerous influential organizations recommend measurement of A1C at least every 6 months to monitor long-term glycemic control (7–9). The A1C concentration is used to evaluate and adjust therapy. Initially, guidelines recommended a single A1C target (e.g., <6.5% or <7%, depending on the source of the guideline) for most adults with diabetes. Over time, guidelines

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Table 1—Clinical, population health, and regulatory value of A1C

A1C measurements are used to:

- Monitor long-term glycemic control
- Evaluate and adjust therapy
- Measure risk for the development of microvascular complications
- Screen for and diagnose diabetes
- Assess quality of diabetes care
- Evaluate new medications for diabetes

have evolved to recommend more individualized A1C targets, taking into consideration factors such as age, risk of hypoglycemia, and coexisting chronic illnesses (7,10). In 2010 (11) and 2011 (12) A1C was recommended—and is now widely accepted—as a criterion in screening for and diagnosing diabetes.

A1C thresholds often are used as measures to assess the quality of diabetes care in health systems. For example, the U.S. Healthcare Effectiveness Data and Information Set measures, covering more than 200 million individuals, include two A1C measures for adults with diabetes (proportion of individuals with A1C $<$8.0% and proportion with A1C $>$9.0%) (13). The U.S. Food and Drug Administration (FDA) (14) and European Medicines Agency (15) use the reduction in A1C concentration ($\geq$0.3%) as a noninferiority criterion in evaluating the efficacy of new diabetes medications. Taken together, these uses demonstrate that A1C is essential in the management and diagnosis of diabetes, in population health and in regulatory decision-making.

STANDARDIZATION OF A1C: FROM CHAOS TO ORDER

Assays to measure glycated hemoglobin became available commercially in 1978 (16). Glycated hemoglobin is quantified by separating the glycated from the nonglycated protein and measuring the amount of each form. Different methods are used to achieve this aim, and initially several different forms of glycated hemoglobin were measured (total glycated hemoglobin, HbA_1, and HbA_{1c}). Not surprisingly, this resulted in a significant variation among results. In 1993, the year the DCCT was published, glycated hemoglobin was reported as A1C by only ~50% of clinical laboratories, while 29% and 21% reported total glycated hemoglobin or HbA_1, respectively (17).

Inspection of the results of the College of American Pathologists (CAP) 1993 Glycohemoglobin Survey EC-B revealed disturbing findings. Values reported for a single sample by 742 participating laboratories ranged from $<$2.5% to $>$7.5% (Fig. 1, left panel). Clearly, these widely disparate glycated hemoglobin assay results were not clinically useful and would not be of use in ranking quality of care among systems or in comparing the results of clinical trials (18). Motivated by this situation, the American Association for Clinical Chemistry (AACC) formed a committee in 1993 to develop a protocol to standardize measurement of glycated hemoglobin (19), and in 1996 the NGSP was established to execute that protocol. The charge for the NGSP was to standardize A1C test results to those of the DCCT and UKPDS (20). The reference method used throughout the DCCT was chosen as the anchor for the NGSP network, and there are published data showing consistency of the results of this method for over 20 years (21,22).

The NGSP structure and processes have previously been described in detail (21). Briefly, the NGSP consists of the Central Primary Reference Laboratory and an international network of primary and secondary reference laboratories. Each laboratory in the network carries out monthly testing of whole blood samples to monitor network performance. In addition, each laboratory has to meet stringent accuracy criteria to remain in the network. There are three basic processes for NGSP certification. Calibration is performed annually by manufacturers of A1C assays in which they adjust their method so that their results are close to those of the NGSP. An assay can be NGSP-certified

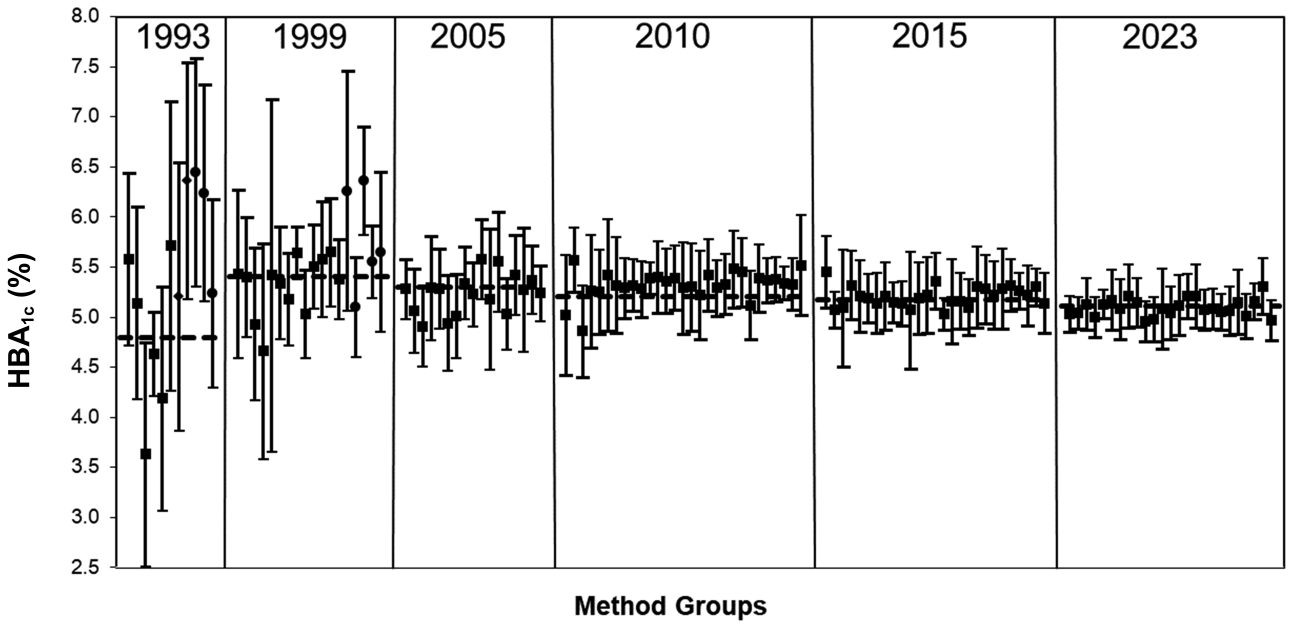

Figure 1—Mean for each method compared with the NGSP/DCCT target (dashed lines) in 1993, 1999, 2005, 2010, 2015, and 2023 based on College of American Pathologists EC, GH2, and GH5 survey data. Symbols represent the mean of laboratory results for each method; error bars are ±2 SD. Results were reported as HbA_{1c} (■), HbA_1 (◆), and total glycated hemoglobin (●). Data used with the permission of the College of American Pathologists.

annually if the manufacturer participates in a 40-sample comparison with an NGSP reference laboratory and meets stringent criteria for the comparison. The NGSP can also certify individual laboratories. Most of these laboratories measure A1C for clinical trials or serve as reference laboratories. A list of certified methods and laboratories is updated monthly and can be found on the NGSP website (20).

Laboratories in the U.S. that perform patient testing in a nonwaived setting are required by law to participate in proficiency testing. Many other countries have similar schemes, often termed external quality assessment schemes. Proficiency testing is another important process for the NGSP. CAP sends three surveys for A1C per year (each containing five samples of whole blood with different concentrations of A1C). The recipient laboratory measures A1C in each sample and reports the results to the CAP. Subsequently, all participating laboratories are sent a summary containing their results, anonymized results obtained by all the other laboratories, and the target values, assigned by laboratories of the NGSP network. Each laboratory can thus determine the accuracy of its A1C instrument used to measure patients' blood. Another important aspect of these proficiency testing surveys is that they provide information of overall accuracy of A1C measurements in the "real world" setting of patient care.

In a strategy different from that of the NGSP, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) developed a primary reference material and a reference method for measuring A1C (23). The IFCC adopted Système International (SI) units for reporting A1C, namely, mmol/mol. The NGSP and IFCC approaches to the standardization of A1C results serve different, but complementary, purposes. The primary objective of IFCC standardization is to ensure that manufacturers' assays are traceable to an accuracy base.

Improvements in A1C Testing Over Time

The standardization processes outlined above have led to a substantial improvement in A1C testing. Starting at a baseline of only 50% of laboratories reporting glycated hemoglobin measures as A1C in 1993, by 2004 essentially all U.S. results were reported as such (Fig. 1). Concurrently, variability within and between methods has also decreased steadily, with means of most methods becoming progressively closer to the NGSP target value and the SDs improving progressively with time (Fig. 1). The improvements in variability have led to several increases in stringency of recommended coefficients of variation (CVs) over time, to the American Diabetes Association (ADA)/AACC recommended intra- and interlaboratory CVs of $<$1.5% and $<$2.5%, respectively, in 2023 (10). The latter target is now attained with most methods, which have interlaboratory CVs $<$2.5%, while many have CVs $<$2% and a few are as low as 1%. The ADA recommends that laboratories that measure A1C should participate in an accuracy-based proficiency testing program that uses fresh whole blood samples with targets set by the NGSP Laboratory Network (10).

POC METHODS FOR A1C

Point-of-care testing (POCT) is performed at or near where the patient is seen for medical care (for A1C, typically in the outpatient clinic). The use of POCT worldwide has been increasing substantially, with the annual global market for POCT rising from approximately $3 billion in 2000 to more than $38 billion by 2020 (24). There are two different types of POC devices to measure A1C: small handheld meters or somewhat larger benchtop devices. For both, strips or cartridges that contain all the reagents needed for the measurement are used. For some devices calibration can be performed by the user with calibration cartridges provided by the manufacturer, while other devices are calibrated by the manufacturer and require no user calibration. POC devices measure A1C from finger stick samples and can report results in minutes. They are generally very easy to use, but some require more steps than others to perform the test. These POC methods are based on immunoassay, boronate affinity binding, or enzymatic principles for measurement. Certification of POC A1C devices by the NGSP follows the same process as that for methods performed in accredited laboratories. Of the ~330 A1C methods that are NGSP certified, over 80 are POC. Only seven of these are available in the U.S., from three manufacturers.

Advantages of POC A1C Testing

Advantages of POC A1C testing are listed in Table 2. Measurement is rapid and results are available within 3–15 min. Studies comparing having POC A1C results available at the time of the clinician visit, compared to (typically delayed) results from the laboratory have shown slightly better (25–27) or no difference in (28) achieved A1C over time. In a systematic review and meta-analysis published in 2011, investigators evaluated seven randomized controlled trials where POC A1C testing was used and concluded that there was no evidence for differences in glycemic control with POC A1C testing, compared with using a laboratory assay (29). Hence, despite potential limitations of POC A1C testing,

Table 2—POC A1C testing in diabetes: advantages and disadvantages

Advantages
- Rapid: result available when patient is seen for diabetes care
- Only one visit required: test done at site where patient receives care
- Convenient: finger stick specimen
- Waived in U.S.: trained laboratory personnel not required
- Has potential for broader reach to low-access populations
- Glycemic outcomes on average as good as those with use of laboratory testing

Disadvantages
- Waived in U.S.: no proficiency testing required, so no evaluation of performance of testing
- Less accurate than laboratory testing
- Greater variability
- Significant bias of most assays
- Interference by Hb variants
- Testing costs higher than those for laboratory measurement
- Limited objective data available regarding performance in patient care
- Accuracy concerns and lack of data weigh against use for diagnosis of diabetes

described more fully below, the increased convenience of immediately available A1C results does not seem to come with a trade-off of worsening glycemic control. Additionally, POC A1C testing, which does not require additional visits for blood drawing before a visit or communication of results after the visit, may increase the reach of such testing to populations with limited access to health care. POC A1C testing may be particularly useful for other populations. For example, in pediatric patients a test requiring only finger stick sampling may be more acceptable than phlebotomy. Despite the known alterations to the relationship between A1C and mean glucose, the ADA recommends that pregnant women with diabetes have A1C measured as frequently as monthly throughout pregnancy (30). In this situation, finger stick POC A1C testing is likely to be preferable to phlebotomy.

POC A1C devices are small and portable, enabling testing to be performed in the doctor's office, outpatient facility, pharmacy, or nursing facility. Little sample (2–10 μL) is required, and measurement can be done with capillary blood obtained from a finger stick. (With some devices, venous blood can also be used.) Finally, trained personnel are not necessary, and anyone is allowed to perform the testing.

Disadvantages of POC A1C Testing

POC A1C Testing Is CLIA-Waived With Little Quality Oversight

In the U.S., the Clinical Laboratory Improvement Amendments (CLIA) regulate laboratory testing and require that clinical laboratories be accredited by Centers for Medicare & Medicaid Services (CMS) before they can accept human samples for testing (31). The FDA categorizes in vitro diagnostic tests in the U.S. by degree of complexity, as waived, moderate complexity, and high complexity (32). Waived tests must meet certain criteria: tests need to be simple and accurate and, importantly, the patient should not be harmed if testing is performed incorrectly. Facilities, such as physician offices, that perform waived testing are only required to obtain a CLIA Certificate of Waiver by completing a simple form and paying a small biennial fee. No education or training is required by CLIA for the personnel who perform waived testing, and sites that perform waived testing are not required to participate in proficiency testing. Thus, no assessment is performed to evaluate the accuracy of measurement of routine patient samples, potentially leading to the reporting of inaccurate results that will not be detected as such. From 2002 to 2016, CMS inspected ∼2% of waived testing sites each year, but routine inspections ceased in 2016.

Waived testing sites often fail to follow correct testing procedures. CMS performed a pilot study and reported in 2001 that 50% of laboratories doing waived testing did not follow the manufacturer's instructions, while 20% did not perform the quality control required by the manufacturer (33). In a more comprehensive study in which CMS surveyed 4,214 waived sites between 2002 and 2004, CMS found that 21% of laboratories doing waived testing did not check the product insert or perform quality control testing as specified; 12% did not have the manufacturer's instructions; 18% did not use correct units when reporting results; 45% did not document the name, lot no., or expiration date of the reagents; and 35% did not keep records of quality control testing (34). Of note, these studies included a variety of analytes measured with POCT, not just A1C, but there is no evidence that sites performing POC A1C testing are any different.

POC A1C Testing Is Less Accurate Than Laboratory Testing

Although there are advantages to using POC devices in some settings, these methods must still be held to the same standards as laboratory-based A1C methods, since they are used for the same purpose. There are POC methods that are NGSP certified. (Three are available in the U.S., namely, DCA, A1cNow, and Afinion.) However, NGSP certification evaluates performance by the manufacturer under ideal conditions using only one lot of reagents. By contrast, multiple different lots are used simultaneously for patient testing, and different results have been observed for different lots (35,36). Methods must also be evaluated through examination of their performance in the hands of the end users. As discussed earlier, this is typically done with proficiency testing. However, as noted above, such testing is not required for waived settings, and as such the vast majority of such sites do not voluntarily undergo proficiency testing. Hence, in the U.S., there is essentially no objective information about the performance of POC A1C devices in the most common clinical setting.

In several studies investigators evaluated the performance of POC A1C measurement methods, done in research laboratories, and compared the results with those of A1C measurements in an accredited laboratory. Overall, a few POC A1C devices performed as well as some laboratory methods in the research setting with excellent precision and accuracy (37–39). However, these and other studies show poor performance of several POC A1C methods. In these studies, two of eight (35) and four of seven (37) POC A1C methods were inaccurate, were imprecise, had large lot-to-lot variability, and did not meet NGSP criteria. A study of POC A1C measurements by nursing staff of patients attending a diabetes research clinic revealed that three of four devices could not be recommended for measurement of A1C outside of the laboratory (40). Other studies also show poor performance of POC A1C devices (41–44). A 2017 systematic review and meta-analysis included 61 studies that compared 13 POC A1C devices with laboratory assays. All 13 exhibited biases: mean bias ranged from −0.96 to 0.67 and was negative (POC A1C result significantly lower than laboratory result) for nine instruments and positive for four. Imprecision in all devices (except one, for which there was only a single evaluation) was poor, with mean CVs >2% at low A1C concentration (45).

The importance of proficiency testing, training, and supervision for POC A1C was documented in a study performed in Norway, where 99% of primary care offices and all hospital laboratories voluntarily participate in the same proficiency testing program (46). The investigators evaluated POC A1C devices in 1,288 physician (general practice) offices, all of which participated in a stringent quality assurance program that included regular visits and courses from laboratory consultants. Analysis of results from 13 proficiency testing surveys using fresh whole blood conducted over 6 years showed that between 60% and 90% of users of Afinion and DCA POC devices met the equivalent of CAP quality specifications (46). By contrast, 60–90% of users of a third device (NycoCard) failed to meet quality specifications. These findings show that not all POC A1C

devices perform well, even with proficiency testing.

POC A1C Testing and Hemoglobin Variants

Variant hemoglobins are common, affecting ~7% of the global population (47). Unfortunately, only a small number of POC A1C devices have been evaluated for interference from common heterozygous Hb variants (HbAS, HbAC, HbAE, HbAD) and/or HbF >15%. Some of these variants result in significant interference in A1C measurement with these devices (48,49). Some POCT A1C devices are known to be subject to interference by Hb variants, yet are approved by the FDA if the manufacturer shows equivalence to a legally marketed device, which is termed the "predicate device."

As with other methods using immunoassay, boronate affinity binding, or enzymatic principles, there is no way to determine whether an individual undergoing POC A1C testing has an Hb variant or increased HbF. Therefore, even if such an interference is stated in the package insert provided with the POC A1C device, the person who performs the test will not know whether the individual has an Hb variant (most of the common heterozygous variants are clinically silent) and an inaccurate result will likely be reported. Erroneous results with these devices may be considered accurate by patients and health care providers. With waived testing there is no laboratory involved to further evaluate the test method and provide information on variant interference to the clinician. In contrast, laboratory methods for measurement of A1C with high-performance liquid chromatography or capillary electrophoresis produce a tracing in which the Hb variant or HbF peak can usually be detected, and the instrument does not report an A1C result. Additionally, the most common laboratory assays for A1C and a few POC methods do not have interference with the most common Hb variants; this information can be found on the NGSP website (20).

Cost

The cost of an A1C test at POC is considerably higher than that in a central laboratory. Depending on the device and the number of tests performed annually, POC A1C testing can be from 3- to as much as 15-fold more expensive than analysis in a central laboratory. This is due to the high costs of the cartridges, which are discarded after a single use. These costs do not, however, account for the indirect or opportunity costs of additional visits for a laboratory draw before an appointment or for communication of results of a laboratory measurement after the visit.

IMPLICATIONS FOR PATIENT CARE

Diagnosis of Diabetes

Diabetes can be diagnosed in most countries through measurement of plasma glucose or A1C (11,12). The recommendations to use A1C for diagnosis are based in part on the improved accuracy and precision in A1C measurement brought about by assay standardization (50). Organizations such as the ADA and AACC recommend that A1C testing for diagnosis of diabetes be performed in an accredited laboratory (10). One argument for using POC A1C to diagnose diabetes would be the potential to reach more people in low-access settings. As noted above, most published comparisons of POC A1C devices with laboratory assays have shown considerably lower accuracy and significant bias in POC measures. A particular concern is bias in the devices. As mentioned above, a 2017 systematic review and meta-analysis published in 2017 revealed that all 13 POC A1C devices exhibited bias, ranging from −0.96% to 0.67% (45). It is important to be aware that even after a manufacturer obtains NGSP certification of a POC A1C device, bias can develop over time and will not be detected without accuracy-based proficiency testing.

Analysis of data from the 1999–2006 National Health and Nutrition Examination Survey (NHANES) showed the number of adults aged ≥20 years without diabetes in the U.S. at A1C cut points between 6.0% and 7.0% (51). Based on these data, it is estimated that 2.4 million adults had A1C ≥6.5%, the diagnostic threshold for diabetes. Assuming a POC device has a positive bias of 0.5%, it would report all A1C values ≥6.0% as being ≥6.5%, because the true A1C would be 0.5% lower than the reported result. Based on the NHANES data (52), this device would yield a diabetes prevalence of 7.1 million. Therefore, ~4.7 million adults without diabetes would be identified as having the disease. Conversely, a POC A1C device with a negative bias of 0.5% would identify only those individuals with A1C ≥7.0% as having diabetes, erroneously missing ~900,000 adults with diabetes. Although these calculations suggest epidemiologic issues, the consequences of false-negative (missed diagnoses) or false-positive (diagnosis of diabetes when it is not present) results due to POC A1C device bias would likely harm individual patients.

The World Health Organization states that for diagnosis of diabetes A1C should be measured "by the best technology available" and POC A1C devices should be used "where this is the only option available or where there is a stringent quality assurance programme in place" (51). However, for most settings we support the ADA recommendation (10,11) that POC A1C testing for use in diabetes screening and diagnosis be restricted to a device approved by the FDA (or an equivalent regulatory body in other countries) and that measurement be performed in a CLIA-certified laboratory that performs testing of moderate complexity or higher. If POC A1C devices are used for screening or diagnosis, consideration should be given to using additional testing by the laboratory to confirm diagnoses or to rule out the diagnosis if suspicion is high, but POCT yields a result near the borderline of diagnostic cut points.

Management of Diabetes

As discussed above, POC A1C tests have higher variability and significant bias compared with NGSP-certified laboratory tests. Although published comparisons of POC A1C testing with laboratory A1C testing suggest that on average glycemic control is similar, there still may be times when clinicians might exercise caution about making significant changes to therapy based solely on the POC A1C measurement. A more global assessment of glycemic status (from continuous glucose monitoring, blood glucose monitoring, confirming the A1C with a laboratory measurement) should be undertaken.

SUGGESTIONS FOR IMPROVING THE UTILITY OF POC A1C

- Sites using POC A1C testing should implement in-depth personnel training following written policies and procedures. Ideally, a qualified person (such as a certified laboratory technologist) should train test personnel and assess

their competency, both initially and periodically.
- Testing personnel should know and strictly adhere to the current instructions from the manufacturer and perform and document quality control testing at the recommended intervals. Sites should perform periodic internal audits of staff knowledge, performance, and documentation.
- Sites that have a certificate of waiver should be encouraged to participate in a regular (at least three times per year) accuracy-based proficiency testing program that uses whole blood samples. If POC A1C fails proficiency testing, the personnel at the site should consult a qualified laboratory professional for advice about their testing protocol.
- CMS should resume their program to ensure that laboratories that perform only waived testing are inspected regularly.
- Health care professionals who order POC A1C testing should be aware of the limitations of the testing, including potential interference by hemoglobin variants, lower accuracy compared with that of laboratory testing, and known bias in the measurements. Making cut point–based diagnoses or treatment decisions based solely on POC A1C results should be avoided, and a more holistic view of glycemia should be obtained with additional data.

CONCLUSIONS

The A1C test is a core component of diabetes care and provides considerable value in screening and diagnosing diabetes. Due to efforts of the NGSP and others, the test, as performed in most laboratories, is now highly standardized. POC A1C testing is convenient, particularly in resource-poor settings and when patients require frequent testing. Moreover, on average, use of POC A1C testing can lead to glycemic control similar to that seen with use of laboratory assays. However, there are caveats to the use of POC A1C testing, related to less accuracy and bias in comparisons with laboratory measurements and the potential for human error due to lack of proficiency in testing at sites where this waived test is performed. These issues support recommendations to avoid using POC A1C testing for diabetes diagnosis. For management of patients with diabetes, clinicians should be aware of these issues and take steps to minimize harm and maximize the benefits of POC A1C testing.

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