

What's New in ...

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... DIABETES TESTING

A1C assay emerges as the new standard diagnostic test

An international expert committee recommends using the glycosylated hemoglobin (A1C) assay as the new standard diagnostic test for diabetes. The committee reports that A1C measurement of chronic glycemic levels provides a better diagnosis than the currently used tests.¹

For the first time, attention was focused on the relationship between glucose levels and the presence of long-term complications. In the past, the National Diabetes Data Group relied on distributions of glucose levels, rather than the relationship between glucose level and diabetes-related complications, to diagnose the disease.

The A1C assay may replace the standard fasting plasma glucose (FPG) test and the oral glucose tolerance test (OGTT). The committee also negated the previously held belief that the 2-hour plasma glucose test is the gold-standard for diagnosing diabetes.

The recommendations set an A1C value of 6.5% or higher as diagnostic. This value appears to be the level at which a person is at risk for developing the complications of diabetes. A diagnosis should be confirmed with a repeat A1C test, unless clinical symptoms and a glucose level higher than 200 mg/dL are present.

Many primary care providers already use the A1C assay as a first-line screen for diagnosis, said Richard Kahn, PhD, Chief Scientific and Medical Officer of the American Diabetes Association, who moderated the press conference at which the recommendations were reported.² Other clinicians use A1C in combination with FPG. One reason for the caution, some say, has been a lack of standardization of the A1C assay. Indeed, previous expert committees expressed concern over the lack of assay standardization. A 2003 follow-up report noted that great strides were made in standardizing most of the assays used in the United States.¹

In addition, glucose measurement is less accurate and less precise than most clinicians realize. A recent analysis of the performance of a variety of clinical laboratory instruments and

methods for measuring glucose revealed that 41% of glucometers have significant bias from the reference method, potentially resulting in the misclassification of more than 12% of patients.¹

▶ ADVANTAGES OF A1C

Proponents say the A1C assay has several major advantages over other diagnostic tests. First, unlike the FPG test or the OGTT, the A1C assay measures the average glucose level during the preceding 2 to 3 months, rather than at just that point in time. Measurements that capture long-term glycaemic exposure may serve as a better biochemical marker of diabetes. Compared with single measures of glucose concentration, the A1C value should provide a better indicator of the presence and severity of the disease. Observational studies have consistently demonstrated a strong correlation between retinopathy and A1C level, but a less consistent relationship has been seen between retinopathy and FPG levels. The correlation between A1C level and diabetes-related complications is also proven in controlled clinical trials and has been used to establish treatment goals.

“The ADA announced that its updated clinical recommendations promote the A1C assay as a diagnostic test for diabetes.”

Second, A1C levels are relatively stable after collection. The recent introduction of a new reference method for calibrating A1C assay instruments should further improve assay standardization in most of the world.

Third, between- and within-patient variability is substantially lower in A1C assay results than in glucose measurements. The A1C value has a day-to-day within-person variance of less than 2%, whereas FPG test results have a 12% to 15% variance.

Fourth, the ease and convenience of sample collection is superior because samples for A1C assay do not require patient preparation; on the other hand, the FPG test requires a timed sample after an 8-hour fast. Finally, A1C samples are stable at room temperature; glucose measurements from FPG samples, however, may decrease after as little as 1 to 4 hours at room temperature.¹

▶ LIMITATIONS OF A1C

Despite the above arguments for the A1C assay as the worldwide standard for diagnosis of diabetes, its use has limitations. The cost of providing the assay may preclude

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TAKE-HOME POINTS

- A1C values may replace previous thresholds for diagnosing diabetes, except in cases that make the A1C assay impossible, impractical, excessively expensive, or inaccurate.
- The threshold of an A1C value of 6.5% or higher is the recommended cut-point for a diagnosis of diabetes.
- Persons with an A1C value higher than 6% should be offered lifestyle interventions, which will vary based on available community resources, size of the target population, and nature of the intervention.

its routine use in some parts of the world.³ In those circumstances, clinicians should continue to use previously recommended methodologies: an FPG value of 126 mg/dL or higher accompanied by symptoms; a casual blood glucose measurement of 200 mg/dL or higher; or a 2-hour OGTT result of 200 mg/dL or higher.⁴

Hemoglobinopathies may interfere with A1C assay methods. Although many assay methods can correct for the presence of the most common hemoglobin traits, any condition that changes red-cell turnover, such as hemolytic anemia, chronic malaria, blood loss, and blood transfusion, will produce erroneous A1C results. Changes in red-cell turnover during pregnancy make using A1C to diagnose diabetes in these patients problematic; therefore, glucose measurements should continue to be used.

A1C levels may not have caught up with an acute elevation in glucose levels in certain clinical settings, such as rapidly evolving type 1 diabetes. An A1C assay performed at this time will likely produce a nondiagnostic result. Most cases of type 1 diabetes, particularly in children and adolescents, should continue to be diagnosed by the classic symptoms of polyuria, polydipsia, polyphagia, unexplained weight loss, and a casual glucose value that is higher than 200 mg/dL.

The new recommendation has already sparked some controversy. William Bornstein, MD, Assistant Professor of Endocrinology at Emory University, Atlanta, Georgia, suggests that the long-established track record of the older methods may make some physicians reluctant to use the A1C assay.⁵ Lori Roust, MD, a board-certified endocrinologist at the Mayo Clinic, Scottsdale, Arizona, points out that not all persons with hemoglobinopathies are aware of their status, so screening these patients for diabetes using the A1C assay may yield inaccurate results. Roust also points out that the normal range for A1C values varies from institution to institution; therefore, results obtained from tests on the same patient could vary from laboratory to laboratory. Furthermore, the new method will likely result in more false negatives, as some patients screened using the new method may be anemic, have renal disease, or have recently received

a blood transfusion, according to Curtiss Cook, MD, also with the Mayo Clinic. Still, doctors are likely to continue to use A1C assay in conjunction with other studies, such as the FPG test, random blood glucose testing, and OGTT.²

ELIMINATION OF SUBCLASSIFICATIONS

The committee warned against identifying an absolute dividing line between normoglycemia and diabetes. Although a level above which complications, such as retinopathy, rapidly escalate was identified, the committee was unable to identify a specific level at which risk for diabetes clearly begins. Furthermore, the clinical states of *prediabetes*, *impaired fasting glucose*, and *impaired glucose tolerance* fail to capture the continuum of risk. The committee thus argues for the elimination of these subclassifications.

On the other hand, the risk of developing diabetes increases as A1C values approach 6.5%. Therefore, the committee recommends that persons with A1C values close to the 6.5% threshold (ie, 6% and higher) should initiate lifestyle interventions. Other risk factors, including elevated triglyceride levels, an elevated BP, a high body mass index, and a family history of diabetes, should be used to determine which persons should be screened using the A1C assay. The level at which preventive services are provided to a population will primarily depend on the resources available, the size of the target population, and the nature of the intervention.

The International Expert Committee was comprised of representatives from the American Diabetes Association, the International Diabetes Federation, and the European Association for the Study of Diabetes. Its recommendations were published in the July 2009 issue of *Diabetes Care*.⁴ In December 2009, the ADA announced that its updated clinical practice recommendations, to be published in early 2010, promote A1C as a diagnostic test for diabetes.⁵ **JAAPA**

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