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Methodological Approach to Updating and Grading Recommendations in Laboratory Medicine Guidelines: National Academy of Clinical Biochemistry Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus

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Nonstandard abbreviations: NACB, National Academy of Clinical Biochemistry; DM, diabetes mellitus; ADA, American Diabetes Association; GRADE, Grading of Recommendations Assessment, Development and Evaluation; AGREE, Appraisal of Guidelines for Research and Evaluation; GPP, good practice point.

Methods for Updating the NACB Diabetes Mellitus Laboratory Medicine Practice Guidelines

The National Academy of Clinical Biochemistry (NACB) has developed evidence-based guidelines on topics related to the practice of laboratory medicine. These guidelines are updated approximately every 5 years and are available on the NACB Web site (http://www.aacc.org/members/nacb). The NACB issued its "Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus" in 2002 *(1)*. These recommendations were reviewed and updated via an evidence-based approach, especially in areas in which new evidence has emerged since the 2002 publication. The process of updating guideline recommendations followed the standard operating procedures for preparing, publishing, and editing NACB laboratory medicine practice guidelines. The key steps are summarized in Fig. 1 in the online Data Supplement, available at http://www.clinchem.org/content/vol57/issue6, and are explained below. The guideline-updating process was designed to fulfill the methodological quality criteria of the Appraisal of Guidelines for Research and Evaluation (AGREE) II Instrument *(2)*.

STEP 1: Determine the Scope and Key Topics of the Guideline

The scope and purpose of this guideline is primarily to focus on the laboratory aspects of testing in the contexts of type 1 and type 2 diabetes mellitus (DM). It does not deal with any issues related to the clinical management of DM that are already covered in the American Diabetes Association (ADA) or WHO guidelines. In January of each year, the ADA publishes in *Diabetes Care* a supplement entitled "Clinical Practice Recommendations." This supplement, a compilation of all ADA position statements related to clinical practice, is an important resource for healthcare professionals who care for people with DM. The intention of the NACB guideline is to supplement the ADA guidelines and to avoid duplication or repetition of information. Therefore, it focuses on practical aspects of care to assist in making decisions related to the use or interpretation of laboratory tests during screening, diagnosing, or monitoring of patients with DM.

STEP 2: Determine the Target Group of the Guideline and Establish a Multidisciplinary Guideline Team

The primary target of these recommendations includes general practitioners, physicians, nurses, and other healthcare practitioners directly involved in the care of diabetic patients, as well as laboratory professionals. The guidelines can be used by patients where relevant (e.g., self-monitoring of blood glucose), policy makers, and payers for healthcare, as well as by researchers. In addition, the guidelines

may advise industry/manufacturers on how to use or develop assays for the laboratory management of DM.

The guideline committee included representatives of key stakeholders to whom the recommendations are meant to apply primarily. Experts of the guideline team are listed in the guideline *(3)* and represented the NACB (D.B. Sacks, D.E. Bruns) and the ADA (M.S. Kirkman). The guideline committee included clinical experts (G.L. Bakris, A. Lernmark, B.E. Metzger, D.M. Nathan) and laboratory experts (D.B. Sacks, D.E. Bruns, M. Arnold, A.R. Horvath) whose key area of research and practice is DM. Some members of the committee provided additional support in evidence-based guideline-development methodology (D.E. Bruns, A.R. Horvath, D.B. Sacks). Members of the guideline committee were mostly from the US. The perspectives and views of various international and national organizations representing the wider laboratory and clinical professions and practice settings, as well as other potential stakeholders (including other healthcare providers, patients, policy makers, regulatory bodies, health insurance companies, researchers, and industry) were taken into account during the public-consultation process (see steps 8 and 10; see Supplementary Table 1).

The guideline committee received no sponsorship, honoraria, or other direct funding related to the development of this guideline. The NACB supported the development process by providing funds to cover the expenses of meetings and consensus conferences and provided administrative support. The views of the NACB officers and staff have not influenced the content of the guideline.

All authors who contributed to the development of the recommendations of this guideline have declared (via the official disclosure form of the NACB) any financial, personal, or professional relationships that might constitute conflicts of interest with this guideline. These disclosures are part of the guideline document published on the NACB Web site.

STEP 3: Identify Key Areas for Revisions and Define the Structure and Methodology of the Updated Guideline

The chairman of the guideline committee (D.B. Sacks) acted as editor and assigned lead authors to each section. Authors reviewed the 2002 edition of the NACB DM guideline *(1)* and identified key areas for revisions and updating. The guideline team discussed the scope and methods of the updating process at a face-to-face meeting, which was followed by numerous teleconferences and e-mail exchanges among authors that were coordinated by the editor and the NACB. The guideline group decided that the structure of the guideline would remain the same as the 2002 document and that it would cover virtually all key analytes that are used primarily in the diagnosis and management of individuals with DM. As before, the testing of lipids and related cardiovascular risk factors is not covered in this update but is addressed in a separate NACB guideline *(4)*. For each area of testing discussed, the guideline highlights the clinical use and rationale for the test or tests; the preanalytical, analytical, and interpretive aspects of each test; and, where relevant, emerging considerations for future research.

STEP 4: Define and Prioritize Key Questions

The lead authors used the review process outlined above to define specific key questions to enter on a standard form developed for this process. These questions were sent to all members of the guideline committee for independent review and prioritization, a process that used preset criteria related to the relationship between testing and outcomes (see Supplementary Table 2). Authors used the categories and explanatory notes provided (see Supplementary Table 2) to document the rationale for prioritization or individually provided their own reasoning. Authors assigned priority scores on a scale of 1 to 4 (most

important, important, moderately important, or least important, respectively). The independent replies collected from all authors were the basis for drafting a consensus priority list. Final key questions with priority scores and categories of reasoning are presented in the evidence tables (see Supplementary Table 3).

STEP 5: Search the Literature Systematically for High-Priority Questions and Select Relevant Key Publications

Key questions that earned the highest priority score were covered by a more systematic approach during the search and evaluation of the evidence currently available in the literature. Other topics that were considered less important were dealt with in a less rigorous way. Because this guideline is an update of the 2002 version, authors limited their searches to the period beginning in January 2002. Guidelines related to the topic were searched in the Agency for Healthcare Research and Quality National Guideline Clearinghouse database (http://www.guideline.gov/). Systematic reviews and metaanalyses were searched by using the Clinical Queries–Find Systematic Reviews function of PubMed. If no such publications were found, PubMed, Embase, and other databases were used to search the primary literature. Because the group of authors included leading experts in their fields, the authors' personal files, communications with experts, and unpublished or ongoing-trial data were also made available to be used in the guideline-updating process. Additional literature citations were added during the comment periods (see below).

Authors selected relevant key publications for updating each section, and the editor of the guideline (D.B. Sacks) and lead authors of other sections (D.E. Bruns, M.S. Kirkman, D.M. Nathan) acted as independent expert reviewers to avoid biased selection of papers. When the guideline team retrieved and agreed with existing guideline recommendations that had already covered the key question comprehensively and had reached concordant conclusions, the guideline team simply adopted and referenced the published recommendations in order to avoid duplicate publication.

STEP 6: Subject Selected Key Publications to Critical Expert Review; Extract Data into Evidence Tables

Critical review of selected key publications formed the basis for establishing the level and quality of the evidence underlying each recommendation (see STEP 7 for details). Section authors and a methodology expert (A.R. Horvath) extracted data into evidence tables (see Supplementary Table 3). These tables list all key questions together with their priority scores (STEP 4). Related recommendations and their grades from the 2002 guideline were aligned with those of the new updated recommendations (see columns 1 and 2 in Supplementary Table 3). In the updated recommendation, authors highlighted changes to the original text in boldface and provided explanation for the changes where necessary (column 3). Key references supporting the new recommendation were listed (column 4).

STEP 7: Define the Quality of Evidence Underlying Each Recommendation

To our knowledge, no uniformly accepted grading scheme exists for rating the quality of evidence and the strength recommendations when questions related to laboratory testing for the screening, diagnosis, prognosis, and monitoring of a condition are addressed *(5)*. The guideline group agreed that the grading scheme of the ADA, which was used in the 2002 version of this guideline *(1)*, is applicable predominantly to therapeutic recommendations and that its use in this diagnostic guideline was thus impracticable. Therefore, we developed a grading system by adapting the key elements of evidence-rating frameworks employed by various international guideline agencies, the US Preventive Services Task Force, and the Grading of Recommendations Assessment, Development and Evaluation

(GRADE) Working Group *(6–12)*. In this system, the overall quality of the body of evidence (STEP 7) and the strength of recommendations (STEP 9) are graded separately. Rating the quality of the *body* of evidence is based on (*a*) the level of evidence of *individual* studies defined by their study design and methodological quality; (*b*) the consistency of results across various studies; (*c*) the directness of comparisons; and (*d*) the precision-of-effect estimates. Supplementary Table 4 provides a detailed explanation of evidence-level categories and these elements of the rating scheme for the quality of evidence.

Members of the guideline committee received detailed explanations and guidance, as well as methodological support, on how to use the grading scheme. At this stage of the guideline-development process, section authors indicated the study design (see column 5 in Supplementary Table 3) and the level of evidence (column 6) of all individual studies listed in the evidence tables. The quality of the totality of the evidence underlying each recommendation was established by means of the criteria mentioned above (column 7).

STEP 8: Release the First Draft of the Guideline for Public Comments

The first draft of the guideline was released on the NACB Web site for soliciting of public review and feedback. The still nongraded draft recommendations were sent to a number of external organizations (see Supplementary Table 1) for peer review and expert comments that could be submitted either via the NACB Web site or by mail. The draft guideline was also presented at the Arnold O. Beckman consensus conference in 2007, and the discussions at this conference were recorded.

STEP 9: Incorporate Comments, Grade Recommendations, and Prepare the Second Draft of the Guideline

The guideline team reviewed and discussed the comments that were received and made many changes to the first draft to reflect the views of external peers, organizations, or individuals. The amended draft of the guideline was also presented at the 2009 AACC annual meeting and used for grading recommendations.

The grade or strength of recommendation refers to the extent of collective confidence that the desirable effects of a recommendation outweigh the potential undesirable effects. Desirable effects of a recommendation may include improved health-related, organizational, or economic outcomes or aspects of care. The quality of evidence (STEP 7, Supplementary Table 4) is only one element in making recommendations for practice. Scientific evidence was supplemented with considered judgment that balanced the potential clinical benefits and harms with perceived patients' preferences, bioethical considerations, and organizational and economic impacts of testing *(5, 6, 9–12)*. Considered judgment therefore may have upgraded or downgraded a recommendation. Categories for grading recommendations are shown in Supplementary Table 5.

During the considered-judgment process, the guideline committee was primarily driven by 2 core bioethical values—beneficence and nonmalevolence. The guideline group also observed the first principle of bioethics, i.e., respect for patients' autonomy and the decision-making capacities of individuals to make their own choices. The guideline group assumes that the target users will also deal with this core bioethical principle when using these guidelines in practice *(13)*. The guideline committee acknowledges that it was not able to cover universally other bioethical principles, such as justice and equity. As mentioned above, the members of the guideline team, as well as individuals who commented on the recommendations, were mostly from North America and other developed countries. Their views and experiences therefore unavoidably affected the considered-judgment and consensus processes

involved in formulating recommendations. The guideline team also could not consider explicitly the cost implications of the recommendations in various resource settings, although recommendations were formulated in a generic way and in a cost-conscious manner.

Recommendations in diagnostic guidelines frequently are supported primarily by expert consensus. This reflects the often poor quality of evidence, or the lack or indirectness of evidence that the intervention is relevant to patient outcomes. To avoid the influence of dominant personalities and overrepresentation of the individual opinions or views of experts, the guideline team reached consensus when the evidence base was inconsistent, weak, or lacking. The matrix in Supplementary Table 6 assisted in the assignment of final grades to recommendations. The methodology expert pregraded recommendations by using the information in columns 5, 6, and 7 of the evidence tables provided by committee members (see Supplementary Table 3). Authors reviewed these grades and returned the amended evidence tables to the methodology expert for completion. Committee members added comments or explanatory notes when necessary (column 8) to enhance the transparency and reproducibility of the considered-judgment and consensus process of grading and to address the adaptability and applicability of the final recommendations. All sections were reviewed by the ADA representative (M.S. Kirkman), a clinical expert (D.M. Nathan), and a methodology expert (A.R. Horvath) and were edited by the chairman of the guideline committee (D.B. Sacks).

STEP 10: Release the Second Draft of the Guideline for Public Comments and Submit the Final Draft to the NACB for Review and Approval

The second draft of the guideline with graded recommendations was posted on the NACB Web site for a last call for public comments. The guideline recommendations were also reviewed by the Professional Practice Committee of the ADA. Several comments were received and incorporated, and the final guideline draft was submitted for review by the joint Evidence-Based Laboratory Medicine Committee of the AACC and the NACB. After addressing the reviewers' comments, the guideline committee referred the guideline to the NACB Board of Directors, which approved it before its official release for publication.

Implementation and Review

To assist implementation, the guideline committee has listed the key recommendations of the guideline in an executive summary. Key diagnostic and risk-assessment criteria are presented in tables, and a diagnostic algorithm is provided for urinary albumin testing. Most recommendations are worded to represent standards of care and thus can be easily converted to key performance indicators for local audit purposes.

Although recommendations have been developed for national and international use and are intended to be generic, certain elements of this guideline will not reflect views that are universally held, and other elements may have limited applicability in healthcare settings that lack sufficient resources for adopting the recommendations. The guideline committee advises users to adapt recommendations to their local settings. During such adaptation processes, the evidence tables provided (see Supplementary Table 3) might assist users in making informed decisions.

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 DM.

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Acknowledgments

We are grateful to Robert Christenson, Christopher Price, and Joseph Watine for insightful suggestions and to Ibolya Bunda and Betsy Garman for expert help in compiling the document. We also thank all of the individuals listed in Supplementary Table 1 who submitted comments on preliminary drafts of the guideline.

References

1. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436–72.

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3. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2011;57:e1–e47.

4. AACC. National Academy of Clinical Biochemistry laboratory medicine practice guidelines. Emerging biomarkers for primary prevention of cardiovascular disease and stroke. Myers GL, ed. 70 p. http://www.aacc.org/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/risk/Pages/toc.aspx (Accessed December 2010).

5. Horvath AR. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. Clin Chem 2009;55:853-5.

6. Scottish Intercollegiate Guidelines Network. SIGN 50: a guideline developer's handbook. Edinburgh, January 2008. 112 p. http://www.sign.ac.uk/guidelines/fulltext/50/index.html (Accessed December 2010).

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8. Agency for Healthcare Research and Quality. National Guideline Clearinghouse. http://www.guidelines.gov/. (Accessed December 2010).

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10. Australian Government National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. December 2009. http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/evidence_statement_form.pdf (Accessed December 2010).

11. Schünemann HJ, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 9. Grading evidence and recommendations. Health Res Policy Syst 2006;4:21.

12. Schünemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ 2008;336:1106–10.

13. Watine J. What sort of bioethical values are the evidence-based medicine and the GRADE approaches willing to deal with? J Med Ethics 2010;37:184–6.

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Supplementary Table 1. Organizations and individuals participating in the public commenting of the NACB Diabetes Mellitus Guidelines

The organizations and individuals listed below were invited to comment on the National Academy of Clinical Biochemistry draft guidelines for laboratory testing of diabetes. We would like to acknowledge and thank those organizations and individuals who reviewed and commented on the draft guidelines. For those organizations that were able to send a representative to the Arnold O. Beckman Conference or provide written comments, the name of the representative is listed with the organization.

Organizations:

ARUP Laboratories
William Roberts, MD, PhD
http://www.aruplab.com/

Agency for Healthcare Research and Quality
www.ahrq.gov

American Academy of Family Physicians
www.aafp.org

American Association of Clinical Endocrinologists
www.aace.com

American Association of Diabetes Educators
www.aadenet.org
Amparo Gonzalez RN, CDE
Karen Fitzner, PhD

American College of Obstetricians and Gynecologists
www.acog.org
Donald Coustan, MD

American College of Physicians
www.acponline.org
Merri Pendergrass, MD

American Diabetes Association
www.diabetes.org
M. Sue Kirkman, MD

Association for Clinical Biochemistry
www.acb.org.uk
Garry John, MD

Association of Public Health Laboratories
www.aphl.org

Bayer HealthCare
Donald Parker, PhD
http://www.bayerhealthcare.com/scripts/pages/en/index.php

Centers for Disease Control and Prevention
www.cdc.gov
Jane Kelly, MD

Centers for Medicare and Medicaid Services
http://www.cms.gov/

College of American Pathologists
www.cap.org
Peter Howanitz, MD

Department of Veterans Affairs
www.va.gov
Leonard Pogach, MD

Diabetes UK
www.diabetes.org.uk

The Endocrine Society
www.endo-society.org
Lisa Marlow

European Association for the Study of Diabetes
www.easd.org
Jonathan Levy, MD

Food and Drug Administration
www.fda.gov
Arleen Pinkos

International Diabetes Federation
www.idf.org

International Federation of Clinical Chemistry and Laboratory Medicine
www.ifcc.org
Mauro Panteghini, MD

International Society of Diabetes and Vascular Disease
http://www.intsocdvd.com/

Italian SIBioC-SIMeL Study Group on Diabetes
http://www.simel.it/en/
http://www.sibioc.it/

Juvenile Diabetes Research Foundation
www.jdrf.org

Lifescan Inc
John Mahoney, BA
http://www.lifescan.com/

National Institute of Diabetes and Digestive and Kidney Diseases (of the National Institutes of Health)
www.nih.gov

National Medical Association
http://www.nmanet.org

North American Nursing Diagnosis Association (NANDA-International)
www.nanda.org
Mary Ann Lavin, ScD, RN, FAAN

Roche Diagnostics
Theresa Bush, PhD
http://www.roche.com/index.htm

Siemens Healthcare Diagnostics
Roma Levy, MS
Tricia Bal, MD
Susan Selgren, PhD
http://www.medical.siemens.com/webapp/wcs/stores/servlet/StoreCatalogDisplay~q_catalogId~e_-101~a_langId~e_-101~a_storeId~e_10001.htm

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Individuals:

Phillip Bach, Primary Children's Medical Center, Salt Lake City, USA

Jim Boyd, University of Virginia, USA

Yu Chen, Dr. Everett Chalmers Regional Hospital/Horizon Health Network, Canada

Rob Christenson, University of Maryland Medical Center, USA

Edgard Delvin, CHU Ste-Justine, Montreal, Canada

Kent Dooley, LifeLabs, British Columbia, Canada

Raymond Gambino, Quest Diagnostics Inc, USA

Mary Lou Gantzer, Siemens Healthcare Diagnostics, USA

Eswari Gudipati, USA (patient view)

Trefor Higgins, DynaLifeDx, Canada

Stephen Kahn, Loyola University, USA

Raymond Karcher (retired), Beaumont Hospital, USA

Eric Kilpatrick, Hull Royal Infirmary, UK

Ben Kukoyi, Houston, USA

Phillip Lee, University of Texas Medical Branch Galveston, USA

Randie Little, University of Missouri-Columbia School of Medicine, USA

John Mahoney, Lifescan, USA

Matthew Meerkin, University of Notre Dame, Australia

Andrea Mosca, University of Milan, Italy

Christian Perier, Hospital Nord, Saint-Etienne, France

Leonard Pogach, VA New Jersey Healthcare System, USA

Chris Price, University of Oxford, UK

Kastoori Ramakrishnan, ProdConcepts, LLC

Maria del Patrocinio Chueca Rodriguez, Hospital Reina Sofia, Spain

Kareena Schnabl, DynaLIFEDx, Canada

Dhastagir Sheriff, Al Arab Medical University, Benghazi, Libya

Robbert Slingerland, Isala Klinieken, The Netherlands

John Tayek, Harbor UCLA Medical Center, USA

Joseph Watine, Hôpital de la Chartreuse, Villefranche-de-Rouergue, France

Shirley Welch, Kaiser Permanente, USA

William E. Winter, University of Florida, USA

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Supplementary Table 2: Criteria for prioritization of key questions

Prioritization criteria	Explanatory notes	Examples
A: The test has high impact on *clinical* outcomes (e.g. morbidity, mortality, prognosis)	**A1:** The test or its characteristics (e.g. its diagnostic or target value or range) are directly or indirectly linked to important clinical outcomes The test is a surrogate (indirect) measure of important clinical outcomes	– Glucose cut-off values for diagnosing DM, IFG or IGT – The impact of maternal glycemia on pregnancy outcomes (direct link to outcome); OGTT diagnostic criteria to detect GDM (indirect link to outcome) – HbA_{1c} is a surrogate measure of morbidity and mortality
	A2: The test and its result have a major impact on clinical management decisions	– Diagnostic criteria for DM to guide initiation of treatment – HbA_{1c} values in guiding decision on changing treatment – Albuminuria results guiding decisions on initiating therapy with ACE-inhibitors
	A3: There is current controversy on the use of the test in practice	– OGTT *vs* FPG for the diagnosis of DM – Diagnostic criteria for GDM
	A4: There is wide variation in practice with unfavorable outcomes (e.g. misdiagnosis of the condition)	– Differing criteria for diagnosing DM or GDM – Variations in the use of random or timed specimens and albumin concentration or albumin excretion rate *vs* ACR for diagnosing albuminuria
	A5: New and substantial evidence has emerged since the publication of the 2002 NACB guideline	– SMBG in type 2 DM – HAPO study in GDM
B: The test has high impact on	**B1:** High volume testing with uncertain impact	SMBG in type 2 DM

***organizational* outcomes**	**B2:** There is public/commercial/ professional/governmental pressure on testing	– Use of portable meters in groceries, by patients, etc. – Changing the expression of HbA_{1c} values due to standardization
C: The test has high impact on *economic* outcomes	**C1:** Testing is associated with high costs	SMBG
	C2: New and substantial evidence has emerged on the cost-effectiveness of the test since the publication of the 2002 NACB guideline	

Abbreviations: ACE: Angiotensin Converting Enzyme; ACR: Albumin Creatainine Ratio; DM: Diabetes Mellitus; FPG: Fasting Plasma Glucose; GDM: Gestational Diabetes Mellitus; HAPO: Hyperglycemia and Adverse Pregnancy Outcome; IFG: Impaired Fasting Glucose; IGT: Impaired Glucose Tolerance; NACB: National Academy of Clinical Biochemistry; OGTT: Oral Glucose Tolerance Test; SMBG: Self-Monitoring of Blood Glucose

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Supplementary Table 3: Evidence table

Chapter 1: GLUCOSE

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
DOES GLUCOSE NEED TO BE MEASURED IN PLASMA FOR THE DIAGNOSIS OF DIABETES MELLITUS?							**[3]Priority: 3 (B2, C1)**	
1.a	Glucose should be measured in plasma in an accredited laboratory to establish the diagnosis of diabetes ***Level A***	When glucose is used to establish the diagnosis of diabetes, it should be measured in venous plasma ***A (high)***	Clarification	American Diabetes Association. Standards of medical care in diabetes --2010. Diab Care 2010; 33 (Suppl 1):S11-61	Guideline expert opinion	Low	High	Direct relationship between glucose and complications of diabetes has been shown in earlier high quality studies incorporated in ADA and WHO guidelines. Difficult to evaluate quality of evidence as plasma glucose has been sole diagnostic criterion for diabetes for many years of clinical practice. Glucometers are not accurate enough to diagnose diabetes. This represents strong agreement of experts. WHO recommends „venous plasma glucose" should be standard, but due to wide-spread use of capillary sampling (especially in under-resourced countries) capillary samples are accepted as a pragmatic solution. However, evidence does NOT support use of capillary samples.
				World Health Organization, Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycermia: Report of a WHO/ IDF Consultation. Geneva: World Health Organization, 2006	Guideline	Low		
				Engelgau MM, et al. Comparison of fasting and 2-hour glucose and HbA1c levels for diagnosing diabetes. Diagnostic criteria and performance revisited. Diab Care 1997;20(5):785-91.	cross-sectional population-based sample	High		
				McCance DR, e al. Comparison of tests for glycated haemo-globin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ. 1994; 308(6940): 1323-8. Erratum in: BMJ 1994; 309(6958):841	Cross sectional and longitudinal analysis	High		Provides evidence on the relation between complications and concomitant results of the three tests. Recommendation upgraded for direct link between glucose and DM complications and outcomes.

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

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No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
DOES GLUCOSE NEED TO BE MEASURED IN PLASMA FOR THE SCREENING OF DIABETES MELLITUS?							**[3]Priority: 3 (B2, C1)**	
1.b	Glucose should be measured in plasma in an accredited laboratory for screening of high-risk individuals ***Level E***	When glucose is used for screening of high-risk individuals, it should be measured in venous plasma ***B (moderate)***	Former recommendation was split for clarification and re-grading	American Diabetes Association. Standards of medical care in diabetes --2010. Diab Care 2010; 33 (Suppl 1):S11-61	Guideline expert opinion	Low	Moderate	WHO accepts glucometers for screening, for pragmatic reasons i.e., lack of access to an accredited central lab in underdeveloped countries. This represents a strong consensus view that it is "better than doing nothing".
				World Health Organization, Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycermia: Report of a WHO/ IDF Consultation. Geneva: World Health Organization, 2006.	Guideline	Low		
				Jesudason DR, et al. Macro-vascular risk and diagnostic criteria for type 2 diabetes: implications for the use of FPG and HbA_{1c} for cost-effective screening. Diab Care 2003; 26:485-90.	Population-based analysis	Moderate - high		
				Knowler WC, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346:393-403.	RCT	High		Recommendation downgraded for indirectness – outcome was to reduce DM with treatment/lifestyle changes.
				Tuomilehto J, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001; 344:1343-50.	RCT	High		
1.c		Plasma glucose should be measured in an accredited laboratory when used for diagnosis of or screening for diabetes ***GPP***	Former recommendation was split for clarification and re-grading					Consensus of experts

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
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No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
ARE SCREENING PROGRAMS FOR DIABETES MELLITUS EFFECTIVE?							**[3]Priority: NOT LISTED**	
1.d		Outcome studies are needed to determine the effectiveness of screening ***C (moderate)***	New recommendation based on additional evidence	Kahn R, et al. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effective-ness analysis. Lancet 2010;375:1365-74	Cost-effectiveness study	High	Moderate	No evidence so far that screening has benefit. Quality of evidence downgraded for indirectness.
				Glumer C, et al. What determines the cost-effectiveness of diabetes screening? Diabetologia 2006; 49:1536-44.	Cost-effectiveness modeling study	Moderate		
				Icks A, et al. Cost-effectiveness of type 2 diabetes screening: results from recently published studies. Gesundheitswesen 2005; 67 Suppl 1:S167-71	Review and cost-effectiveness analysis	Moderate - low		
				Hoerger TJ, et al. Screening for type 2 diabetes mellitus: a cost-effectiveness analysis. Ann Intern Med 2004; 140:689-99.	Cost-effectiveness analysis by Markov model	Moderate		
				Dallo FJ, Weller SC. Effectiveness of diabetes mellitus screening recommendations. Proc Natl Acad Sci USA 2003; 100:10574-9.	Cross-sectional analysis of population-based study	High		
				Jesudason DR, et al. Macro-vascular risk and diagnostic criteria for type 2 diabetes: implications for the use of FPG and HbA_{1c} for cost-effective screening. Diab Care 2003; 26:485-90.	Population-based analysis	Moderate - high		
				Perry RC, et al. HbA_{1c} measurement improves the detection of type 2 diabetes in high-risk individuals with nondiagnostic levels of fasting plasma glucose: the Early Diabetes Intervention Program (EDIP). Diab Care 2001; 24:465-71	RCT	High		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
DOES GLUCOSE NEED TO BE MEASURED IN PLASMA FOR THE MONITORING OF DIABETES MELLITUS?							**[3]Priority: 3 (B2, C1)**	
1.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. ***Level 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)***	No change	American Diabetes Association. Standards of medical care in diabetes --2010. Diab Care 2010; 33 (Suppl 1):S11-61.	Guideline expert opinion	Low	Low	
WHAT ARE THE PRE-ANALYTICAL CONSIDERATIONS IN GLUCOSE TESTING?							**[3]Priority: NOT LISTED**	
1.f	Blood for fasting plasma glucose analysis should be drawn after the subject has fasted overnight (at least 8 h). ***Level B***	Blood for fasting plasma glucose analysis should be drawn in the morning after the individual has fasted overnight (at least 8 h) ***B (low)***	Clarification	WHO Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia: Report of a WHO/IDF Consultation. Geneva: World Health Organization, 2006	Guideline	Low	Low	Evidence reveals a diurnal variation in FPG, with mean FPG higher in the morning than in the afternoon, indicating that many cases of diabetes would be missed in patients seen in the afternoon. No RCT compared morning vs afternoon testing in terms of diagnostic accuracy or outcomes. Therefore quality of evidence is downgraded for indirectness. However, there is strong consensus of experts that a fasting plasma specimen drawn in the morning should be used.
				Troisi RJ, et al. Diurnal variation in fasting plasma glucose: implications for diagnosis of diabetes in patients examined in the afternoon. JAMA 2000; 284:3157-9.	Retrospective population-based study	High		
				American Diabetes Association. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diab Care 1997; 20:1183-97.	Guideline	Low		
1.g	Plasma should be separated from the cells within 60 min; if this is not possible, a tube containing a glycolytic inhibitor such as sodium fluoride should be used for collecting the sample ***Level B***	To minimize glycolysis, one should place the sample tube immediately in an ice–water slurry, and the 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)***	Clarification	Gambino R et al. Acidification of blood is superior to sodium fluoride alone as an inhibitor of glycolysis. Clin Chem 2009;55:1019-21.	Observational	High	Moderate	A consistent body of good evidence that delay in sample processing leads to reduction in glucose in sample, and thus strong consensus that this may alter diagnostic accuracy. However, no study is available to determine if this leads to unfavorable outcomes or increased rate of complications. Therefore quality of evidence is downgraded for indirectness.

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation ?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
				Bruns DE, Knowler WC. Stabilization of glucose in blood samples: Why it matters. Clin Chem [Editorial] 2009;55:850-2.	Editorial	Low		*In vitro* decrease of glucose may lead to missed diagnoses of diabetes in the large proportion of the population who have glucose concentrations near the diagnostic cut points for diabetes.
				Sacks DB. Carbohydrates. In: Burtis CA, Ashwood ER, Bruns DE, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 4th ed. St. Louis: Elsevier Saunders, 2006:837	Review (book chapter)	Moderate-low		
				Boyanton BL, Jr., Blick KE. Stability studies of twenty-four analytes in human plasma and serum. Clin Chem 2002; 48:2242-7	Observational	High		
				Stahl M, et al. Optimization of preanalytical conditions and analysis of plasma glucose. 1. Impact of the new WHO and ADA recommendations on diagnosis of diabetes mellitus. Scand J Clin Lab Invest 2001; 61:169-79	Observational	High		
				Chan AY, et al. Effectiveness of sodium fluoride as a preservative of glucose in blood. Clin Chem 1989; 35:315-7.	Observational	High		
				Ladenson JH. Nonanalytical sources of variation in clinical chemistry results. In: Sonnenwirth A, Jarett L, eds. Clinical Laboratory Methods and Diagnosis. St. Louis, MO: C.V. Mosby Co., 1980:149	Review (book chapter)	Moderate-low		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
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No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
DO ANALYTICAL GOALS FOR GLUCOSE ANALYSIS NEED TO CHANGE/IMPROVE WITH THE LOWERED CUTOFF FOR IFG?							**[3]Priority: 2 (A1-3, B2)**	
1.h		On the basis of biological variation, glucose measurement should have an analytical imprecision ≤2.9%, a bias ≤2.2%, and a total error ≤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)***	New recommendation for setting analytical performance goals for achieving better diagnostic accuracy around diagnostic thresholds.	Ricos C et al. Current databases on biological variation: pros, cons and progress. Scand J Clin Lab Invest. 1999;59:491-500	Review	Moderate	Low	Quality of evidence is downgraded for indirectness to outcomes and for lack of primary studies linking analytical performance to outcomes. However, there is strong expert consensus that analytical uncertainty of glucose measurement could result in misclassification of patients. The related recommendation therefore was upgraded to reflect this potential impact on patient centered outcomes.
				Fraser CG. The necessity of achieving good laboratory performance. Diabet Med 1990; 7:490-3.	Expert opinion	Low		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

Chapter 2: GLUCOSE METERS

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
SHALL PORTABLE METERS BE USED IN DIAGNOSIS AND SCREENING OF DIABETES MELLITUS?							**[3]Priority: 2 (A3-4, B2, C1)**	
2.a	There are no published data to support a role for portable meters in the diagnosis of diabetes or for population screening. The imprecision of the meters, coupled with the substantial differences among meters, precludes their use in the diagnosis of diabetes and limits their usefulness in screening for diabetes ***Level E***	There are insufficient published outcome data to support a role for portable meters and skin-prick (finger-stick) blood samples in diagnosis of diabetes or for population screening ***C (moderate)***	New evidence emerged since 2002 and clarification. Prior recommendation was split into two separate recommendations for clarity and regarding.	Dungan K, et al. Glucose measurement: Confounding issues in setting targets for inpatient management. Diab Care 2007; 30(2): 403-409.	Review	Low	Moderate	WHO recommends plasma, but accepts capillary whole blood using glucometer. WHO accepts meters for screening for practical and financial reasons. This represents a strong consensus view that it is "better than doing nothing". Glucometers are not accurate enough to diagnose diabetes. This represents strong agreement of experts. Quality of evidence downgraded for inconsistency and indirectness of evidence.
				The Diabetes Research in Children Network (DirecNet) Study Group. Accuracy of newer generation home blood glucose meters in a Diabetes Research in Children Network (DirecNet) inpatient exercise study. Diabetes Technology and Therapeutics 2005; 7(5): 675-680.	Observational (Analytical evaluations)	High		
2.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)***		Bohme P, *et al.* Evolution of analytical performance in portable glucose meters in the last decade. Diab Care 2003; 26(4): 1170-1175.	Observational (Analytical evaluations)	High		
HOW SHOULD PORTABLE METERS BE USED IN MONITORING TYPE 1 DIABETES MELLITUS?							**[3]Priority: NOT LISTED**	
2.c	SMBG is recommended for all insulin-treated patients with diabetes. For type 1 patients, SMBG is recommended three or more times a day. SMBG may be desirable in patients treated with sulfonylureas or other insulin secretagogues and in all patients not achieving goals ***Level B***	Self-monitoring of blood glucose (SMBG) is recommended for all insulin-treated patients with diabetes ***A (high)***	Clarification	American Diabetes Association. Standards of medical care in diabetes--2010. Diab Care 2010;33 (Suppl 1):S11-61	Guideline expert opinion	Low	High	Intensive glycemic control in patients with type 1 diabetes was achieved in the DCCT by participants performing SMBG at least four times per day, hence the ADA recommendation and a strong consensus for SMBG to be performed three or more times per day in type 1 diabetes.
				DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-986.	RCT	High		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
SHOULD PORTABLE METERS BE USED IN MONITORING TYPE 2 DM?							**[3]Priority: 2 (A3, A5, B1-2, C1)**	
2.d	In patients with type 2 diabetes, SMBG may help achieve better control, particularly when therapy is initiated or changed. However, there are no data to support this concept. The role of SMBG in patients with stable type 2 diabetes controlled by diet alone is not known ***Level C***	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)***	New evidence emerged since the 2002 publication	Allemann S, Houriet C, Diem P, Stettler C. Self-monitoring of blood glucose in non-insulin treated patients with type 2 diabetes: a systematic review and meta-analysis. Curr Med Res Opin 2009;25:2903-13	Systematic Review	High	High	In spite of the number of high quality new studies and evidence reviews, there is insufficient evidence to claim improved outcomes for SMBG in type 2 DM. Therefore clear recommendations for or against SMBG in type 2 DM cannot be made at this stage.
				Poolsup N, Suksomboon N, Rattanasookchit S. Meta-analysis of the benefits of self-monitoring of blood glucose on glycemic control in type 2 diabetes patients: an update. Diabetes Technol Ther. 2009;11:775-84	Systematic Review	High		
				Farmer A, et al. Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. BMJ 2007;21;335:132	RCT	High		
				Martin S, at al. The ROSSO Study Group. Self-monitoring of blood glucose in type 2 diabetes and long-term outcome: an epidemio-logical study. Diabetologia 2006;49:271–8.	Epidemiolo-gical cohort study	Moderate		
				Karter AJ, et al.Longitudinal study of new and prevalent use of self-monitoring of blood glucose. Diab Care 2006;29:1757–63.	Observational study	High		
				Welschen LMC, et al. Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. Cochrane Database of Systematic Reviews 2005;Issue 2. Art. No.: CD005060.	Systematic review	High		Systematic review of 6 RCTs
				Welschen LMC, et al. Self-moni-toring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. Diab Care 2005;28:1510–7.				

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
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[3]For priority codes, see SupplementaryTable 2.

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No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
				Davidson MB. Counter-point: Self-Monitoring of Blood Glucose in Type 2 Diabetic Patients not Receiving Insulin: A waste of money. Diab Care 2005;28:1531-3.	Expert opinion	Low		
				Franciosi M, et al., the QuED Study Group. Self-monitoring of blood glucose in non-insulin-treated diabetic patients: a longitudinal evaluation of its impact on metabolic control. Diab Med 2005;22:900–6.	Observational study	High		
				Guerci B, et al., the ASIA Group. Self-monitoring of blood glucose significantly improves metabolic control in patients with type 2 diabetes mellitus: the Auto-Surveillance Intervention Active (ASIA) study. Diabetes Metab 2003; 29:587–94.	Multi-center, prospective open label, randomized trial	Moderate		
				Harris MI. Frequency of blood glucose monitoring in relation to glycemic control in patients with type 2 diabetes. Diab Care 2001;24:979-82.	Cross-sectional study	High		NHANES study
				Coster S, et al. Self-monitoring in Type 2 diabetes mellitus: a meta-analysis. Diab Med 2000;17:755-761.	Meta-analysis	High		Meta-analysis of 8 RCTs
				Faas A, et al. The efficacy of self-monitoring of blood glucose in NIDDM subjects. Diab Care 1997;20:1482-1486.	Systematic review	High		11 studies reviewed, including 6 RCTs

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
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No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
WHAT ARE THE PRE-ANALYTICAL CONSIDERATIONS FOR GLUCOSE METERS?							**[3]Priority: 2 (A2-3, B1-2, C1)**	
2.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 accuracy of patient results. ***Level B***	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)***	Clarification and new data	Kristensen GB, et al. Standardized evaluation of nine instruments for self-monitoring of blood glucose. Diab Technol and Therap 2008;10:467-77.	Observational	High	Moderate	
				Kristensen GB, et al. Standardized evaluation of instruments for self-monitoring of blood glucose by patients and a technologist. Clin Chem 2004; 50:1068-71.	Observational	High		
				Kabadi UM, et al. The effect of recurrent practice at home on the acceptability of capillary blood glucose readings. Accuracy of self blood glucose testing. Diab Care 1994;10:1110-23.	Observational	Moderate		
WHAT ARE THE ANALYTICAL CONSIDERATIONS FOR GLUCOSE METERS?							**[3]Priority: 2 (A2-3, B1-2, C1)**	
2.f	Multiple performance goals for portable glucose meters have been proposed. These targets vary widely and are highly controversial. No published study has achieved the goals proposed by the ADA. Manufacturers should work to improve the imprecision of current meters ***Level E***	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 ≤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)***	Clarification and new data	Kristensen GB, et al. Standardized evaluation of nine instruments for self-monitoring of blood glucose. Diab Technol and Therap 2008;10:467-77.	Observational	High	Low	Performance goal targets vary widely and are highly controversial. No evidence is available that the ADA targets of less than 5% total error can be achieved in practice. Downgraded evidence for inconsistency, indirectness and lack of consensus of experts.
				The Diabetes Research in Children Network (DirecNet) Study Group. Accuracy of newer generation home blood glucose meters in a Diabetes Research in Children Network (DirecNet) Inpatient Exercise Study. Diab Technol Ther 2005;7:675-83.	Observational (Analytical evaluation)	Moderate		
				Bohme P, et al. Evolution of Analytical Performance in Portable Glucose Meters in the Last Decade Diab Care 2003;26:1170-5.	Observational	High		
				Skeie S, et al. Instruments for self-monitoring of blood glucose: comparisons of testing quality achieved by patients and a technician. Clin Chem 2002;48:994-1003.	Observational	High		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
				Weitgasser R, et al. Newer portable glucose meters - analytical improvement compared with previous generation devices? Clin Chem 1999;45:1821-1825.	Observational	High		
				American Diabetes Association. Self-monitoring of blood glucose. Diab Care 1996;19 (S 1):S62-66.	Guideline	Low		
				Novis DA, Jones BA. Interinstitutional comparison of bedside blood glucose monitoring program characteristics, accuracy performance, and quality control documentation. Arch Pathol Lab Med 1998;122:495-502.	Observational	High		Q-probe
				Barr JT, et al. Ancillary (bedside) blood glucose testing in acute and chronic care facilities. NCCLS 1994;14:1-14.	Guideline	Low		
2.g	We recommend meters that measure and report plasma glucose concentrations to facilitate comparison with assays performed in accredited laboratories. ***Level E***	Meters should measure and report plasma glucose concentrations to facilitate comparison with assays performed in accredited laboratories *GPP*	No change, rewording		Expert consensus	Low	Very low	

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
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No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
ARE GLUCOSE METERS ADEQUATE FOR WIDESPREAD USE IN INTENSIVE CARE UNITS?							**[3]Priority: 2 (A1-3, B2, C1)**	
2.h	Clinical studies are needed to determine the analytic goals for glucose meters. At a minimum, the end points should be glycated hemoglobin and frequency of hypoglycemic episodes. Ideally, outcomes (e.g., long-term complications and hypoglycemia) should also be examined ***Level E***	Studies are needed to determine the analytical goals (quality specifications) for glucose meters in SMBG and in intensive care units ***C (moderate)***	Clarification and expansion of scope of recommendation to intensive care setting	Meynaar IA, et al. Accuracy of AccuChek glucose measurement in intensive care patients. Crit Care Med 2009;37:2691-6.	Observational study	High	Moderate-low	
2.i		Recommendations for future research: Important end points in studies of SMBG should include, at a minimum, hemoglobin A_{1c} (Hb A_{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***		Boyd JC, Bruns DE. Monte Carlo simulation in establishing analytical quality requirements for clinical laboratory tests meeting clinical needs. Methods Enzymol 2009;467:411-33.	Simulation modeling	Moderate		
				Scott MG, et al. Tight glucose control in the intensive care unit: Are glucose meters up to the task? Clin Chem 2009; 55:18-20.	Expert opinion	Low		
				Scott MG, et al. Tight glucose control in critically ill adults [Letter]. JAMA 2008; 300(23):2726-7.	Expert opinion	Low		
				Wiener RS, et al. Benefits and risks of tight glucose control in critically ill adults. JAMA 2008;300(8):933-944.	Systematic review and meta-analysis	Moderate		
				Hoedemaekers CW, et al. Accuracy of bedside glucose measurement from three gluco-meters in critically ill patients. Crit Care Med 2008;36(11):3062-6.	Observational study	High		
				Dungan K, et al. Glucose measurement: confounding issues in setting targets for inpatient management. Diabetes Care 2007;30:403-9.	Narrative review	Low		
				Finkielman J, et al: Agreement between bedside blood and plasma glucose measurement in the ICU setting. Chest 2005;127:1749-51.	Observational study	Low		
				van den Berghe G, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345(19):1359-1367.	RCT	Moderate		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

Chapter 3: CONTINUOUS MINIMALLY-INVASIVE GLUCOSE ANALYSES

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
ARE THERE ADEQUATE WELL CONTROLLED STUDIES DEMONSTRATING THE IMPACT OF CONTINUOUS GLUCOSE MONITORS ON INTERMEDIATE OUTCOMES (E.G. HbA_{1c}) TO JUSTIFY WIDESPREAD ADOPTION OF THE TECHNOLOGY? **GIVEN THE HIGH COSTS OF THE TECHNOLOGY, ARE THERE EVIDENCE-BASED SELECTION CRITERIA FOR ITS USE AND POTENTIAL REIMBURSEMENT?**							**[3]Priority: 2 (A1, A3, B2, C1)** **[3]Priority: 2 (A3, C1)**	
3.a	Noninvasive glucose analyses cannot be recommended as replacements for SMBG or glucose measurements by an accredited laboratory. Ongoing developments in the field, such as use of the new Gluco Watch Biographer, may influence this recommendation. ***Level E***	Real-time continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens can be a useful tool to lower Hb A_{1c} in selected adults (age >25 years) with type 1 diabetes ***A (high)***	Gluco Watch technology is no longer on market and has been supplanted by subcutaneous CGM devices. Additional evidence is available about effectiveness of real-time CGM.	The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group: N.Engl.J.Med. 2008;359:1464-1476	RCT	High	High	Three age subgroups pre-specified for outcome assessment
3.b		Although the evidence for lowering Hb A_{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)***	New recommendation based on additional evidence	The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group: N.Engl.J.Med. 2008;359:1464-1476	RCT	Moderate	Moderate	This was a per-protocol post-hoc analysis of the relationship between HbA_{1c} lowering and days per week of use, not an intention-to-treat analysis or the primary outcome. Therefore the quality of evidence and the strength of recommendation were downgraded.
3.c		Real-time CGM may be a supplemental tool to SMBG in individuals with hypoglycemia unawareness and/or frequent episodes of hypoglycemia ***B (low)***	New recommendation based on additional evidence	Garg S, et al. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor - a randomized controlled trial. Diab Care 2006;29:44-50	RCT	Moderate	Low	Comparison of real-time vs. blinded CGM (outcomes were patients' time in hyper-glycemic and hypoglycemic ranges). Evidence is indirect as the outcome was a surrogate biochemical marker (although patient-related), i.e. not clinical episodes of hypoglycemia.

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
ARE CONTINUOUS GLUCOSE MONITORS SUFFICIENTLY ACCURATE FOR CLINICAL USE BY PATIENTS?							**[3]Priority: 1 (A1-4, B1-2, C1)**	
3.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*	New recommendation		Clinical experience and FDA labeling of the device	Low	Very low	FDA labeling of the device (for trend assessment, not treatment decisions - use SMBG for insulin dosing)

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

Chapter 4: NONINVASIVE GLUCOSE ANALYSIS

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
SHOULD PRESENT NON-INVASIVE GLUCOSE SENSING TECHNOLOGY BE RECOMMENDED FOR MONITORING GLYCEMIA?							**[3]Priority: 3 (A3, A5, B2)**	
4.a	Noninvasive glucose analyses cannot be recommended as replacements for SMBG or glucose measurements by an accredited laboratory. Ongoing developments in the field, such as use of the new Gluco Watch Biographer may influence this recommendation. ***Level E***	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)***	New recommendation and clarification	Arnold MA, et al. Selectivity assessment of noninvasive glucose measurements based on analysis of multivariate calibration vectors. J Diabetes Sci Technol 2007;1:454-62.	Animal model	Low	Very low	Demonstration of selectivity issues. Downgraded for indirectness
				Tura A, et al. Non-invasive glucose monitoring: assessment of technologies and devices according to quantitative criteria. Diabetes Res Clin Pract 2007;77:16-40.	Review of technologies	Low		Review with assessment of feasibility of each approach
				Arnold MA, Small GW. Noninvasive glucose sensing. Anal Chem 2005;77:4529-39.	Review of technologies	Low		Review with listing of critical analytical parameters
				Khalil OS. Non-invasive glucose measurements at the dawn of the new millennium: An update. Diabetes Technol Ther 2004;6:660-697.	Review of technologies	Low		Review with assessment of feasibility of each approach
				Gutman S, et al. Regulatory aspects of noninvasive glucose measurements. Diabetes Technol Ther 2002;4:779-81.	Consensus statement	Low		Listing of anticipant FDA requirements for approval of any future non-invasive sensing technology.

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

Chapter 5: GESTATIONAL DIABETES MELLITUS (GDM)

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
WHAT ARE THE STRATEGIES FOR DETECTION AND DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS?							**[3]Priority: 1 (A5, B2)**	
5.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)*	New recommendation based on additional evidence of associations of maternal glycemia and perinatal outcome and RCT results showing benefit from treating mild GDM and expert consensus.	American Diabetes Association. Standards of medical care in diabetes --2011. Diab Care 2011;34 (Suppl 1):S11-61	Guideline, position statement	High	High	Based on the HAPO study and the IADPS criteria, ADA recommends that women with risk factors for type 2 diabetes are screened for diabetes at the first prenatal visit.
				International Association of Diabetes and Pregnancy Study Groups. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diab Care 2010;33:676-82.	Guideline, expert consensus	High		Expert Consensus Panel appointed by IADPSG recommended "outcome based" criteria for the classification of glucose concentrations in pregnancy.
				Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group: Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: Associations with neonatal anthropometrics. Diabetes 2009;58:453-459.	Prospective observational study of a multicenter cohort	High		
				Landon MB, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009;361:1339	RCT	High		This RCT does not deal with the diagnosis of GDM directly but provides evidence that treating mild GDM improves outcome.
				Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group (Metzger BE, HAPO Study PI). Hyperglycemia and Adverse Pregnancy Outcomes. N Engl J Med 2008;358:1991-2002	Prospective observational study of multicenter cohort	High		Strong evidence for continuous association between maternal glucose levels and pregnancy outcome
				Crowther CA, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477	RCT	High		This RCT does not deal with the diagnosis of GDM directly but provides evidence that treating mild GDM improves outcome.

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
5.b		GDM should be diagnosed by a 75-g OGTT according to the IADPSG criteria derived from the HAPO study *A (moderate)*	New recommendation based on additional evidence and expert consensus.	International Association of Diabetes and Pregnancy Study Groups. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diab Care 2010;33:676-82.	Guideline, expert consensus	High	Moderate*	This guideline was based on the HAPO study and on the opinions of the IADPSG Consensus Panel members because associations between maternal glycemia and clinical outcomes were continuous with no obvious thresholds at which risks increased. Therefore a consensus was required to translate these results into clinical practice.
				Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. Diabetes 2009;58:453	Prospective multi-national epidemiologic study	High		The study of 25,000 participants revealed strong, graded, predominantly linear and continuous associations between maternal glycemia and primary study outcomes
				Metzger, et al. Summary and Recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. Diab Care 2007;30:S251-S260.	Conference review	Moderate-low		Opinion of world-wide experts based on findings of the HAPO outcome study.

* NB: The HAPO study and the subsequent guideline published suggest setting diagnostic thresholds at OR 1.75, but OR 1.5 and 2.0 were also considered.

The authors themselves suggest the followings:

It is likely that additional well-designed randomized controlled trials and other clinical studies will be needed to determine
1) cost-effective therapeutic strategies for treatment of GDM diagnosed by the IADPSG Consensus Panel–recommended criteria;
2) optimal glycemic treatment targets;
3) appropriate follow-up of mothers to determine risks for later development of diabetes, other metabolic disorders, or CVD risk factors; and
4) follow-up of children to assess potential associations of maternal glycemia with long-term risks of obesity, altered glucose metabolism, and CVD risk factors.

Therefore recommendations are likely to change as more evidence becomes available or modified locally for resource considerations. Therefore the quality of evidence is downgraded to moderate but, due to strong consensus on the current criteria, the strength of recommendation is A.

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

Chapter 6: URINARY GLUCOSE

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
IS THERE A ROLE FOR URINE GLUCOSE TESTING IN THE MANAGEMENT OF DIABETES MELLITUS?							**[3]Priority: NOT LISTED**	
6.a	Semi-quantitative urine glucose testing is not recommended for routine care of patients with diabetes mellitus ***Level C***	Semiquantitative urine glucose testing is not recommended for routine care of patients with diabetes mellitus ***B (low)***	No change	Goldstein DE, et al. Tests of glycemia in diabetes. Diab Care 2004;27:1761-73.	Guideline	Low	Low	Downgraded for low quality and indirectness of evidence. However, consensus is strong against the use of this test. IDF supports urine glucose monitoring where blood glucose is not available or affordable.
				American Diabetes Association. Tests of glycemia in diabetes. Diab Care 1999;22:S77-9.	Guideline	Low		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

Chapter 7: KETONE TESTING

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
WHICH PATIENTS SHOULD BE ADVISED TO MEASURE URINE OR BLOOD KETONES AT HOME, AND UNDER WHAT CIRCUMSTANCES?							**[3]Priority: 2 (A2-4)**	
7.a	Ketones should be measured in urine or blood by patients with diabetes in the home setting and in the clinic/hospital setting as an adjunct to the diagnosis of diabetic ketoacidosis ***Level E***	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*	No change	ADA: Standards of Medical Care in Diabetes—2009; Diab Care 2009; 32 (Suppl 1):S13-S61	Guideline expert opinion	Low	Very low	Expert opinion, clinical experience
				ADA: Hyperglycemic crises in diabetes (position statement). Diab Care 2004; 27 (Suppl 1):S94-102	Guideline expert opinion	Low		
7.b	Urine ketone determinations should not be used to diagnose or monitor the course of DKA ***Level A***	Urine ketone measurements should not be used to diagnose or monitor the course of DKA *GPP*	No change	ADA Tests of glycemia position statement, DiaB Care 2001; 23 (Suppl 1):S80-82).	Guideline expert opinion	Low	Very low	Based on lack of measurement of beta-hydroxybutyrate by nitroprusside
ARE DIRECT MEASUREMENTS OF βHBA PREFERABLE TO NITROPRUSSIDE MEASUREMENTS OF KETONES?							**[3]Priority: 3 (A2)**	
7.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 treatment of DKA. Specific measurement of βHBA in blood can be used for diagnosis and monitoring of DKA. Further studies are needed to determine if the test offers any clinical advantage over more traditional management approaches (e.g., measurements of serum CO_2, anion gap, or pH). ***Level E***	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-hydroxybutiric acid in blood can be used for diagnosis and monitoring of DKA *B (moderate)*	No change	Wiggam MI, et al. Treatment of diabetic ketoacidosis using normalization of blood 3-hydroxybutyrate concentration as the end point of emergency management. A randomized controlled study. Diabetes Care 1997;20:1347-52.	RCT	Moderate	Moderate	Outcome not clinically meaningful Downgraded for indirectness of evidence
				Umpierrez GE, et al. Clinical utility of beta-hydroxybutyrate determined by reflectance meter in the management of diabetic ketoacidosis. Diab Care 1995;18:137-8.	Observational cohort study	Moderate		Comparison of two strategies of monitoring DKA
				Noyes KJ, et al. Hydroxybutyrate near-patient testing to evaluate a new endpoint for intravenous insulin therapy in the treatment of diabetic ketoacidosis in children. Pediatr Diabetes 2007;8:150-156	Observational cohort study	Moderate		Comparison of two strategies of monitoring DKA

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

Chapter 8: HEMOGLOBIN A_{1c}

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
HOW GLYCATED HEMOGLOBIN SHOULD BE USED IN MONITORING DIABETES MELLITUS?							**[3]Priority: NOT LISTED**	
8.a	Glycated hemoglobin (GHb) should be measured routinely in all patients with diabetes mellitus to document their degree of glycemic control. *Level A*	Hb A_{1c} should be measured routinely in all patients with diabetes mellitus to document their degree of glycemic control *A (moderate)*	Clarification	American Diabetes Association. Standards of medical care in diabetes--2010. Diab Care 2011;34 (Suppl 1):S11-61.	Guideline	Moderate	Moderate	The DCCT and UKPDS had determined the relationship between the results of a specific GHb test (HbA_{1c}) and long-term complications in patients with type 1 and type 2 diabetes, respectively HbA_{1c} has become a surrogate outcome measure in DM but this represents indirect evidence and therefore of moderate quality. However there is strong consensus for measuring HbA_{1c} routinely in DM monitoring. Therefore the recommendation is upgraded.
				Nathan DM, et al. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2006;49:1711-21.	Consensus statement	Low		
				U.K. Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837-53	RCT	High		
				DCCT. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.	RCT	High		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
WHAT ARE THE ANALYTICAL CONSIDERATIONS AND GOALS FOR HbA_{1c} MEASUREMENT?							**[3]Priority: 2 (A1)**	
8.b	Laboratories should use only GHb assay methods that are certified by the National Glycohemoglobin Standardization Program as traceable to the DCCT reference. In addition, laboratories that measure GHb should participate in a proficiency-testing program, such as the CAP Glycohemoglobin Survey, that uses fresh blood samples with targets set by the National Glycohemoglobin Standardization Program Laboratory Network ***Level B***	Laboratories should use only Hb A_{1c} assay methods that are certified by the National Glycohemoglobin Standardization Program (NGSP) as traceable to the DCCT reference. The manufacturers of Hb A_{1c} assays should also show traceability to the IFCC reference method *GPP*	Clarification and addition of new recommendation based on expert consensus	Hanas R, John G. 2010 consensus statement on the worldwide standardization of the hemoglobin A1c measurement. Clin Chem 2010;56:1362-4	Consensus statement	Moderate	Low	Differences in HbA_{1c} reported led to an agreement among IFCC and the major diabetes organizations to report HbA_{1c} results as the IFCC result and as the equivalent NGSP DCCT-aligned result. Some, but not all, organizations have agreed to report HbA_{1c} as the DCCT-aligned percentage and the IFCC value. Impact on patient outcomes is unknown and indirect, therefore quality of evidence is downgraded. However, there is strong consensus of experts on HbA_{1c} reporting.
				Weykamp C, et al. The IFCC reference measurement system for HbA1c: a 6-year progress report. Clin Chem 2008;54:240-8	Progress report	Moderate		
				Goldstein DE, et al. Tests of glycemia in diabetes. Diab Care 2004;27:1761-73	Positions statement	Low		
				Hoelzel W, et al. IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem 2004;50:166-74.	Method-comparison study	High		
8.c		Laboratories that measure Hb A_{1c} should participate in a proficiency-testing program, such as the College of American Pathologists (CAP) Hb A_{1c} survey, that uses fresh blood samples with targets set by the NGSP Laboratory Network *GPP*		Jeppsson JO, et al. Approved IFCC reference method for the measurement of HbA1c in human blood. Clin Chem Lab Med 2002;40:78-89.	Method development	High		
				Little RR, et al. The national glycohemoglobin standardization program: a five-year progress re-port. Clin Chem 2001;47:1985-92.	Analytical study	Moderate		Retrospective analysis of analytical performance of the NGSP network and clinical labs in HbA_{1c} measurement
				Little RR, Goldstein DE. Standardization of glycohemoglobin measurements. AACC Endo 1995;13:109-24	Analytical study	Low		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
8.d	Laboratories should be aware of potential interferences, including hemoglobinopathies that may affect GHb test results. In selecting assay methods, laboratories should consider the potential for interferences in their particular patient population ***Level A***	Laboratories should be aware of potential interferences, including hemoglobinopathies,that may affect Hb A_{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*	Clarification and new recommendation based on experience and published reports.	Ziemer DC, et al. Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. Ann Intern Med 2010;152:770-7	Cross-sectional study	Moderate	Low	Quality of evidence downgraded for indirectness
				Selvin E, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800-11	Observational cohort study	High		
				Bry L, et al. Effects of hemoglobin variants and chemically modified derivatives on assays for glycohemoglobin [Review]. Clin Chem 2001;47:153-63.	Review	Low		
				Schnedl WJ, et al. Evaluation of HbA1c determination methods in patients with hemoglobinopathies. Diab Care 2000;23:339-44.	Test comparison study	Moderate		
				Roberts WL, et al. Glycohemo-globin results in samples with hemoglobin C or S trait: a comparison of four test systems. Clin Chem 1999;45:906-9	Test comparison study	Moderate		
				Weykamp CW, et al. Influence of hemoglobin variants and derivatives on glycohemoglobin determinations, as investigated by 102 laboratories using 16 methods. Clin Chem 1993;39:1717-23.	Multi/center method comparison study	Moderate		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

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No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[3] (high-moderate-low)	7. Quality of evidence[3] (high-moderate-low-very low)	8. Comments
8.e	Laboratories should use GHb assay methods with an interassay CV<5% (ideally <3%). At least two control materials with different mean values should be analyzed as an independent measure of assay performance. Laboratories should verify specimens below the lower limit of the reference interval or greater than 15% by repeat testing. If Schiff base (labile pre-HbA1c) interferes with the assay method, it should be removed prior to assay ***Level C***	Desirable specifications for Hb A_{1c} measurement are an intralaboratory CV <2% and an interlaboratory CV <3.5%. At least 2 control materials with different mean values should be analyzed as an independent measure of assay performance *B (low)*	Clarification and rewording of recommendations	Little RR, et al. Status of HbA1c measurement and goals for improvement: From chaos to order for improving diabetes care. Clin Chem 2011;*in press*	Review	Moderate	Low	This study used the reference change value (also called critical difference) to calculate an appropriate analytical goal
				Sacks DB. CAP Surveys: Participant Summary for Glycohemoglobin Survey 2010 Set GH2-A. Northfield, IL: College of American Pathologists, 2010.	National survey (<10% from outside US)	Moderate		The body of evidence is of low quality for indirectness of the data to clinical outcomes, but there is strong consensus of experts for appropriate analytical specifications to avoid unfavorable outcomes of misclassifications and mismanagement of patients. Therefore the recommendation was upgraded.
8.f		Samples with Hb A_{1c} results below the lower limit of the reference interval or >15% Hb A_{1c} should be verified by repeat testing *B (low)*		Goodall I, et al. Desirable performance standards for HbA(1c) analysis - precision, accuracy and standardisation: consensus statement of the Australasian Association of Clinical Biochemists (AACB), the Australian Diabetes Society (ADS), the Royal College of Pathologists of Australasia (RCPA), Endocrine Society of Australia (ESA), and the Australian Diabetes Educators Association (ADEA). Clin Chem Lab Med 2007;45:1083-97.	Consensus statement	Low		
8.g		Hb A_{1c} values that are inconsistent with the clinical presentation should be investigated further *GPP*		Bry L, et al. Effects of hemoglobin variants and chemically modified derivatives on assays for glycohemoglobin [Review]. Clin Chem 2001;47:153-63	Review	Low		
				Marshall SM, Barth JH. Standardization of HbA1c measurements: a consensus statement. Ann Clin Biochem 2000;37:45-6	Consensus statement	Low		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
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No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
WHAT ARE THE HbA_{1c} TREATMENT GOALS IN DIABETES MELLITUS?							**[3]Priority: 2 (A1, A2)**	
8.h	Treatment goals should be based on ADA recommendations which include maintaining GHb concentrations <7% and reevaluation of the treatment regimen for GHb values > 8%. (Note that these values are applicable only if the assay method is certified as traceable to the DCCT reference.) ***Level B***	Treatment goals should be based on American Diabetes Association recommendations, which include generally maintaining Hb A_{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 a 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)***	Clarification	ADA. Standards of medical care in diabetes--2010. Diab Care 2010;33 (Suppl 1):S11-61.	Guideline	Moderate	High	Converging validity of several controlled clinical trials on patient-centered outcomes in type 1 and type 2 diabetes. Upgraded for directness and consistency and strong consensus of experts and several clinical organizations.
				Duckworth W, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129-39	RCT	High		
				Gerstein HC, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59	RCT	High		
				Patel A, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.	RCT	High		
				Berg AH, Sacks DB. Haemoglobin A1c analysis in the management of patients with diabetes: from chaos to harmony. J Clin Pathol 2008;61:983-7.	Review	Low		
				Qaseem A, et al. Glycemic control and type 2 diabetes mellitus: the optimal hemoglobin A1c targets. A guidance statement from the American College of Physicians. Ann Intern Med 2007;147:417-22	Guideline, consensus statement	Moderate		
				ADA. Implications of the Diabetes Control and Complications Trial (position statement). Diab Care 2000;23 (Suppl 1):S24-6	Position statement	Low		
				DCCT. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 1995;44:968-83	RCT	High		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
WHAT SHOULD BE THE FREQUENCY OF HbA_{1c} MONITORING IN DIABETES MELLITUS?							**[3]Priority: NOT LISTED**	
8.i	GHb testing should be performed at least biannually in all patients and quarterly for patients whose therapy has changed or are not meeting treatment goals ***Level B***	Hb A_{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)***	No change	ADA. Standards of medical care in diabetes--2010. Diab Care 2010;33 Suppl 1:S11-61.	Guideline	Moderate	Low	240 patients; followed x1 year; 50% had HbA_{1c} measured every 3 months; 50% no HbA_{1c} measured. Does not directly evaluate frequency – only testing *vs* no testing. Moreover, the best correlations of HbA_{1c} with complications have been based on quarterly HbA_{1c} testing for capturing overall glycemic exposure. However, there is no consensus on the optimal frequency of HbA_{1c} testing. Most recommendations are based on strong expert consensus.
				Larsen ML, Horder M, Mogensen EF. Effect of long-term monitoring of glycosylated hemoglobin levels in insulin-dependent diabetes mellitus. N Engl J Med 1990;323:1021-5	RCT	Moderate		
SHOULD HbA_{1c} BE USED FOR SCREENING AND DIAGNOSIS OF DIABETES MELLITUS?							**[3]Priority: 1 (A1-5, B2, C1)**	
8.j		Hb A_{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 Hb A_{1c} assay will preclude its use in diagnosis ***A (moderate)***	New recommendation based on additional evidence and consensus of experts	ADA. Standards of medical care in diabetes--2010. Diab Care 2010;33 (Suppl 1):S11-61.	Guideline	Moderate	Moderate	The data supporting the use of HbA_{1c}, i.e. its relationship with risk of retinopathy, is similar to the data that support glucose testing as the means of diagnosis. These are definitional issues. Both the ADA and the American Endocrinology societies endorsed the HbA_{1c} test for diagnosis. Other international organizations, including the WHO and IDF, are considering HbA_{1c} for diabetes diagnosis and screening, therefore there is an emerging strong consensus on the topic, which resulted in upgrading the recommendation.
				American Association of Clinical Endocrinologists/American College of Endocrinology statement on the use of hemoglobin A1c for the diagnosis of diabetes. Endocr Pract 2010;16:155-6	Guideline	Moderate		
				Cheng YJ, et al. Association of A1C and fasting plasma glucose levels with diabetic retinopathy prevalence in the U.S. population: Implications for diabetes diagnostic thresholds. Diab Care 2009;32(11): 2027-32	Population-based cross sectional	High		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
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[3]For priority codes, see SupplementaryTable 2.

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No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
				Nathan DM et al. for the International Expert Committee on the Diagnosis of Diabetes. Report on the Role of the Glycated Hemoglobin (A1C) Assay in the Diagnosis of Diabetes. Diab Care 2009;32:1327-34	Expert consensus	Low		A HbA_{1c} value of 6.5% or greater was considered diagnostic based on the observed relationship with retinopathy in more than 28,000 persons. This represents direct relationship to outcomes and thus quality of evidence is upgraded.
				Sabanayagam C, et al. Relationship between glycated haemoglobin and microvascular complications: is there a natural cut-off point for the diagnosis of diabetes? Diabetologia 2009;52(7):1279-89.	Population-based cross sectional	High		
				Ito C, et al. Importance of OGTT for diagnosing diabetes mellitus based on prevalence and incidence of retinopathy. Diab Res Clin Pract. 2000;49(2-3): 181-6	Population-based cross sectional	High		
8.k		Point-of-care Hb A_{1c} assays are not sufficiently accurate to use for the diagnosis of diabetes *B (moderate)*	New recommendation	American Diabetes Association. Standards of medical care in diabetes --2011. Diab Care 2011;34 (Suppl 1):S11-61	Guideline	Moderate	Moderate	The ADA cautions that POCT devices for HbA_{1c} should not be used for diagnosis.
				Lenters-Westra E, Slingerland RJ. Six of eight hemoglobin A1c point-of-care instruments do not meet the general accepted analytical performance criteria. Clin Chem 2010;56:44-52	Analytical study	Moderate		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
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SUPPLEMENTARY DATA

Chapter 9: GENETIC MARKERS

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
IS THERE A ROLE FOR GENETIC TESTING IN TYPE 1 DIABETES MELLITUS?							**[3]Priority: NOT LISTED**	
9.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, valuable information can be obtained with definition of diabetes-associated mutations ***Level E***	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)***	New information is available on mutations in the proinsulin and other genes that are linked to neonatal diabetes	Concannon P, et al. Genetics of type 1A diabetes. N Engl J Med 2009;360:1646	Review	Moderate	Moderate	Useful review of genetic factors outside the HLA region.
				Murphy R, et al. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. Nat Clin Pract Endocrinol Metab 2008;4:200-13.	Linkage analyses	High		Monogenic diabetes below the age of six needs to be considered for monogenic diabetes
				Edghill EL, et al. Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood. Diabetes 2008;57:1034	Linkage analyses in multiple familes	High		Many mutations than known hitherto affect the human preproinsulin gene
				Støy J, et al. Neonatal Diabetes International Collaborative Group. Insulin gene mutations as a cause of permanent neonatal diabetes. Proc Natl Acad Sci USA. 2007;104(38):15040-4	Linkage analyses	Moderate		Diabetes below the age of six months needs to be considered for monogenic diabetes.
				Hagopian WA, et al. TEDDY-- The Environ-mental Determinants of Diabetes in the Young: an observational clinical trial. Ann N Y Acad Sci 2006;1079:320-6.	Observational study	High		In contrast to other studies, the TEDDY study has sufficient statistical power to answer questions related to environmental triggers for islet autoimmunity and type 1 diabetes.
				Barker JM, et al. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. Diab Care 2004;27:1399-404.	Screening study of children at risk for type 1 diabetes	Moderate		Early diagnosis may prevent hospitalization with ketoacidosis and preserve residual beta cells. More outcome studies are needed to prove this.

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
				Graham J, et al. Genetic effects on age-dependent onset and islet cell auto- antibody markers in type 1 diabetes. Diabetes 2002;51:1346-55	Population-based case-control study	Moderate		First time INS VNTR were found to be associated with INS VNTR.
				Fajans SS, et al. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. N Engl J Med 2001;345:971-80	Review	Low		Careful analysis of family history of diabetes is important to the detection of monogenic diabetes.
				Kukreja A, Maclaren NK. Autoimmunity and diabetes. J Clin Endocrinol Metab 1999;84:4371	Review	Moderate		
				Rewers M, et al. Newborn screening for HLA markers associated with IDDM: diabetes autoimmunity study in the young (DAISY). Diabetologia 1996;39:807	Screening study of children at risk for type 1 diabetes	Moderate		It is possible to screen newborn children to identify those at increased risk for developing type 1 diabetes. This strategy cannot be recommended until there is a proven intervention available to delay or prevent the disease.
				Ziegler AG, et al. Prophylactic insulin treatment in relatives at high risk for type 1 diabetes. Diabetes Metab Rev 1993;9:289	Review	Moderate		
IS THERE A ROLE FOR GENETIC TESTING IN TYPE 2 DIABETES MELLITUS?							**[3]Priority: NOT LISTED**	
9.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 ***Level E***	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)***	No change	Meigs JB, et al. Genotype score in addition to common risk factors for prediction of type 2 diabetes. N Engl J Med 2008;359:2208-19.	Genome wide association case-control study	Moderate	Moderate	Risk alleles in these loci all have relatively small effects (odds ratios 1.1 to 1.3) and do not significantly enhance our ability to predict risk of type 2 diabetes
				Scott LJ, et al. A genome- wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science 2007;316:1341	Genome wide association case-control study	Moderate		
				Saxena R, et al. Genome wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 2007;316: 1331	Genome wide association case-control study	Moderate		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

Chapter 10: AUTOIMMUNE MARKERS

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
SHOULD GAD65, IA-2 OR INSULIN AUTOANTIBODIES BE USED FOR THE DIAGNOSIS, SCREENING, MONITORING OF TYPE 1 AND TYPE 2 DIABETES?							**[3]Priority: 1.5 (A1-5, C1)** **[3]Priority: 3 (A3-4, C1)**	
10.a	Islet cell autoantibodies are recommended for screening of non-diabetic family members who wish to donate part of their pancreas for transplantation to a relative with end stage, immune-mediated (type 1) diabetes. Islet cell autoantibodies are not recommended for routine diagnosis of diabetes nor for screening ***Level E***	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)***	Considerable progress has been made to standardize islet cell autoantibody tests.	Bingley PJ,et al. Measurement of islet cell antibodies in the Type 1 Diabetes Genetics Consortium: efforts to harmonize procedures among the laboratories. Clin Trials. 2010;7(1 Suppl):S56-64.	Analytical test evaluation	Moderate	Low	International workshops using serum exchange exercises provide measures of inter-laboratory variation. Quality of evidence is downgraded for indirectness.
10.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)***		Törn C, et al. Participating Laboratories. Diabetes Antibody Standardization Program: evaluation of assays for autoantibodies to glutamic acid decarboxylase and islet antigen-2. Diabetologia. 2008;51(5):846-52.	Analytical test evaluation	Moderate		
10.c	Screening from GAD65 antibodies in patients diagnosed with type 2 diabetes is not recommended at present to be reclassified with type 1 diabetes. ***Level E***	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 diabetes patients to identify possible mechanisms of secondary failures of treatment of type 2 diabetes ***B (low)***	Considerable progress has been made to standardize islet autoantibody tests. It is not clear to what extent a positive islet autoantibody test would suffice to alter diagnostic criteria.	Rolandsson O, Palmer JP. Latent autoimmune diabetes in adults (LADA) is dead: long live autoimmune diabetes! Diabetologia. 2010;53(7):1250-3.	Review	Low	Low	Review suggesting that islet autoantibody positivity should suffice to classify adult diabetes patients with "autoimmune diabetes" is GAD65 autoantibody positive. Strength of recommendation is upgraded for strong consensus

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
10.d	Screening of relatives of patients with type 1 diabetes or of persons in the general population for islet cell autoantibodies is not recommended at present ***Level E***	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)***	Clarification and addition of new recommendation based on new evidence	Patterson CC, et al. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet 2009;373: 2027-33	Multicentre prospective registration study	Moderate	Low	Epidemiology data
				Maclaren N, et al. Only multiple autoantibodies to islet cells (ICA), insulin, GAD65, IA-2 and IA-2beta predict immune-mediated (Type 1) diabetes in relatives. J Autoimmun 1999;12:279-87	Review	Low		Data only applicable to first degree relatives who comprise only 10-15% of newly diagnosed type 1 diabetes children. Quality of the overall body of evidence was downgraded for lack of suitably powered studies or RCTs investigating the value of islet cell autoantibody testing for screening purposes
				Verge CF, et al. Prediction of type I diabetes in first- degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. Diabetes 1996;45:926-33.	Multicentre prospective registration study	Moderate		
10.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 some clinical trials as surrogate endpoints ***Level 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)***	No change	Sosenko JM et al. Glucose excursions between states of glycemia with progression to type 1 diabetes in the diabetes prevention trial-type 1 (DPT-1). Diabetes Prevention Trial-Type 1 Study Group. Diabetes. 2010;59(10):2386-9.	Prospective family study of islet autoantibody positive subjects	Moderate	Low	Data on first degree relatives suggest an important contribution of insulin sensitivity on glucose tolerance. Quality of the overall body of evidence was downgraded for lack of sufficient data from multiple studies
10.f	It is important that autoantibodies be measured only in an accredited laboratory with an established quality control program and participation in a proficiency testing program ***Level E***	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***	Clarification, but no change	Bonifacio E, et al Harmonization of glutamic acid decarboxylase and islet antigen-2 autoantibody assays for national institute of diabetes and digestive and kidney diseases consortia. J Clin Endocrinol Metab. 2010;95(7):3360-7.	Analytical test evaluation	Moderate	Moderate	Standardization was possible between three expert laboratories.

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2] Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3] For priority codes, see SupplementaryTable 2.

Chapter 11: LOW LEVELS OF ALBUMINURIA (FORMERLY MICROALBUMINURIA)

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
WHEN TESTING FOR LOW LEVELS OF ALBUMINURIA IS INDICATED?							**[3]Priority: 1 (A5, A1-2)**	
11.a	Annual microalbumin testing of patients without clinical proteinuria should begin in pubertal or postpubertal individuals five years after diagnosis of type 1 diabetes and at the time of diagnosis of type 2 diabetes. The role of testing is unclear in patients under treatment with angiotensin-converting enzyme inhibitors and in those with short life expectancy. ***Level E***	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)***	Clarification	American Diabetes Association. Standards of medical care in diabetes --2010. Diab Care 2010; 33 (Suppl 1):S11-61.	Guideline expert opinion	Low	Moderate	There is a higher incidence of obesity and metabolic derangements that accompany this problem including an increase in cardiovascular risk. Low levels of albuminuria is a risk marker for cardiovascular events and predictive of cardiovascular events. This is especially true in diabetes.
				Vassalotti JA, et al. Testing for chronic kidney disease: a position statement from the National Kidney Foundation. Am J Kidney Dis 2007;50 (2):169-180 .	Position statement	Low		
				KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. Am J Kidney Dis 2007;49 (2 Suppl 2):S12-154	Guideline	Moderate		
				Klausen KP, et al. Very low level of microalbumin-uria is associated with increased risk of death in subjects with cardio-vascular or cerebro-vascular diseases. J Intern.Med. 2006;260 (3):231-237	Cohort study	Low		
				Klausen KP, et al. New definition of microalbuminuria in hyper-tensive subjects: association with incident coronary heart disease and death. Hypertension 2005;46 (1):33-37	Observational study	Low		
				Kistorp K, et al. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. JAMA 2005;293:1609-1616.	Meta-analysis	Moderate		
				Gansevoort RT, et al. The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population. Kidney Int Suppl 2005; (94):S28-S35	Observational study	Moderate		Study in the Netherlands of more than 30,000 people

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
				Ibsen H, et al. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for end point reduction in hypertension study. Hypertension 2005;45 (2):198-202	Post hoc analysis	Moderate		Post hoc analysis of clinical cardiovascular outcome trials
				Arnlov J, et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. Circulation 2005;112 (7):969-975	Observational study	Moderate		Study of cardiovascular outcomes
				Chobanian AV, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42 (6):1206-1252	Guideline statement from NIH	Moderate		
				Lepore G, et al. Cost-effectiveness of two screening programs for microalbuminuria in type 2 diabetes. Diab Care 2002;25 (11):2103-2104	Cost-effectiveness analysis	Moderate		
WHAT IS THE RELATIONSHIP BETWEEN ALBUMINURIA AND CARDIOVASCULAR OUTCOMES?							**[3]Priority: 1 (A5, A1-2)**	
11.b		Urine albumin at concentrations ≥30 mg/g creatinine should be considered a continuous risk marker for cardiovascular events *B (moderate)*	New recommendation	G. Pambianco, et al. The prediction of major outcomes of type 1 diabetes: a 12-year prospective evaluation of three separate definitions of the metabolic syndrome and their components and estimated glucose disposal rate: the Pittsburgh Epidemiology of Diabetes Complications Study experience. Diab Care 2007;30(5):1248-1254.	Observational cohort study	Moderate	Moderate	This was an observational study in patients with type 1 diabetes followed for 12 years.
				Klausen KP, et al. Very low level of microalbuminuria is associated with increased risk of death in subjects with cardiovascular or cerebro-vascular diseases. J Intern Med 2006;260 (3):231-237.	Cohort study	Moderate		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
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[3]For priority codes, see SupplementaryTable 2.

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No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
				Ratto E, et al. Microalbuminuria and cardiovascular risk assessment in primary hypertension: should threshold levels be revised? Am J Hypertension 2006;19 (7):728-734	Observational cohort study	Low		The study evaluated level of microalbuminuria relative to development of left ventricular hypertrophy; not cardiovascular outcome
				Klausen KP, et al. New definition of microalbuminuria in hyperten-sive subjects: association with incident coronary heart disease and death. Hypertension 2005;46 (1):33-37	Observational cohort study	Low		
				K. Wachtell, et al. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. Ann.Intern.Med. 2003;139 (11):901-906.	Prospective randomized trial	High		This clinical trial evaluated changes in albuminuria over a 5 year period in high risk patients for cardiovascular events all of whom had left ventricular hypertrophy.
				R. Rachmani, et al. Considerations about the threshold value of micro-albuminuria in patients with diabetes mellitus: lessons from an 8-year follow-up study of 599 patients. Diab.Res.Clin. Pract. 2000;49 (2-3):187-194.	Observational cohort study	Moderate		This was an 8 year follow-up of 599 people with diabetes evaluating changes in cardiovascular risk markers including microalbuminuria
WHAT ARE THE ANALYTICAL CONSIDERATIONS WHEN TESTING FOR LOW LEVELS OF ALBUMINURIA?							**[3]Priority: NOT LISTED**	
11.c	The analytical CV of methods to measure micro-albuminuria should be <15% ***Level E***	The analytical CV of methods to measure albuminuria should be <15% ***B (moderate)***	No change	Sarafidis PA, et al. A comparative evaluation of various methods for microalbuminuria screening. Am.J Nephrol. 2008;28 (2):324-329.	Randomized study	Moderate	Moderate	Comparative studies of different validated assays
				Gansevoort RT, et al. The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population. Kidney Int.Suppl 2005;(94):S28-S35	Observational study	Moderate		
				Incerti J, et al. Evaluation of tests for microalbuminuria screening in patients with diabetes. Nephrol Dial.Transplant. 2005;20 (11):2402-2407	Observational study	Moderate		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
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SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
				Meinhardt U, et al. Microalbuminuria in diabetes mellitus: efficacy of a new screening method in comparison with timed overnight urine collection J Diab Complications 2003;17 (5):254-257	Observational study	Moderate		
11.d	Semiquantitative or qualitative screening tests for microalbuminuria should be positive in >95% of patients with microalbuminuria to be useful for screening. Positive results must be confirmed by analysis in an accredited laboratory ***Level E***	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*	No change	Sarafidis PA,et al. A comparative evaluation of various methods for microalbuminuria screening. Am.J Nephrol. 2008;28 (2):324-329.	Randomized study	Moderate	Moderate	Most recent studies do have >95% for Hemocue and Immunodip but only one study confirmed against standard lab for Hemocue
				Shaikh A, et al. Comparison between immunoturbidimetry, size-exclusion chromatography, and LC-MS to quantify urinary albumin. Clin Chem 2008;54 (9):1504-1510	Analytical study	Moderate		Recommendation downgraded for indirectness of analytical data to clinical outcomes
11.e		Currently available dipstick tests do not have adequate analytical sensitivity to detect albuminuria *B (moderate)*	New recommendation according to recent literature on the topic	Gansevoort RT, et al. The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population. Kidney Int.Suppl 2005; (94):S28-S35.	Observational study	Moderate	Moderate	There is no convincing evidence in multiple studies for any specific test achieving >95% diagnostic sensitivity in two or more different studies. Due to this, no specific screening test can be recommended. "Dipstick" tests for microalbuminuria cannot be recommended as replacement for the quantitative tests.
				Incerti J, et al. Evaluation of tests for microalbuminuria screening in patients with diabetes. Nephrol Dial. Transplant. 2005;20(11):2402-2407.	Observational study	Moderate		
				Davidson MB, et al. ImmunoDip: an improved screening method for microalbuminuria. Am J Nephrol 2004;24:284-8.	Observational study	Moderate		
				Meinhardt U, et al. Microalbuminuria in diabetes mellitus: efficacy of a new screening method in comparison with timed overnight urine collection. J Diab Complications 2003;17 (5): 254-257.	Observational study	Moderate		
				Fernandez Fernandez I, et al. Rapid screening test evaluation for microalbuminuria in diabetes mellitus. Acta Diabetol 1998; 35:199-202	Observational study	Moderate		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
				Leong SO, et al. The use of semi-quantitative urine test-strip (Micral Test) for microalbuminuria screening in patients with diabetes mellitus. Singapore Med J 1998;39:101-3.	Randomized trial	Moderate		
				Poulsen PL, et al. Evaluation of a dipstick test for micro-albuminuria in three different clinical settings, including the correlation with urinary albumin excretion rate. Diabetes Metab 1992;18:395-400.	Observational study	Low		
WHAT ARE THE PREANALYTICAL CONSIDERATIONS WHEN TESTING FOR LOW LEVELS OF ALBUMINURIA?							**[3]Priority: 3 (A3-4)**	
11.f	Acceptable samples to test for increased urinary albumin excretion are timed (e.g., 12 or 24 hour) collections for measurement of albumin concentration and timed or untimed samples for measurement of the albumin:creatinine ratio. For screening, an untimed sample for albumin measurement (without creatinine) may be considered if a concentration cutoff is used that allows high sensitivity for detection of an increased albumin excretion rate. ***Level E***	Acceptable samples to test for increased urinary albumin excretion are timed collections (e.g., 12 or 24 h) for measurement of the albumin concentration and timed or untimed samples for measurement of the albumin–creatinine ratio ***B (moderate)***	No change, but new evidence supports recommendation	Lambers Heerspink HJ, et al. Comparison of different measures of urinary protein excretion for prediction of renal events. J Am Soc Nephrol 2010;21:1355-60	Prospective cohort	High	Moderate	The albumin:creatinine ratio is the superior method to predict renal events in patients with type 2 diabetes
				Ibsen H, et al. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for end point reduction in hypertension study. Hypertension 2005;45:198-202.	Observational study	Moderate		
				Gansevoort RT, et al. The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population. Kidney Int.Suppl 2005;(94):S28-S35	Observational study	Moderate		
				Meinhardt U, et al. Microalbumin-uria in diabetes mellitus: efficacy of a new screening method in comparison with timed overnight urine collectionJ Diabetes Compli-cations 2003;17 (5):254-257	Observational study	Moderate		
				Hishiki S, et al. Circadian variation of urinary microalbumin excretion and ambulatory blood pressure in patients with essential hypertension. J Hypertens 1998;16:2101-8.	Observational study	Low		
No	**1. NACB 2002**	**2. NACB 2011 updated/new**	**3. Why was it**	**4. Key references**	**5. Study**	**6. Level of**	**7. Quality of**	**8. Comments**

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

	recommendation and its grade[1]	recommendation with its grade and quality of evidence[2]	necessary to modify the recommendation?	supporting the new recommendation	design	evidence[2] (high-moderate-low)	evidence[2] (high-moderate-low-very low)	
				Howey JE, et al. Biologic variation of urinary albumin: consequences for analysis, specimen collection, interpretation of results, and screening programs. Am J Kidney Dis 1989;13:35-7.	Observational study	Moderate		
WHAT IS THE OPTIMAL TIME OF DAY TO MEASURE ALBUMINURIA?							**[3]Priority: 2 (A2-4)**	
11.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*	New recommendation	Witte EC, Lambers Heerspink HJ, de Zeeuw D, Bakker SJ, de Jong PE, and Gansevoort R. First morning voids are more reliable than spot urine samples to assess microalbuminuria. J Am.Soc. Nephrol. 2009;20 (2):436-443.	Prospective non-randomized	Moderate	Low	Collected three different urines and analyzed in three different ways. One study only that investigates this topic. Recommendation downgraded for indirectness of evidence and lack of more data.
HOW FREQUENTLY ALBUMINURIA SHOULD BE MEASURED?							**[3]Priority: 1 (A5, A1-2)**	
11.h		Low urine albumin concentrations (i.e., <30 mg/g creatinine) are not associated with high cardiovascular risk if the eGFR is >60 mL · min^{-1} · (1.73 m^2)$^{-1}$ and the patient is normotensive. If the eGFR is <60 mL · min^{-1} · (1.73 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)*	New recommendation	Levey AS, et al. The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011;*in press*	Consensus report	Moderate	Moderate	Strong consensus of experts upgraded the recommendation
				Yuyun MF, et al. Micro-albuminuria independently predicts all-cause and cardiovascular mortality in a British population: The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. Int.J Epidemiol. 2004;33 (1):189-198	Prospective cohort	Moderate		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
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Chapter 12: MISCELLANEOUS POTENTIALLY IMPORTANT ANALYTES

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
IS THERE A ROLE FOR MEASUREMENT OF INSULIN AND C-PEPTIDE CONCENTRATIONS TO DISTINGUISH TYPE 1 FROM TYPE 2 DIABETES MELLITUS?							**[3]Priority: 2 (A3-4)**	
12.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, in most cases, be made based on the clinical presentation and subsequent course. There is no role for measurement of insulin concentration in the diagnosis of the metabolic syndrome because knowledge of this value does not alter the management of these patients. ***Level E***	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)***	Changed wording. Many groups, including ADA, are moving beyond the categorical concept ("diagnosis") of metabolic syndrome to that of continuous and more global measures of risk for diabetes and cardiovascular disease.	Rutter MD, et al. Use of Alternative thresholds defining insulin resistance to predict incident type 2 diabetes and cardiovascular disease. Circulation. 2008;117:1003-1009.	Cohort study	Moderate	Moderate	Models of predictive baseline measures of insulin resistance (which include measures of insulin) in a large population. Surrogate IR measures (which all included measures of insulin) had modest performance at the 76th centile, with no threshold effects. Prediction was particularly poor for CVD.
				Wilson PW et al. Prediction of incident diabetes mellitus in middle-aged adults: The Framingham Offspring Study. Arch Intern Med 2007;167:1068-74.	Cohort study	Moderate		Models of predictive baseline values in a large population. Factors easily obtainable on history, exam, or standard lab tests (glucose, lipids) predicted incident DM strongly. Addition of more complex factors, including fasting insulin, did not add significantly.
				Despres J-P et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 1996;334:952-7.	Case-control study	Moderate		Case-control study looking at baseline fasting insulin levels in Quebec Heart Study. High fasting insulin levels appeared to be an independent risk factor for IHD. However, only excluded clinically diagnosed DM (in early 1990s, probably many undiagnosed) and did not adjust for any measures of glycemia or BMI

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
12.a	These assays are useful primarily for research purposes and, in rare cases, to identify patients with an absolute requirement for insulin before switching to oral agents, or to assist patients in obtaining insurance coverage for continuous subcutaneous infusion pumps. ***Level E***	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)***	New evidence regarding using C-peptide to clarify diagnosis	Balasubramanyam A et al. Accuracy and predictive value of classification schemes for ketosis-prone diabetes. Diab Care 2006; 29:2575-9.	Observational prognostic/ diagnostic study	Moderate	Moderate - low	Investigation of patients presenting with ketosis, with absent or preserved C-peptide function at one year the outcome. Unclear how direct the outcome is, whether this is better than current care
	A possible role for measurement of fasting insulin or the assessment of insulin resistance is in the evaluation of patients with polycystic ovary syndrome who may be candidates for treatment aimed at lowering insulin resistance in the absence of overt diabetes or glucose intolerance ***Level E***	None	Prior recommendation deleted. No evidence that this is better than clinical evaluation for signs of insulin resistance; not recommended by ACOG or other groups.	American College of Obstetrics and Gynecology. ACOG practice bulletin. Polycycstic ovary syndrome. Number 41, December 2002. Int J Gynecol Obstet 2003; 80:335-48	Guideline/ Expert consensus	Low	Very low	Prior recommendation was also supported by expert opinion only
IS THERE A ROLE FOR MEASUREMENT OF INSULIN CONCENTRATIONS OR INDIRECT MEASURES OF INSULIN RESISTANCE IN THE ASSESSMENT OF PATIENTS' CARDIOMETABOLIC RISK OR TO DETERMINE USE OF INSULIN SENSITIZING DRUGS IN DIABETIC OR NON-DIABETIC PATIENTS?							**[3]Priority: 2 (A3)**	
12.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)***	New recommendation	Rutter MD, et al. Use of Alternative thresholds defining insulin resistance to predict incident type 2 diabetes and cardiovascular disease. Circulation. 2008;117:1003-9.	Cohort study	Moderate	Moderate	
				Wilson PW et al. Prediction of incident diabetes mellitus in middle-aged adults: The Framingham Offspring Study. Arch Intern Med 2007;167:1068-74.	Cohort study	Moderate		
				Despres J-P et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 1996;334:952-7.	Case-control study	Moderate		

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

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No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
DO INSULIN MEASUREMENTS NEED TO BE HARMONIZED?							**[3]Priority: 2 (A3)**	
12.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*		Staten M, et al, for the Insulin Standardization Workgroup. Insulin assay standardization: leading to measures of insulin sensitivity and secretion for practical clinical care. Diab Care 2010;33:205-6	Expert consensus	Low	Low	Commentary summarizes the above papers and calls for a standardized insulin assay based on above.
				Miller WG, et al for the Insulin Standardization Work Group. Toward standardization of insulin immunoassays. Clin Chem 2009;55:1011-8	Investigation of alternate preparation for insulin reference materials	Moderate		Most assays can achieve consistent performance with calibration traceability based on individual serum samples with insulin concentrations set by isotope dilution mass spectrometry.
				Marcovina S, et al. Standardization of insulin immunoassays: report of the American Diabetes Association Workgroup. Clin Chem 2007; 53:711-6	Comparison of different insulin assays currently on the market in the US.	Moderate		Current FDA-approved commercially available insulin assays provide a wide range of values for the same samples. There clearly is a need to standardize the reference system and protocols to enable all assays to achieve consistent and uniform results and to report insulin in identical units.

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

No	1. NACB 2002 recommendation and its grade[1]	2. NACB 2011 updated/new recommendation with its grade and quality of evidence[2]	3. Why was it necessary to modify the recommendation?	4. Key references supporting the new recommendation	5. Study design	6. Level of evidence[2] (high-moderate-low)	7. Quality of evidence[2] (high-moderate-low-very low)	8. Comments
IS THERE A ROLE FOR INSULIN AUTOANTIBODY TESTING IN MANAGING PATIENTS WITH DIABETES MELLITUS?							**[3]Priority: NOT LISTED**	
12.d	There is no published evidence to support the use of insulin antibody testing for routine care of patients with diabetes ***Level E***	There is no published evidence to support the use of insulin antibody testing for routine care of patients with diabetes. *C (very low)*	No change	Bingley PJ,et al. Measurement of islet cell antibodies in the Type 1 Diabetes Genetics Consortium: efforts to harmonize procedures among the laboratories. Clin Trials 2010;7(1 Suppl):S56-64.	Analytical test evaluation	Moderate	Very low	International workshops using serum exchange exercises provide measures of inter-laboratory variation. Standardization was possible between three expert laboratories. Quality of evidence and strength of recommendation are downgraded for indirectness.
				Bonifacio E, et al Harmonization of glutamic acid decarboxylase and islet antigen-2 autoantibody assays for national institute of diabetes and digestive and kidney diseases consortia. J Clin Endocrinol Metab. 2010;95(7):3360-7.	Analytical test evaluation	Moderate		
				Törn C, et al. Participating Laboratories. Diabetes Antibody Standardization Program: evaluation of assays for autoantibodies to glutamic acid decarboxylase and islet antigen-2. Diabetologia. 2008;51(5):846-52.	Analytical test evaluation	Moderate		
IS THERE A ROLE FOR AMYLIN AND LEPTIN TESTING IN MANAGING PATIENTS WITH DIABETES MELLITUS?							**[3]Priority: NOT LISTED**	
	Assays for amylin are not clinically useful in the management of diabetes. These studies should be confined to the research setting ***Level E***	None	The evidence accumulated in the last six to seven years has failed to identify any clinical value in measuring these analytes in patients with diabetes.					
	Routine measurement of plasma leptin concentrations is not of value at this time for the evaluation or management of patients with diabetes or obesity ***Level E***	None	Recommendation removed for reasons mentioned above					

[1] Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-72.
[2]Explanations for grading the level and quality of evidence and for grades of recommendations are given in Supplementary Table 4-5.
[3]For priority codes, see SupplementaryTable 2.

SUPPLEMENTARY DATA

Supplementary Table 4. Grading the quality of evidence.

THE QUALITY OF THE BODY OF EVIDENCE IS BASED ON:
Level of evidence: This refers to the detailed study methods and the quality of their execution, i.e., the methodological quality of *individual* studies. The level of evidence can be: – *High:* if the study has an appropriate design for the question being asked and if it is well conducted in representative populations and is free from design-related biases. – *Moderate:* if the study has an appropriate design for the question being asked but suffers from some design-related biases that might influence the conclusions to a certain extent but would not affect patient-important outcomes or conclusions significantly. – *Low:* if the study is wrongly designed and conducted and there is a high likelihood that its conclusions are grossly biased and misleading.
Consistency of results across various studies: i.e., when results are heterogeneous across studies, inconsistency of results lowers the strength of evidence.
Directness of comparisons: Indirectness applies and lowers quality when, for example: - Evidence is indirectly related to the actual question; - The study population differs from that to which the study results would be applied in practice; - The test in the study differs (e.g., in its analytical performance, or a new generation of the same test has emerged) from the one commonly used or recommended in practice; - The outcome of interest for the guideline differs from the one studied in the trial.
Precision-of-effect estimates: If the study is relatively small and includes few patients or events, the confidence interval around the effect estimate is relatively large, and imprecision of results leads to downgrading the quality of evidence.
RATING SCALE FOR THE OVERALL QUALITY OF THE BODY 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; by the generalizability of results to routine practice; or indirect nature of the evidence.

SUPPLEMENTARY DATA

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 with evidence that 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.

SUPPLEMENTARY DATA

Supplementary Table 5. 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 level 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, 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 GOOD PRACTICE POINT

Good practice points (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 predominantly 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, etc.

SUPPLEMENTARY DATA

Supplementary Table 6. Matrix for the assignment of grades to guideline recommendations.

Strength of recommendation (Supplementary Table 5)	Quality of evidence (Supplementary Table 4)	Agreement of experts
A: Strongly recommended	High	Strong–very strong
	Moderate	
B: Recommended	Moderate	Moderate
	Low	Strong–very strong
	Very low	Very strong
C: Insufficient information to make recommendation	Very low	No agreement or very weak
	Low, moderate, high	
GPP: Good practice point	Expert consensus on best practice	

SUPPLEMENTARY DATA

Supplementary Figure 1: Process of updating the NACB Diabetes Mellitus guideline

STEP 1: Determine the scope and key topics of the guideline
STEP 2: Determine the target group of the guideline and establish a multidisciplinary guideline team
STEP 3: Identify key areas for revisions and define the structure and methodology of the updated guideline
STEP 4: Define and prioritize key questions
STEP 5: Search the literature systematically for high priority questions and select relevant key publications
STEP 6: Subject selected key publications to critical expert review Extract data into evidence tables
STEP 7: Define the quality of evidence underlying each recommendation
STEP 8: Release the first draft of the guideline for public comments
STEP 9: Incorporate comments, grade recommendations and prepare the second draft of the guideline.
STEP 10: Release the second draft of the guideline for public comments and submit the final draft to NACB for review and approval