

Position Statement Executive Summary: Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus

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BACKGROUND—Multiple laboratory tests are used in the diagnosis and management of patients with diabetes mellitus. The quality of the scientific evidence supporting the use of these assays varies substantially.

APPROACH—An expert committee compiled evidence-based recommendations for the use of laboratory analysis in patients with diabetes. A new system was developed to grade the overall quality of the evidence and the strength of the recommendations. A draft of the guidelines was posted on the Internet, and the document was modified in response to comments. The guidelines were reviewed by the joint Evidence-Based Laboratory Medicine Committee of the AACC and the National Academy of Clinical Biochemistry and were accepted after revisions by the Professional Practice Committee and subsequent approval by the Executive Committee of the American Diabetes Association.

CONTENT—In addition to the long-standing criteria based on measurement of venous plasma glucose, diabetes can be diagnosed by demonstrating increased hemoglobin A_{1c} (HbA_{1c}) concentrations in the blood. Monitoring of glycemic control is performed by the patients measuring their own plasma or blood glucose with meters and by laboratory analysis of HbA_{1c}. The potential roles of noninvasive glucose monitoring, genetic testing, and measurement of autoantibodies, urine albumin, insulin, proinsulin, C-peptide, and other analytes are addressed.

SUMMARY—The guidelines provide specific recommendations based on published data or derived from expert consensus. Several analytes are found to have minimal clinical value at the present time, and measurement of them is not recommended.

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See accompanying article, p. e61.

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized and overproduced, leading to hyperglycemia. Diabetes is a common disease. The current worldwide prevalence is estimated to be approximately 250×10^6 and is expected to reach 380×10^6 by 2025 (1). The most recent data, derived from the 2005–2006 National Health and Nutrition Examination Survey, show a prevalence of diabetes in the U.S. in persons ≥ 20 years of age of 12.9% (equivalent to approximately 40×10^6 people) (2), 40% (approximately 16×10^6) of whom are undiagnosed. The prevalence of diabetes has also increased in other parts of the world. Recent estimates suggest 110×10^6 diabetic individuals in Asia in 2007 (3), but the true number is likely to be substantially greater, because China alone was thought to have 92.4×10^6 adults with diabetes in 2008 (4). The worldwide costs of diabetes in 2007 were approximately \$232 billion and are likely to be \$302 billion by 2025 (1). The mean annual per capita healthcare costs for an individual with diabetes are approximately 2.3-fold higher than those for individuals who do not have diabetes (5). The high costs of diabetes are attributable to care for both acute conditions (such as hypoglycemia and ketoacidosis) and debilitating chronic microvascular and macrovascular complications (6). Together, they make diabetes the fourth most common cause of death in the developed world (7).

The National Academy of Clinical Biochemistry (NACB) issued its “Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus” in 2002 (8). These recommendations were reviewed and updated by a multidisciplinary guideline team using an evidence-based approach, especially in key areas in which new evidence has emerged since the previous edition. The guideline committee, whose membership was mostly from the U.S., included clinical, laboratory, and

evidence-based guideline methodology experts. Members of the guideline committee have disclosed any financial, personal, or professional relationships that might constitute conflicts of interest with this guideline and have received no direct funding related to the development of the recommendations. The perspectives and views of various international and national organizations, as well as other potential stakeholders (e.g., health-care providers, patients, policy makers, regulatory bodies, health insurance companies, researchers, and industry) were taken into account during the public-consultation process. A new system was developed to grade both the overall quality of the evidence (Table 1) and the strength of recommendations (Table 2). The process of updating guideline recommendations followed the standard operating procedures for issuing NACB laboratory medicine practice guidelines, and the key steps are detailed in the guideline and accompanying supplements available in the Supplementary Data that accompanies the online version of this report.

This guideline focuses on the practical aspects of care in order to assist with decisions related to the use or interpretation of laboratory tests while screening, diagnosing, or monitoring patients with diabetes. It covers the rationale and pre-analytical, analytical, postanalytical, and, where applicable, emerging considerations, the last of which alert the reader to ongoing studies and potential future aspects relevant to each analyte. The recommendations intend to supplement the American Diabetes Association guidelines and thus do not address any issues related to the clinical management of patients. The full version of this guideline and its accompanying supplements are available in the Supplementary Data that accompanies the online version of this

report. Key recommendations are summarized below.

These recommendations primarily target laboratory professionals, general practitioners, physicians, nurses, and other healthcare practitioners involved in the care of diabetic patients. The guidelines can be used by patients (where relevant, e.g., self-monitoring of blood glucose [SMBG]), policy makers, and payers for healthcare, as well as by researchers and manufacturers. Although the recommendations were developed for national and international use and were intended to be generic, certain recommendations may not reflect views that are universally held or may have limited applicability in healthcare settings with differing organizational, cultural, and economic backgrounds. The guideline committee therefore advises users to adapt recommendations to local settings.

The next review of this guideline is planned in 5 years, unless substantial new evidence emerges earlier for high-priority areas in the laboratory management of patients with diabetes mellitus.

RECOMMENDATIONS—Capital letters denote the grade of recommendations, and categories in brackets refer to the quality of the underlying body of evidence supporting each recommendation. The grading system is described in Tables 1 and 2.

1. Glucose

- a. When glucose is used to establish the diagnosis of diabetes, it should be measured in venous plasma. **A (high)**
- b. When glucose is used for screening of high-risk individuals, it should be measured in venous plasma. **B (moderate)**
- c. Plasma glucose should be measured in an accredited laboratory when used for

diagnosis of or screening for diabetes. **GPP (good practice point)**

d. Outcome studies are needed to determine the effectiveness of screening. **C (moderate)**

e. Routine measurement of plasma glucose concentrations in an accredited laboratory is not recommended as the primary means of monitoring or evaluating therapy in individuals with diabetes. **B (low)**

f. Blood for fasting plasma glucose analysis should be drawn in the morning after the individual has fasted overnight (at least 8 h). **B (low)**

g. To minimize glycolysis, one should place the sample tube immediately in an ice-water slurry, and plasma should be separated from the cells within 30 min. If that cannot be achieved, a tube containing a rapidly effective glycolysis inhibitor, such as citrate buffer, should be used for collecting the sample. Tubes with only enolase inhibitors, such as sodium fluoride, should not be relied on to prevent glycolysis. **B (moderate)**

h. On the basis of biological variation, glucose measurement should have an analytical imprecision $\leq 2.9\%$, a bias $\leq 2.2\%$, and a total error $\leq 6.9\%$. To avoid misclassification of patients, the goal for glucose analysis should be to minimize total analytical error, and methods should be without measurable bias. **B (low)**

2. Glucose meters

a. There are insufficient published data to support a role for portable meters and skin-prick (finger-stick) blood samples in the diagnosis of diabetes or for population screening. **C (moderate)**

b. The imprecision of the results, coupled with the substantial differences among meters, precludes the use of glucose meters from the diagnosis of diabetes and limits their usefulness in screening for diabetes. **A (moderate)**

Table 1—Rating scale for the quality of evidence

| |
|---|
| High: Further research is very unlikely to change our confidence in the estimate of effect. The body of evidence comes from high-level individual studies that are sufficiently powered and provide precise, consistent, and directly applicable results in a relevant population. |
| Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate and the recommendation. The body of evidence comes from high-/moderate-level individual studies that are sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the included studies; generalizability of results to routine practice; or indirect nature of the evidence. |
| Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate and the recommendation. The body of evidence is of low level and comes from studies with serious design flaws, or evidence is indirect. |
| Very low: Any estimate of effect is very uncertain. Recommendation may change when higher-quality evidence becomes available. Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information. |

Table 2—Grading the strength of recommendations

A. The NACB strongly recommends adoption
 Strong recommendations for adoption are made when

- There is high-quality evidence and strong or very strong agreement of experts that the intervention improves important health outcomes and that benefits substantially outweigh harms; or
- There is moderate-quality evidence and strong or very strong agreement of experts that the intervention improves important health outcomes and that benefits substantially outweigh harms.

Strong recommendations against adoption are made when

- There is high-quality evidence and strong or very strong agreement of experts that the intervention is ineffective or that benefits are closely balanced with harms, or that harms clearly outweigh benefits; or
- There is moderate-quality evidence and strong or very strong agreement of experts that the intervention is ineffective or that benefits are closely balanced with harms, or that harms outweigh benefits.

B. The NACB recommends adoption
 Recommendations for adoption are made when

- There is moderate-quality evidence and level of agreement of experts that the intervention improves important health outcomes and that benefits outweigh harms; or
- There is low-quality evidence but strong or very strong agreement and high level of confidence of experts that the intervention improves important health outcomes and that benefits outweigh harms; or
- There is very low-quality evidence but very strong agreement and very high level of confidence of experts that the intervention improves important health outcomes and that benefits outweigh harms.

Recommendations against adoption are made when

- There is moderate-quality evidence and level of agreement of experts that the intervention is ineffective or that benefits are closely balanced with harms, or that harms outweigh benefits; or
- There is low-quality evidence but strong or very strong agreement and high level of confidence of experts that the intervention is ineffective or that benefits are closely balanced with harms, or that harms outweigh benefits; or
- There is very low-quality evidence but very strong agreement and very high levels of confidence of experts that the intervention is ineffective or that benefits are closely balanced with harms, or that harms outweigh benefits.

C. The NACB concludes that there is insufficient information to make a recommendation
 Grade C is applied in the following circumstances:

- Evidence is lacking or scarce or of very low quality, the balance of benefits and harms cannot be determined, and there is no or very low level of agreement of experts for or against adoption of the recommendation.
- At any level of evidence—particularly if the evidence is heterogeneous or inconsistent, indirect, or inconclusive—if there is no agreement of experts for or against adoption of the recommendation.

GPP. The NACB recommends it as a good practice point
 GPPs are recommendations mostly driven by expert consensus and professional agreement and are based on the information listed below and/or professional experience, or widely accepted standards of best practice. This category applies predominately to technical (e.g., preanalytical, analytical, postanalytical), organizational, economic, or quality-management aspects of laboratory practice. In these cases, evidence often comes from observational studies, audit reports, case series or case studies, nonsystematic reviews, guidance or technical documents, non-evidence-based guidelines, personal opinions, expert consensus, or position statements. Recommendations are often based on empirical data, usual practice, quality requirements and standards set by professional or legislative authorities or accreditation bodies, and so forth.

c. SMBG is recommended for all insulin-treated patients with diabetes. **A (high)**

d. In patients with type 2 diabetes treated with diet and oral agents, SMBG may help achieve better control, particularly when therapy is initiated or changed. Data are insufficient, however, to claim an associated improvement of health outcomes. The role of SMBG in patients with stable type 2 diabetes controlled by diet alone is not known. **C (high)**

e. Patients should be instructed in the correct use of glucose meters, including quality control. Comparison between SMBG and concurrent laboratory glucose analysis should be performed at regular intervals to evaluate the performance of the meters in the patient's hands. **B (moderate)**

f. Multiple performance goals for portable glucose meters have been proposed. These

targets vary widely and are highly controversial. Manufacturers should work to improve the imprecision of current meters, with an intermediate goal of limiting total error for 95% of samples to $\leq 15\%$ at glucose concentrations ≥ 5.6 mmol/L (100 mg/dL) and to < 0.8 mmol/L (15 mg/dL) at glucose concentrations < 5.6 mmol/L (100 mg/dL). Lower total error would be desirable and may prove necessary in tight glucose-control protocols and for avoiding hypoglycemia in all settings. **C (low)**

g. Meters should measure and report plasma glucose concentrations to facilitate comparison with assays performed in accredited laboratories. **GPP**

h. Studies are needed to determine the analytical goals (quality specifications) for glucose meters in SMBG and in intensive care units. **C (moderate)**

i. Recommendations for future research: Important end points in studies of SMBG should include, at a minimum, hemoglobin A_{1c} (HbA_{1c}) and frequency of hypoglycemic episodes to ascertain whether improved meters enable patients to achieve better glucose control. For studies of meter use in intensive or critical care, important end points include mean blood glucose, frequency of hypoglycemia, and variation of glucose control. Ideally, outcomes (e.g., long-term complications) should also be examined. **GPP**

3. Continuous minimally invasive glucose analyses

a. Real-time continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens can be a useful tool to lower HbA_{1c} in selected adults

(age >25 years) with type 1 diabetes.

A (high)

b. Although the evidence for lowering HbA_{1c} is not as strong for children, teens, and younger adults, real-time CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device. **B (moderate)**

c. Real-time CGM may be a supplemental tool to SMBG in individuals with hypoglycemia unawareness and/or frequent episodes of hypoglycemia. **B (low)**

d. Patients require extensive training in using the device. Available devices must be calibrated with SMBG readings, and the latter are recommended for making treatment changes. **GPP**

4. Noninvasive glucose analysis

a. No noninvasive sensing technology is currently approved for clinical glucose measurements of any kind. Major technological hurdles must be overcome before noninvasive sensing technology will be sufficiently reliable to replace existing portable meters, implantable biosensors, or minimally invasive technologies. **C (very low)**

5. Gestational diabetes mellitus

a. All pregnant women not previously known to have diabetes should undergo testing for gestational diabetes mellitus (GDM) at 24–28 weeks of gestation.

A (high)

b. GDM should be diagnosed by a 75-g oral glucose tolerance test according to the IADPSG (International Association of the Diabetes and Pregnancy Study Groups) criteria derived from the HAPO (Hyperglycemia and Adverse Pregnancy Outcome) study. **A (moderate)**

6. Urinary glucose

a. Semiquantitative urine glucose testing is not recommended for routine care of patients with diabetes mellitus. **B (low)**

7. Ketone testing

a. Ketones measured in urine or blood in the home setting by patients with diabetes and in the clinic/hospital setting should be considered only an adjunct to the diagnosis of diabetic ketoacidosis (DKA). **GPP**

b. Urine ketone measurements should not be used to diagnose or monitor the course of DKA. **GPP**

c. Blood ketone determinations that rely on the nitroprusside reaction should be used only as an adjunct to diagnose DKA and should not be used to monitor DKA treatment. Specific measurement of

β-hydroxybutyric acid in blood can be used for diagnosis and monitoring of DKA. **B (moderate)**

8. HbA_{1c}

a. HbA_{1c} should be measured routinely in all patients with diabetes mellitus to document their degree of glycemic control.

A (moderate)

b. Laboratories should use only HbA_{1c} assay methods that are certified by the National Glycohemoglobin Standardization Program (NGSP) as traceable to the DCCT (Diabetes Control and Complications Trial) reference. The manufacturers of HbA_{1c} assays should also show traceability to the IFCC reference method. **GPP**

c. Laboratories that measure HbA_{1c} should participate in a proficiency-testing program, such as the College of American Pathologists (CAP) HbA_{1c} survey, that uses fresh blood samples with targets set by the NGSP Laboratory Network. **GPP**

d. Laboratories should be aware of potential interferences, including hemoglobinopathies, that may affect HbA_{1c} test results, depending on the method used. In selecting assay methods, laboratories should consider the potential for interferences in their particular patient population. In addition, disorders that affect erythrocyte turnover may cause spurious results, regardless of the method used. **GPP**

GPP

e. Desirable specifications for HbA_{1c} measurement are an intralaboratory CV <2% and an interlaboratory CV <3.5%. At least two control materials with different mean values should be analyzed as an independent measure of assay performance. **B (low)**

f. Samples with HbA_{1c} results below the lower limit of the reference interval or >15% HbA_{1c} should be verified by repeat testing. **B (low)**

g. HbA_{1c} values that are inconsistent with the clinical presentation should be investigated further. **GPP**

h. Treatment goals should be based on American Diabetes Association recommendations, which include generally maintaining HbA_{1c} concentrations at <7% and more-stringent goals in selected individual patients if they can be achieved without significant hypoglycemia or other adverse treatment effects. Somewhat higher intervals are recommended for children and adolescents and may be appropriate for patients with limited life expectancy, extensive comorbid illnesses, a history of severe hypoglycemia, or advanced complications

(note that these values are applicable only if the NGSP has certified the assay method as traceable to the DCCT reference). **A (high)**

i. HbA_{1c} testing should be performed at least biannually in all patients and quarterly for patients whose therapy has changed or who are not meeting treatment goals. **B (low)**

j. HbA_{1c} may be used for the diagnosis of diabetes, with values ≥6.5% being diagnostic. An NGSP-certified method should be performed in an accredited laboratory. Analogous to its use in the management of diabetes, factors that interfere with or adversely affect the HbA_{1c} assay will preclude its use in diagnosis. **A (moderate)**

k. Point-of-care HbA_{1c} assays are not sufficiently accurate to use for the diagnosis of diabetes. **B (moderate)**

9. Genetic markers

a. Routine measurement of genetic markers is not of value at this time for the diagnosis or management of patients with type 1 diabetes. For selected diabetic syndromes, including neonatal diabetes, valuable information can be obtained with definition of diabetes-associated mutations. **A (moderate)**

b. There is no role for routine genetic testing in patients with type 2 diabetes. These studies should be confined to the research setting and evaluation of specific syndromes. **A (moderate)**

10. Autoimmune markers

a. Islet cell autoantibodies are recommended for screening nondiabetic family members who wish to donate part of their pancreas for transplantation into a relative with end-stage type 1 diabetes. **B (low)**

b. Islet cell autoantibodies are not recommended for routine diagnosis of diabetes, but standardized islet cell autoantibody tests may be used for classification of diabetes in adults and in prospective studies of children at genetic risk for type 1 diabetes after HLA typing at birth. **B (low)**

c. Screening patients with type 2 diabetes for islet cell autoantibodies is not recommended at present. Standardized islet cell autoantibodies are tested in prospective clinical studies of type 2 diabetic patients to identify possible mechanisms of secondary failures of treatment of type 2 diabetes. **B (low)**

d. Screening for islet cell autoantibodies in relatives of patients with type 1 diabetes or in persons from the general population is not recommended at present. Standardized islet cell autoantibodies

are tested in prospective clinical studies.

B (low)

e. There is currently no role for measurement of islet cell autoantibodies in the monitoring of patients in clinical practice. Islet cell autoantibodies are measured in research protocols and in some clinical trials as surrogate end points. **B (low)**

f. It is important that islet cell autoantibodies be measured only in an accredited laboratory with an established quality-control program and participation in a proficiency-testing program. **GPP**

11. Albuminuria (formerly microalbuminuria)

a. Annual testing for albuminuria in patients without clinical proteinuria should begin in pubertal or postpubertal individuals 5 years after diagnosis of type 1 diabetes and at the time of diagnosis of type 2 diabetes, regardless of treatment. **B (moderate)**

b. Urine albumin at concentrations ≥ 30 mg/g creatinine should be considered as a continuous risk marker for cardiovascular events. **B (moderate)**

c. The analytical CV of methods to measure albuminuria should be $< 15\%$. **B (moderate)**

d. Semiquantitative or qualitative screening tests should be positive in $> 95\%$ of patients with albuminuria to be useful for screening. Positive results must be confirmed by analysis in an accredited laboratory. **GPP**

e. Currently available dipstick tests do not have adequate analytical sensitivity to detect albuminuria. **B (moderate)**

f. Acceptable samples to test for increased urinary albumin excretion are timed collections (e.g., 12 or 24 h) for the measurement of albumin concentration and timed or untimed samples for measurement of the albumin-creatinine ratio. **B (moderate)**

g. The optimal time for spot urine collection is the early morning. All collections should be at the same time of day to minimize variation. The patient should not have ingested food within the preceding 2 h, but should be well hydrated (i.e., not volume depleted). **GPP**

h. Low urine albumin concentrations (i.e., < 30 mg/g creatinine) are not associated with high cardiovascular risk if the estimated glomerular filtration rate (eGFR) is $> 60 \text{ mL} \cdot \text{min}^{-1} \cdot (1.73 \text{ m}^2)^{-1}$ and the patient is normotensive. If the eGFR is $< 60 \text{ mL} \cdot \text{min}^{-1} \cdot (1.73 \text{ m}^2)^{-1}$ and/or the level of albuminuria is ≥ 30 mg/g creatinine on a spot urine sample, a repeat measurement should be taken within the year to assess change among people with hypertension. **A (moderate)**

12. Miscellaneous potentially important analytes

a. There is no role for routine testing for insulin, C-peptide, or proinsulin in most patients with diabetes. Differentiation between type 1 and type 2 diabetes may be made in most cases on the basis of the clinical presentation and the subsequent course. These assays are useful primarily for research purposes. Occasionally, C-peptide measurements may help distinguish type 1 from type 2 diabetes in ambiguous cases, such as patients who have a type 2 phenotype but present in ketoacidosis. **B (moderate)**

b. There is no role for measurement of insulin concentration in the assessment of cardiometabolic risk, because knowledge of this value does not alter the management of these patients. **B (moderate)**

c. Because current measures of insulin are poorly harmonized, a standardized insulin assay should be developed to encourage the development of measures of insulin sensitivity that will be practical for clinical care. **GPP**

d. There is no published evidence to support the use of insulin antibody testing for routine care of patients with diabetes. **C (very low)**

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