**SUPPLEMENT 8: EVIDENCE TABLE FOR HEMOGLOBIN A1c**

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| **No** | **1. Updated/new recommendation with its grade and quality of evidence*(2)*** | **2. NACB 2011 recommendation and its grade*(1)*** | **3. Why was it necessary to modify the recommen-dation?** | **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 HbA1c BE USED FOR SCREENING AND DIAGNOSIS OF DIABETES MELLITUS?** | | | | | | | | | |
| a | **Laboratory-based HbA1c testing can be used to diagnose**  **a) diabetes, with a value ≥ 6.5% (>48 mmol/mol) diagnostic of diabetes, and**  **b) prediabetes (or high risk for diabetes) with a HbA1c level of 5.7% to 6.4% (39-46 mmol/mol)**  ***A (moderate)*** | **Hb A1c 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 A1c assay will preclude its use in diagnosis.**  ***A (moderate)*** | Refinement and expansion of recommendation to prediabetes | International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes. Diabetes Care. 2009;32(7):1327–34. | Guideline Expert consensus | Moderate | Moderate | | The data supporting the use of HbA1c, 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 HbA1c test for diagnosis.  The risk for developing diabetes follows HbA1c levels as a continuum. The International Expert Committee ecommended HbA1c levels from 6.0 to 6.4% and the ADA has recommended HbA1c levels from 5.7 to 6.4% as those that define high risk to develop future diabetes (prediabetes). The level chosen to define high risk may depend on resources available to address prevention. |
| American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes 2022. Diab Care 2021;45 (Suppl 1): S17-S38. | Guideline Expert consensus | Moderate |
| Sacks DB. A1C versus glucose testing: a comparison. Diabetes Care. 2011 Feb;34(2):518–23. | Expert consensus | Moderate |
| Selvin E, Wang D, Matsushita K, Grams ME, Coresh J. Prognos-tic implications of single-sample confirmatory testing for undiag-nosed diabetes: a prospective cohort study. Ann Int Med 2018;169:156-64 | Prospective cohort study | Moderate |
| Droumaguet C, et al, The DESIR Study Group. Use of HbA1c in predicting progression to diabetes in French men and women: data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) Diab Care 2006;29:1619-25. | Epidemio-logical study | Moderate |

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|  |  |  |  | Edelman D, Olsen MK, Dudlye TK, Harris AC, Oddine EZ, Utility of the hemoglobin A1c in predicting diabetes risk. J Gen Int Med 2004;19:1175-80. | Prospective cohort study | Moderate |  |  |
| Little RR, England JD, Wiedemeyer HM, et al. Glycated haemoglobin predicts progression to diabetes mellitus in Pima Indians with impaired glucose tolerance. Diabetologia 1994;37:252-6 | Prospective cohort study | Moderate |

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| **No** | **1. Updated/new recommendation with its grade and quality of evidence*(2)*** | **2. NACB 2011 recommendation and its grade*(1)*** | **3. Why was it necessary to modify the recommen-dation?** | **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 POINT-OF-CARE DEVICES FOR MEASURING HbA1c SUITABLE FOR SCREENING AND DIAGNOSIS OF DIABETES MELLITUS?** | | | | | | | | |
| b | **Point-of-care HbA1c testing for diabetes screening and diagnosis should be restricted to FDA approved devices at CLIA-certified laboratories that perform testing of moderate complexity or higher.**  ***B (low)*** | **Point-of-care HbA1c assays are not sufficiently accurate to use for the diagnosis of diabetes.**  ***B (moderate)*** |  | American Diabetes Association. Standards of medical care in diabetes--2022. Diab Care 2022;45 Suppl 1:S1 | Guideline Expert consensus | Moderate | Low |  |
| 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 performance study | Moderate |  |
| Hirst JA, McLellan JH, Price CP,et al. Performance of point-of-care HbA1c test devices: implications for use in clinical practice: a systematic review and meta-analysis. Clin Chem Lab Med. 2017;55(2):167-180 | Systematic review and meta-analysis of analytical performance studies | Moderate | This study compared the analy-tical performance of commercially available 13 POC HbA1c devices to a laboratory method and reported accuracy ranging from −0.9 to 0.7 percentage points from the laboratory value, with 9 devices exhibiting lower and 4 higher values. |
| Nathan DM et al. Accuracy of a point-of-care hemoglobin A1c assay. J Diab Sci Technol 2019;13(6):1149-1153 | Comparative analytical performance study | Moderate |
| CLIA Brochures | CMS [Internet]. [cited 2022 Aug 26]. Available from: [https://www.cms.gov/Regulations-and-Guidance/Legislation/ CLIA/CLIA\_Brochures](https://www.cms.gov/Regulations-and-Guidance/Legislation/%20CLIA/CLIA_Brochures) |  |  |  |

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| **No** | **1. Updated/new recommendation with its grade and quality of evidence*(2)*** | **2. NACB 2011 recommendation and its grade*(1)*** | **3. Why was it necessary to modify the recommen-dation?** | **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 HbA1c BE USED IN MONITORING DIABETES MELLITUS?** | | | | | | | | |
| c | **HbA1c should be measured routinely (usually every 3 months until acceptable, individualized targets are achieved and then no less than every 6-months) in most individuals with diabetes mellitus to document their degree of glycemic control.**  ***A (moderate)*** | **Hemoglobin A1c (HbA1c) should be measured routinely in all patients with diabetes mellitus to document their degree of glycemic control**.  ***A (moderate)*** | Clarification and making recommendation more specific including advice on frequency of testing | The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes. 1995 Aug;44(8):968–83. |  |  | Moderate |  |
| Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–12 | Prospective observatio-nal study | 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 | The DCCT and UKPDS had determined the relationship between the results of HbA1c and long-term complications in patients with type 1 and type 2 diabetes, respectively. HbA1chas become a surrogate outcome measure in treating DM and thus it represents indirect evidence in terms of health outcomes. Therefore, the evidence is of moderate strength and there is very strong consensusfor measuring HbA1c routinely in DM monitoring, which results in a strong recommendation. |
| 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). Lancet 1998;352:837–53 | RCT | High |
| American Diabetes Association Professional Practice Committee. 6. Glycemic Targets: Standards of Medical Care in Diabetes - 2022.Diab Care 2021;45 (Supp1):S83–96. | Guideline | Moderate |  |

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|  |  |  |  | Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan D, Peterson CM, Sacks DB. Tests of glycemia in diabetes. Diabetes Care 2004;27:1761–73 | Review | Low |  |  |
| American Diabetes Association. Implications of the Diabetes Control and Complications Trial. Diab Care 2000;23(Suppl1):S24–6 | Position statement | Moderate |  |
| Nathan DM, Buse JB, Davidson MB, Heine RJ, 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/ Moderate |  |
| 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 | High |  |

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| **No** | **1. Updated/new recommendation with its grade and quality of evidence*(2)*** | **2. NACB 2011 recommendation and its grade*(1)*** | **3. Why was it necessary to modify the recommen-dation?** | | **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 HbA1c TREATMENT GOALS IN DIABETES MELLITUS?** | | | | | | | | | |
| d | **Treatment goals should be based on ADA recommendations which include maintaining HbA1c concentrations <7% (<53 mmol/mol) for many nonpregnant patients with diabetes and more stringent goals in selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment.**  **Higher target ranges are recommended for children and adolescents and are appropriate for individuals with limited life expectancy, extensive co-morbid illnesses, a history of severe hypoglycemia and advanced complications.** (Note that these values are applicable only if the assay method is certified by the NGSP as traceable to the DCCT reference.)  ***A (high)*** | **Treatment goals should be based on American Diabetes Association recommendations, which include generally maintaining Hb A1c concentrations at <7% and more-stringent goals in selected individual patients if they can be achieved without significant hypoglycemia or other adverse treatment effects.**  **Somewhat higher intervals are recommended for children and adolescents and may be appropriate for patients with limited life expectancy, extensive comorbid illnesses, a history of severe hypoglycemia, or advanced complications (note that these values are applicable only if the NGSP has certified the assay method as traceable to the DCCT reference).**  ***A(high)*** | |  | American Diabetes Association Professional Practice Committee. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. Diabetes Care. 2021;45 (Supplement\_1):S17–38. | Guideline | Moderate | High | Converging validity of several controlled clinical trials on patient-centered outcomes in type 1 and type 2 diabetes. Upgraded for consistency of evidence coming from RCTs and strong consensus of experts and several clinical organizations. |
| Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macro-vascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405–12. | Prospective observatio-nal study | High |
| Nathan DM, Cleary PA, Backlund JYC, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353(25):2643–53. |  |  |
| UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of compli-cations in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837–53. | RCT | High |
|  |  |  | |  | American Diabetes Association Professional Practice Committee. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2022. Diabetes Care. 2021; 45(Supplement\_1):S83–96. | Position statement | Moderate |  |  |
| 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 | Moderate |
| Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, et al. Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. N Engl J Med. 2019 31;381(18):1707–17. | RCT | High |

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| **No** | **1. Updated/new recommendation with its grade and quality of evidence*(2)*** | **2. NACB 2011 recommendation and its grade*(1)*** | **3. Why was it necessary to modify the recommen-dation?** | **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 HbA1c TREATMENT GOALS IN DIABETES MELLITUS DURING PREGNANCY?** | | | | | | | | |
| e | **During pregnancy and in preparation for pregnancy, women with diabetes should try to achieve HbA1c goals that are more stringent than in the non-pregnant state, aiming ideally for <6.0% (<42 mmol/mol) during pregnancy to protect the fetus from congenital malformations and the baby and mother from perinatal trauma and morbidity owing to large-for-date babies.**  ***A (moderate)*** |  |  | American Diabetes Association Professional Practice Committee. 15. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes—2022. Diabetes Care. 2021; 45(Supplement\_1):S232–43. | Guideline/ expert consensus | Low/  Moderate |  | ADA recommends: “Due to increased red cell turnover during pregnancy, HbA1c is slightly lower in non-diabetic mothers during pregnancy than during the non=pregnant state. Ideally, the HbA1c target in pregnancy is <6% if this can be reached without significant hypoglycemia, but the target may be relaxed to <7% if necessary to prevent hypoglycemia” |
| Kitzmiller JL, Block JM, Brown FM, Catalano PM, Conway DL, Coustan DR, et al. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommend-dations for care. Diab Care 2008;31:1060–79 | Guideline | Moderate |  |

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| **No** | **1. Updated/new recommendation with its grade and quality of evidence*(2)*** | **2. NACB 2011 recommendation and its grade*(1)*** | **3. Why was it necessary to modify the recommen-dation?** | **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 PREANALYTICAL CONSIDERATIONS AND GOALS FOR HbA1c MEASUREMENT?** | | | | | | | | |
| f  g  h  i | **Laboratories should be aware of potential interferences, including hemoglobin variants that may affect HbA1c test results depending on the method used. In selecting assay methods, laboratories should consider the potential for interferences in their particular patient population. *GPP***  **HbA1c measurements in individuals with disorders that affect red blood cell turnover may provide spurious (generally falsely low) results regardless of the method used and glucose testing will be necessary for screening, diagnosis and management. *GPP*** | **Laboratories should be aware of potential interferences, including hemoglobinopathies that may affect HbA1c 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*** | Split recommendations for clarity | Goldstein DE, et al. Tests of glycemia in diabetes. Diab Care 2004;27:1761-73 | Review | Moderate | Low | Quality of the body of evidence downgraded for indirectness. The literature covers mostly technical issues related to interferences of HbA1c measurement. |
| Malka R, Nathan DM, Higgins JM. Mechanistic modeling of hemoglobin glycation and red blood cell kinetics enables personalized diabetes monitoring. Sci Transl Med 2016; 8: 359. | Mathemati-cal model | Moderate |
| Davie SJ, Gould BJ, Yudkin JS. Effects of vitamin C on glycosylation of proteins. Diabetes 1992;41:167–73 | Prospective clinical trial | Moderate |
| Ceriello A, Giugliano D, Quatraro A, Donzella C, Dipalo G, Lefebvre PJ. Vitamin E reduction of protein glycosylation in diabetes. New prospect for prevention of diabetic complications? Diabetes Care 1991;14:68–72 | Prospective clinical trial | Low |
| Tarim O, Kucukerdogan A, Gunay U, Eralp O, Ercan I. Effects of iron deficiency anemia on hemoglobin A1c in type 1 diabetes mellitus. Pediatr Int 1999;41:357–62 | Prospective cohort study | Low |
| Goldstein DE, Little RR, Wiedmeyer HM, England JD, McKenzie EM. Glycated hemoglobin: methodologies and clinical applications. Clin Chem 1986;32:B64–70 | Review | Low |
| **Assays of other glycated proteins, such as fructosamine or glycated albumin, may be used in clinical settings where abnormalities in red blood cell turnover, hemoglobin variants or other interfering factors compromise interpretation of HbA1c test results, although they reflect a shorter period of average glycemia than HbA1c. *GPP***  **HbA1c cannot be measured and should not be reported in individuals who do not have HbA, e.g., those with homo-zygous hemoglobin variants, such as HbSS or HbEE; glycated proteins, such as fructosamine or glycated albumin, may be used. *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 |
| Schnedl WJ, et al. Evaluation of HbA1c determination methods in patients with hemoglobinopathies. Diab Care 2000;23:339-44. | Test comparison study | Moderate |
| Rohlfing C, Hanson S, Estey MP, Bordeleau P, Little RR. Evaluation of interference from hemoglobin C, D, E and S traits on measurements of hemoglobin A1c by fifteen methods. Clin Chim Acta. 2021;522:31–5. | Test evaluation and comparison study | High |
| Little RR, La’ulu SL, Hanson SE, Rohlfing CL, Schmidt RL. Effects of 49 Different Rare Hb Variants on HbA1c Measurement in Eight Methods. J Diabetes Sci Technol. 2015;9(4):849–56. | Test evaluation and comparison study | High |

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| **No** | **1. Updated/new recommendation with its grade and quality of evidence*(2)*** | **2. NACB 2011 recommendation and its grade*(1)*** | **3. Why was it necessary to modify the recommen-dation?** | **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 HbA1c MEASUREMENT?** | | | | | | | | |
| j | **Laboratories should use only HbA1c assay methods that are certified by the NGSP as traceable to the DCCT reference. The manufacturers of HbA1c assays should also show traceability to the IFCC reference method.**  ***GPP*** | **Laboratories should use only HbA1c assay methods that are certified by the National Glyco-hemoglobin Standardization Program (NGSP) as traceable to the DCCT reference. The manufacturers of assays for HbA1c should also show traceability to the IFCC reference method.**  ***GPP*** |  | American Diabetes Association Professional Practice Committee. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2022. Diabetes Care. 2021;45 (Supplement\_1):S83–96. | Guideline | Moderate | Low | Differences in HbA1c reported led to an agreement among IFCC and the major diabetes organizations to report HbA1c results as the IFCC result and as the equivalent NGSP DCCT-aligned result. Some, but not all, organizations have agreed to report HbA1c 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 HbA1creporting. |
| Rifai N. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2017. | Textbook review | Low |
| Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan D, Peterson CM, Sacks DB. Tests of glycemia in diabetes. Diabetes Care 2004;27:1761–73 | Review | Low/  Moderate |
| Goldstein DE, Little RR, Wiedmeyer HM, England JD, McKenzie EM. Glycated hemoglobin: methodologies and clinical applications. Clin Chem 1986;32:B64–70 | Review | Low |
| 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 |
| Weykamp CW, Penders TJ, Muskiet FA, van der Slik W. Effect of calibration on dispersion of glycohemoglobin values determined by 111 laboratories using 21 methods. Clin Chem 1994;40:138–44 | Compara-tive analy-tical perfor-mance study | Moderate |

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| **No** | **1. Updated/new recommendation with its grade and quality of evidence*(2)*** | **2. NACB 2011 recommendation and its grade*(1)*** | **3. Why was it necessary to modify the recommen-dation?** | **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** |
| k | **Laboratories that measure HbA1c should participate in an accuracy-based proficiency-testing program that uses fresh whole blood samples with targets set by the NGSP Laboratory Network*. GPP*** | **Laboratories that measure HbA1c should participate in a proficiency-testing program, such as the CAP Glycohemoglobin Survey, that uses fresh blood samples with targets set by the NGSP Laboratory Network.**  ***GPP*** |  | Little RR, Rohlfing CL, Sacks DB. The National Glycohemoglobin Standardization Program: Over 20 years of improving hemoglobin A1c measurement. Clin Chem 2019; 65:839-848. | Review of analytical methods | Moderate | Low | Retrospective analysis of analytical performance of the NGSP network and clinical labs in HbA1cmeasurement |
| Little RR, Rohlfing CL, Wiedmeyer HM, Myers GL, Sacks DB, Goldstein DE, et al. The national glycohemoglobin standardization program: a five-year progress report. Clin Chem. 2001;47(11):1985–92 | Program report | Moderate | Evidence is downgraded due to its indirectness to patient outcomes.  Recommendation is a good practice point to ensure that laboratories maintain a high quality HbA1c assay that is suitable for both diagnosis and monitoring and that their assay meets the recommended analytical performance requirements. |
| Goldstein DE, Little RR. Bringing order to chaos: the National Glycohemoglobin Standardization Program. Contemp Int Med 1997;9:27–32. | Review | Low |
| Steffes M, Cleary P, Goldstein D, Little R, et al. Hemoglobin A1c measure-ments over nearly two decades: sustaining comparable values throughout the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study. Clin Chem. 2005;51(4):753–8. | Comparative study | Low |
| Little RR, Rohlfing CL, Sacks DB. Status of HbA1c measurement and goals for improvement: from chaos to order for improving diabetes care. Clin Chem 2011;57:205–14 | Review | Low |
| 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 |
| 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 |
| Weykamp C, John WG, Mosca A, Hoshino T, et al. The IFCC reference measurement system for HbA1c: a 6-year progress report. Clin Chem 2008;54:240–8 | Interlaboratory analytical performance study | Moderate |

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| **No** | **1. Updated/new recommendation with its grade and quality of evidence*(2)*** | **2. NACB 2011 recommendation and its grade*(1)*** | **3. Why was it necessary to modify the recommen-dation?** | **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** |
| l | **The goals for imprecision for HbA1c measurement are intra-laboratory CV <1.5% and inter-laboratory CV <2.5% (using at least two control samples with different HbA1c levels), and ideally no measurable bias.**  ***B (low)*** | **Desirable specifications for HbA1c measurement are intra-laboratory CV <2% and inter-laboratory CV <3.5%. At least two control materials with different mean values should be analyzed as an independent measure of assay performance**.  ***B (low*** |  | Little RR, Rohlfing CL, Sacks DB. Status of HbA1c measure-ment and goals for improve-ment: from chaos to order for improving diabetes care. Clin Chem 2011;57:205–14 | Review | Moderate/Low | Low | This study used the reference change value (also called critical difference) to calculate an appropriate analytical goal |
| Marshall SM, Barth JH. Standardization of HbA1c measurements: a consensus statement. Ann Clin Biochem 2000;37:45–6 | Consensus statement | Moderate/Low | Recommendation is B in spite of overall low quality of evidence as it is shown that analytical performance of the HbA1c assay impacts clinical decisions and thus indirectly patient outcomes. |
| Sacks DB. CAP Surveys: Participant Summary for Hemoglobin A1c Survey 2020 Set GH5-C. Northfield, IL: College of American Pathologists. | Expert opinion | Low |
| EFLM Biological variation database <https://biologicalvariation.eu/> | Database of biological variation studies | High | Database of systematically reviewed biological variation studies |

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| **No** | **1. Updated/new recommendation with its grade and quality of evidence*(2)*** | **2. NACB 2011 recommendation and its grade*(1)*** | **3. Why was it necessary to modify the recommen-dation?** | **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 POSTANALYTICAL CONSIDERATIONS FOR REPORTING AND INTERPRETING HbA1c MEASUREMENT RESULTS?** | | | | | | | | |
| m | **Hemoglobin A1c should be reported as a percentage of total hemoglobin or as mmol/mol of total hemoglobin.**  ***GPP*** |  |  | Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR, Goodall I, et al. IFCC reference system for measure-ment 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 | Moderate | Moderate | Strong consensus of experts on standardization of the measurement and reporting units for HbA1c but the use of the IFCC units has not gained universal acceptance. The recommendation is downgraded to GPP due to no direct evidence to show that using one measurement unit vs the other would improve patient management decisions and thus would have any impact on diabetes outcomes. |
| Geistanger A, Arends S, Berding C, Hoshino T, Jeppsson J-O, Little R, Siebelder C and Weykamp C, on behalf of the IFCC Working Group on Standardization of HbA1c: Statistical Methods for Monitoring the Relationship between the IFCC Reference Measurement Procedure for Hemoglobin A1c and the Designated Comparison Methods in the United States, Japan and Sweden. Clin Chem 2008; 54(8): 1379-8 | Method-comparison study | Moderate |

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| **No** | **1. Updated/new recommendation with its grade and quality of evidence*(2)*** | **2. NACB 2011 recommendation and its grade*(1)*** | **3. Why was it necessary to modify the recommen-dation?** | **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** |
| n | **HbA1c may also be reported as estimated average glucose (eAG) to facilitate comparison with the self-monitoring results obtained by patients and make the interpretation of the HbA1c more accessible to people with diabetes.**  ***GPP*** | N/A | New, more patient-centred recommendation | Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. Translating the hemoglobin A1c assay into estimated average glucose values. Diabetes Care 2008;31:1473–8 | Multicenter longitudinal observational study | Moderate | Moderate | This study defined the mathematical relationship between HbA1c and average glucose (AG) levels |
| Murata GH, Hoffman RM, Duckworth WC, Wendel CS, Shah JH. Contributions of weekly mean blood glucose values to hemoglobin A1c in insulin-treated type 2 diabetes: the Diabetes Outcomes in Veterans Study (DOVES). Am J Med Sci 2004;327:319–23 | Multicenter study | Moderate | This study evaluated the weekly contribution of glucose readings to HbA1c during an 8-week period |
| Nathan DM, Turgeon H, Regan S. Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia 2007;50:2239–44 | Longitudinal observational study | Moderate | This study determined the relationship between an accurate measure of mean glucose levels over time and the HbA1c level |
| Hanas R, John G, International HbA(1c) Consensus Committee. 2010 consensus statement on the worldwide standardization of the hemoglobin A1c measurement. Clin Chem. 2010 Aug;56(8):1362–4. | Expert consensus | Moderate/ Low | The recommendation is downgraded to GPP due to no direct evidence to show that reporting eAG improves diabetes outcomes. |
| Sacks DB. 2011 consensus meeting on the worldwide standardization of hemoglobin A(1c) measurement. Clin Chem. 2013;59(5):857–8. | Expert consensus | Low |

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| **No** | **1. Updated/new recommendation with its grade and quality of evidence*(2)*** | **2. NACB 2011 recommendation and its grade*(1)*** | **3. Why was it necessary to modify the recommend-dation?** | **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** |
| o | **Laboratories should verify by repeat testing specimens with HbA1c results below the lower limit of the reference interval or greater than 15% (140 mmol/mol) HbA1c.**  ***GPP*** | **Samples with HbA1c results below the lower limit of the reference interval or >15% HbA1c should be verified by repeat testing.**  ***B (low)*** |  | Bry L, Chen PC, Sacks DB. Effects of hemoglobin variants and chemically modified derivatives on assays for glycohemoglobin [Review]. Clin Chem 2001;47:153–63 | Review | Low | Low | See details and references in earlier recommendations (f-h) above |