Hemoglobin A1c

Policy Number: AHS – G2006 – Hemoglobin A1c	Prior Policy Name and Number, as applicable:
Effective Date: 11/01/2022	

I. Policy Description

Glycated hemoglobin (A1c) results from post-translational attachment of glucose to the hemoglobin in red blood cells at a rate dependent upon the prevailing blood glucose concentration. Therefore, their levels correlate well with glycemic control over the previous 8 to 12 weeks (Elizabeth Selvin, 2022). The measurement of hemoglobin A1c is recommended for diabetes management, including screening, diagnosis, and monitoring for diabetes and prediabetes.

Diabetes describes several heterogeneous diseases in which various genetic and environmental factors can result in the progressive loss of β-cell mass and/or function that manifests clinically as hyperglycemia (Skyler et al., 2017).

II. Related Policies

Policy Number	Policy Title
AHS-G2009	Preventive Screening in Adults
AHS-G2035	Prenatal Screening (Nongenetic)

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website https://www.cms.gov/medicare-coverage-database/search.aspx or the manual website.

1) Measurement of hemoglobin A1c **MEETS COVERAGE CRITERIA** for individuals with a diagnosis of either Type 1 or Type 2 diabetes as follows:
   a) Upon initial diagnosis to establish a baseline value and to determine treatment goals.
   b) Twice a year (every 6 months) in individuals who are meeting treatment goals and who, based on daily glucose monitoring, appear to have stable glycemic control.
   c) Quarterly in individuals who are not meeting treatment goals for glycemic control.
   d) Quarterly in individuals whose pharmacologic therapy has changed.

2) Measurement of hemoglobin A1c **MEETS COVERAGE CRITERIA** to help in detection and diagnosis of pre-diabetes or Type 2 diabetes in the following populations once every three years:
   a) asymptomatic individuals who are overweight or obese as defined by the ADA and who have one or more of the following risk factors:
      i) First-degree relative with diabetes; OR
      ii) High-risk race/ethnicity (e.g., African American, Latino or Hispanics, Native American, Asian American, Pacific Islanders); OR
      iii) History of cardiovascular disease; OR
      iv) Hypertension (≥140/90 mmHg or on therapy for hypertension); OR
      v) HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L); OR
      vi) Individuals with polycystic ovary syndrome; OR
      vii) Physical inactivity; OR
      viii) Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   b) individuals who were previously diagnosed with gestational diabetes

3) For pre-diabetic individuals, screening for type 2 diabetes with hemoglobin A1c measurement once a year **MEETS COVERAGE CRITERIA.**

4) Diabetes screening with a hemoglobin A1c determination **MEETS COVERAGE CRITERIA** once every 3 years for asymptomatic children (age 10 years and older OR after the onset of puberty, whichever occurs earlier) with the following characteristics:
   a) Overweight (BMI ≥85th percentile) or obese (BMI ≥95th percentile) as defined by ADA AND
   b) Must have one or more of the following additional risk factors:
      i) Maternal history of diabetes or gestational diabetes mellitus during the child's gestation; OR
      ii) Family history of type 2 diabetes in first- or second-degree relative; OR
      iii) High-risk race/ethnicity (e.g., African American, Latino or Hispanics, Native American, Asian American, Pacific Islanders); OR

iv) Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight)

5) Measurement of hemoglobin A1c **MEETS COVERAGE CRITERIA** for pregnant individuals up to once per month during pregnancy.

6) Measurement of hemoglobin A1c **DOES NOT MEET COVERAGE CRITERIA** in the following circumstances:

   a) as the sole diagnostic test in children and adolescents, except as previously described; OR

   b) in individuals with a condition associated with increased red blood cell turnover, such as sickle cell disease, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy; OR

   c) in conjunction with measurement of fructosamine; OR

   d) to diagnose the acute onset of type 1 diabetes in individuals of all ages; OR

   e) as a screening test for cystic fibrosis-related diabetes.

NOTE: The American Diabetes Association states that "to test for prediabetes and type 2 diabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1c are equally appropriate," but also notes that "in a patient with classic symptoms, measurement of plasma glucose is sufficient to diagnose diabetes."

IV. Table of Terminology

Term	Definition
1,5AG	1,5-Anhydroglucitol
2-h PG	2-h plasma glucose
A1c	Glycated hemoglobin
AACE	American Association of Clinical Endocrinologists
AAFP	American Academy of Family Physicians
ACE	American College of Endocrinology
ACP	American College of Physicians
ADA	American Diabetes Association
aRR	Adjusted risk ratios
ARV	Antiretroviral
BMI	Body mass index
BP	Blood pressure
CAP	College of American Pathologists
CF	Cystic fibrosis
CFPD	Cystic fibrosis-related prediabetes
CFRD	Cystic fibrosis-related diabetes
CHF	Congestive heart failure
CKD	Chronic kidney disease
CMS	Centers For Medicare and Medicaid Services
CV	Coefficient of variation
CVA	Cerebrovascular accident

CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
FA	Fructosamine
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GA	Glycated albumin
GDM	Gestational diabetes mellitus
HbA1c	Hemoglobin A1C/Glycated hemoglobin
HDL	High-density lipoprotein
HIV/AIDS	Human immunodeficiency virus, acquired immunodeficiency syndrome
HPLC	High-performance liquid chromatography
IFCC	International Federation of Clinical Chemistry
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IHD	Ischemic heart disease
ISPAD	International Society for Pediatric and Adolescent Diabetes
KDIGO	Kidney Disease: Improving Global Outcomes Diabetes Working Group
LDTs	Laboratory developed tests
MACE	Major adverse cardiovascular events
MODY	Maturity-onset diabetes of the young
NACB	National Academy of Clinical Biochemistry
NGSP	National Glycohemoglobin Standardization Program
NICE	National Institute for Health and Care Excellence
OGTT	Oral glucose tolerance test
OR	Odds ratio
POC	Point of care
ROC-AUC	Receiver operative characteristic, area under the curve
SES	Socioeconomic status
SMBG	Self-monitoring of blood glucose
T1D	Type 1 Diabetes
TIA	Transient ischemic attack
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

V. Scientific Background

Diabetes is a major health concern in the United States. According to the Centers for Disease Control and Prevention:

- Prevalence: In 2018, 34.2 million Americans, or 10.5% of the population, had diabetes. Approximately 1.25 million American children and adults have type 1 diabetes.
- Undiagnosed: Of the 34.2 million, 27.1 million were diagnosed, and 7.3 million were undiagnosed.
- Prevalence in seniors: The percentage of Americans aged 65 and older remains high, at 26.8%, or 14.3 million seniors (diagnosed and undiagnosed).

- New Cases: 1.5 million Americans are diagnosed with diabetes every year.
- Prediabetes: In 2018, 88 million Americans aged 18 and older had prediabetes.
- Deaths: Diabetes remains the 7th leading cause of death in the United States in 2017, with 83,564 death certificates listing it as the underlying cause of death, and a total of 270,702 death certificates listing diabetes as an underlying or contributing cause of death.
- Total economic cost of diabetes care in the United States: $327 billion in 2017 (ADA, 2017; CDC, 2020).

Diabetes can be classified into the following general categories:

- "Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency)"
- "Type 2 diabetes (due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance)"
- "Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)"
- "Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)" (ADA, 2021a). The diagnosis of diabetes mellitus is easily established when a patient presents with classic symptoms of hyperglycemia, which include polyuria, polydipsia, nocturia, blurred vision, and, infrequently, weight loss. The frequency of symptomatic diabetes has been decreasing in parallel with improved efforts to diagnose diabetes earlier through screening. Increasingly, the majority of patients are asymptomatic, and hyperglycemia is noted on routine laboratory evaluation, prompting further testing (Inzucchi, 2021).

Glycated hemoglobin A1c (also known as HbA1c, A1c, glycohemoglobin, hemoglobin A1c) testing plays a key role in the management of diabetes. New hemoglobin enters circulation with minimal glucose attached. However, glucose irreversibly binds to hemoglobin based on the surrounding blood glucose concentration. Therefore, A1c is considered a measure of blood glucose level, albeit an indirect one. It is best correlated with the mean glucose level over the last 8 to 12 weeks as red blood cells experience significant turnover. Various factors may affect the reliability of A1c (atypical hemoglobins or hemoglobinopathies, chronic kidney disease, et al.), but most assays have been standardized to the Diabetes Control and Complications Trial (DCCT) standard, which "estimated the mean blood glucose concentrations derived from seven measurements a day (before and 90 minutes after each of the three major meals, and before bedtime), performed once every three months and compared the average glucose concentration with A1c values in patients with type 1 diabetes" (Elizabeth Selvin, 2022).

The HbA1c assay provides information about the degree of long-term glucose control (Nathan, Singer, Hurxthal, & Goodson, 1984), and has been recommended for the diagnosis and monitoring of diabetes (ADA, 2010; IEC, 2009). Various methods of HbA1c measurement include chromatography based HPLC assay, boronate affinity, antibody-based immunoassay, and enzyme based enzymatic assay (Kanyal

Butola, Ambad, Kanyal, & Vagga, 2021). Long term blood sugar control has been associated with decreased risk of retinopathy, nephropathy, neuropathy, and cardiovascular disease, peripheral arterial, cerebrovascular disease (Hanssen, Bangstad, Brinchmann-Hansen, & Dahl-Jorgensen, 1992) and myocardial fibrosis in adults with diabetes (Al-Badri et al., 2018). Higher HbA1c variability has been associated with higher all-cause mortality in patients with Type 2 Diabetes (Gu et al., 2018).

Analytical Validity

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Working Group on HbA1c Standardization has developed a reference measurement system and the measurement of HbA1c is currently well-standardized (Hoelzel et al., 2004), and a sound reference system is in place to ensure continuity and stability of the analytical validity of HbA1c measurement (Weykamp et al., 2008). In contrast, plasma glucose concentration remains difficult to assay with consistent accuracy (Gambino, 2007). HbA1c has greater analytical stability (consistency with repetitive sample testing) and less day-to-day variability than either the fasting plasma glucose (FPG)or 2-h PG (Petersen, Jorgensen, Brandslund, De Fine Olivarius, & Stahl, 2005; Rohlfing et al., 2002). For any given individual, the HbA1c exhibits little short-term biologic variability; its coefficient of variation (CV) is 3.6%, compared to FPG (CV of 5.7%) and 2-h PG (CV of 16.6%) (Malkani & Mordes, 2011; E. Selvin, Crainiceanu, Brancati, & Coresh, 2007).

A sample proficiency testing survey performed by the National Glycohemoglobin Standardization Program (NGSP) and College of American Pathologists (CAP) evaluated the accuracy of A1c assays. The survey found that “method-specific, between-laboratory CV’s [*sic*] ranged from 0.9% to 4.5%” and “approximately 91% of laboratories are using methods with CVs <3.5% at all four HbA1c levels.” The survey also noted the current pass limit was ±6%, but using a pass rate of 5%, 92.9% to 96.1% of labs passed (NGSP, 2019).

Clinical Validity

A1c, FPG, and 2-h PG measure different aspects of glycemia and are frequently discordant for diagnosing diabetes. A1c ≥6.5% identifies fewer individuals as having diabetes than glucose-based criteria; however, a recent study concluded that 12% of patients can be misclassified with respect to diabetes diagnosis due to laboratory instrument error in measuring glucose (Miller et al., 2008). The New Hoorn Study analyzed the diagnostic properties of the A1c, using OGTT as the diagnostic criterion (van 't Riet et al., 2010). The analysis suggested that an A1c of 5.8% had a sensitivity of 72% and specificity of 91%. This compares with specificity of 24% and sensitivity of 99% for the A1c cut-point of 6.5%. On the other hand, the 6.5% cutpoint had a positive predictive value of 93%, compared with a positive predictive value of only 24% for a cut-point of 5.8% (Malkani & Mordes, 2011).

Cowie et al. “examined prevalences of previously diagnosed diabetes and undiagnosed diabetes and high risk for diabetes using recently suggested A1c criteria in the U.S. during 2003–2006. We compared these prevalences to those in earlier surveys and those using glucose criteria.” 14611 individuals were included (completed a household interview) and classified for diagnosed diabetes and by A1c, fasting, and 2-h glucose challenge values. Diagnostic values for A1c were ≥6.5% for “undiagnosed” diabetes and 6%-6.5% for “high risk” of diabetes. The authors found that by these A1c diagnostic values, the “crude prevalence” of diabetes in adults older than 20 years was 20.4 million, of which 19% went undiagnosed based on A1c ≥ 6.5%. The authors then stated that the A1c criteria only diagnosed 30% of the undiagnosed diabetic group (Cowie et al., 2010).

Mamtora et al. (2021) assessed the clinical utility of point of care (POC) HbA1c testing in the ophthalmology outpatient setting. Forty-nine patients with diabetic retinopathy underwent POC HbA1c testing and blood pressure measurement. Of the 49 patients, 81.6% had POC readings above the recommended HbA1c levels and only 16.3% of these patients were aware of their elevated HbA1c levels. 14 patients (33.3%) with high HbA1c readings were referred to secondary diabetic services and 88.8% of patients felt like the test was useful. The authors suggest that POC HbA1c testing is a "cost-effective, reproducible and clinically significant tool for the management of diabetes in an outpatient ophthalmology setting, allowing the rapid recognition of high-risk patients and appropriate referral to secondary diabetic services" (Mamtora, Maghsoudlou, Hasan, Zhang, & El-Ashry, 2021).

Clinical Utility

Goodney et al. (2016) evaluated the consistency of A1c testing of diabetes patients and its effect on cardiovascular outcomes. 1574415 Medicare patients with diabetes mellitus were included, and the consistency of testing was separated into three categories: “low (testing in 0 or 1 of 3 years), medium (testing in 2 of 3 years), and high (testing in all 3 years).” 70.2% of patients received high-consistency testing, 17.6% received medium-consistency, and 12.2% received low-consistency. Major adverse cardiovascular events (MACE) included “death, myocardial infarction, stroke, amputation, or the need for leg revascularization”. Low-consistency patients was associated with death or other adverse events (hazard ratio: 1.21). The authors concluded that “consistent annual hemoglobin A1c testing is associated with fewer adverse cardiovascular outcomes in this observational cohort of Medicare patients of diabetes mellitus (Goodney et al., 2016).”

The GOAL study (Al Mansari et al., 2018) used A1c to assess diabetes control in a real-world practice study aimed to assess predictive factors for achieving the glycemic hemoglobin A1c (HbA1c) at 6 months as targeted by the treating physician in adults with type 2 diabetes. 2704 patients with a mean A1c of 9.7% were enrolled. After 6 months, lower baseline A1c (≥ 8.5% vs <7%) was found to be a predictive factor for achieving glycemic control. The authors also observed “absolute changes in the mean HbA1c of −1.7% and −2% were observed from baseline to 6 and 12 months, respectively (Al Mansari et al., 2018).”

Mitsios et al. (2018) evaluated the association between A1c and stroke risk. 29 studies (n=532779) were included. The authors compared the non-diabetic A1c range (<5.7%) to the diabetic range (≥6.5%) and found that the diabetic range was associated with a 2.15-fold increased risk of first-ever stroke. The pre-diabetes range of 5.7%-6.5% was also not associated with first-ever stroke. The authors also observed that for every 1% increase in A1c, the hazard ratio of first-ever stroke increased (1.12-fold for non-diabetic ranges, 1.17 for diabetic ones). This increased risk was also seen for ischemic stroke, with a hazard ratio of 1.49 for non-diabetic ranges and 1.24 for diabetic ranges (Mitsios, Ekinci, Mitsios, Churilov, & Thijs, 2018).

Ludvigsson et al. (2019) evaluated the association between preterm birth risk and periconceptional HbA1c levels in pregnant individuals with type 1 diabetes (T1D). Preterm birth was defined as <37 weeks and several secondary outcomes were also examined, which were “neonatal death, large for gestational age, macrosomia, infant birth injury, hypoglycemia, respiratory distress, 5-minute Apgar score less than 7, and stillbirth”. A total of 2474 singletons born to individuals with T1D and 1165216 reference infants (children born to mothers without T1D) were included. The authors identified 552 preterm births in the T1D cohort (22.3%) compared to 54287 in the control cohort (4.7%). Incidences of preterm birth were measured at several separate thresholds, including <6.5%, 6.5%-7.8%, 7.8%-9.1%, and >9.1%. The T1D cohort’s adjusted risk ratios (aRR) of preterm birth compared to the control cohort were as follows: 2.83

for <6.5%, 4.22 for 6.5%-7.8%, 5.56 for 7.8%-9.1%, and 6.91 for >9.1%. The corresponding aRRs for "medically indicated preterm birth" (n=320) were 5.26, 7.42, 11.75 and 17.51 respectively. Increased HbA1c levels were also found to be associated with the secondary clinical outcomes. The authors concluded that "the risk for preterm birth was strongly linked to periconceptional HbA1c levels. (Ludvigsson et al., 2019)"

Saito et al. (2019) examined the association of HbA1c variability (defined as visit-to-visit) and later onset of malignancies. The authors included 2640 patients 50 years or older, with diabetes. A total of 330 patients (12.5%) developed malignancies during follow-up. The authors stratified the patients into quartiles of glycemic variability (defined as standard deviation of HbA1c) and found a "dose-dependent association with tumorigenesis" in the three highest quartiles. The odds ratios were as follows: 1.20 for the second quartile, 1.43 for the third, and 2.19 for the highest. The authors concluded that "these results demonstrated that visit-to-visit HbA1c variability is a potential risk factor for later tumorigenesis. The association may be mediated by oxidative stress or hormone variability. (Saito, Noto, Takahashi, & Kobayashi, 2019)"

Mañe et al. (2019) evaluated the "suitability of first-trimester fasting plasma glucose and HbA1c levels in non-diabetic range to identify [individuals] without diabetes at increased pregnancy risk". Primary outcomes were defined as "macrosomia and pre-eclampsia" and secondary outcomes were defined as "preterm delivery, Caesarean section and large-for-gestational age". A total of 1228 pregnancies were included. Pregnant individuals with an HbA1c of ≥5.8% were found to have an increased risk of marcosomia (odds ratio [OR] = 2.69), an HbA1c of ≥5.9% was found to be associated with a three-fold risk of pre-eclampsia, and an HbA1c of ≥6% was found to be associated with a four-fold risk of "large-for-gestational age". Fasting plasma glucose levels were not found to be associated with any pregnancy outcome. (Mañé et al., 2019).

Arbiol-Roca et al. (2021) studied the clinical utility of HbA1c testing as a biomarker for detecting gestational diabetes mellitus (GDM) and as a screening test to avoid the use of the oral glucose tolerance test (OGTT). HbA1c levels were measured in 745 pregnant individuals and GDM was diagnosed in 38 patients based on HbA1c, age, and BMI. A cut off HbA1c value of 4.6% was determined to decide whether OGTT was needed or if it could be avoided. Using 4.6% HbA1c as the cut off value prevented two false negatives, but only decreased the number of OGTTs performed by 7.2%. The authors conclude that "adoption of HbA1c as a screening test for GDM may eliminate the need of OGTT." Although the HbA1c test does not have sufficient sensitivity and specificity to be used as the sole diagnostic test, " the use of a rule-out strategy in combination with the OGTT could be useful" (Arbiol-Roca et al., 2021).

However, the use of hemoglobin A1c testing is not useful in predicting all forms of dysglycemia. Tommerdahl et al. (2019) evaluated several biomarkers for their accuracy in screening for cystic fibrosis (CF)-related diabetes. These biomarkers included "hemoglobin A1c (HbA1c), 1,5-anhydroglucitol (1,5AG), fructosamine (FA), and glycated albumin (GA)" and were compared to the current gold standard, OGTT 2-hour glucose. Fifty-eight patients with CF were included and "area under the receiver operative characteristic (ROC-AUC) curves were generated." All ROC-AUCs for each biomarker were "low" both for cystic fibrosis-related prediabetes (CFPD, ROC-AUC 0.52-0.67) and CF-related diabetes (CFRD) (0.56-0.61). For CFRD, HbA1c was measured to have a 78% sensitivity and 41% specificity at a cutoff of 5.5%, which corresponds to a ROC-AUC of 0.61. The authors concluded that "All alternate markers tested demonstrate poor diagnostic accuracy for identifying CFRD by 2hG (Tommerdahl et al., 2019)."

In a retrospective review of the UMass Memorial Health System electronic medical records from between 1997 and 2019, Darukhanavala et al. (2021) evaluated the appropriateness of HbA1c as a screening tool for identifying patients with pre-CFRD (cystic fibrosis-related diabetes) dysglycemia to minimize the burden of annual two-hour oral glucose tolerance tests (OGTTs). The study included 56 patients categorized according to OGTT results (American Diabetes Association criteria): normal glucose tolerance (n=34), indeterminant glycemia (INDET, n=6), impaired fasting glucose (IFG, n=7), or impaired glucose tolerance (IGT, n=9). It was found that HbA1c was positively correlated with blood glucose levels at the various time cut-points (hour 0, hour 1, and hour 2), though the associations were quite weak ($r = 0.248$, $r = 0.219$, and $r = 0.369$, respectively). Furthermore, t-tests conducted suggested that the mean HbA1c was not significantly different between patients with normal glucose tolerance and those in the INDET ($p = 0.987$), IFG ($p = 0.690$), and IGT ($p = 0.874$) groups, confirmed by ANOVA ($p = 0.250$). Consequently, "Our [The authors'] results do not support the use of HbA1c as a possible screening tool for pre-CFRD dysglycemic states, specifically INDET, IFG, and IGT" (Darukhanavala et al., 2021).

By combining administrative datasets from the Veterans Health Administration and Medicare, Zhao, Prentice, Mohr, and Conlin (2021) evaluated the impact of hemoglobin A1c (A1c) variability—the coefficient of variation, described by A1c standard deviation divided by the average A1c value overall and expressed as a percent—on the risk of hypoglycemia-related hospitalization (HRH) in veterans with diabetes mellitus. In this study sample of 342059 patients, the authors identified a "consistent and positive relationship between A1c variability and HRH" and noted that "Average A1c levels were also significantly and independently associated with HRH, with levels <7.0% (53 mmol/mol) associated with lower risk and levels >9% (75 mmol/mol) conferring greater risk". Due to these different levels of variability all remaining strong predictors of HRH risk up to three years following the baseline period, authors concluded that "tracking A1c levels alone may be insufficient to mitigate risk". It was also acknowledged that a few limitations affected the generalizability of the study, such as the lack of socioeconomic data, the study sample being predominantly white males, and including only veterans, the latter of which is a population where comorbidities are more prevalent. Consequently, these data may be reflective of "the complex interplay of disease severity, treatment, and sociodemographic factors", as is the case with other clinical findings (Zhao et al., 2021).

While poor outcomes of coronavirus disease 2019 (COVID-19) have been linked to diabetes, its relation to pre-infection glycemic control is still unclear. Because of this, Merzon et al. (2021) investigated the association between pre-infection HemoglobinA1c (A1C) levels and COVID-19 severity as assessed by need for hospitalization in a cohort of 2068 patients (ages 14 to 103) with diabetes tested for COVID-19 in Leumit Health Services, Israel, between February 1 and April 30, 2020. Of the patients in this cohort, 183 (8.85%) were diagnosed with COVID-19. A comparison of the mean HbA1c of those who were COVID-19 positive (7.19%, 95% CI: 6.81%-7.57%) and the mean of those who were COVID-19 negative (6.59%, 95% CI: 6.52%-6.65%) was found to be statistically significant ($p<0.05$). The authors expounded further by reporting the clinical characteristics of patients with diabetes hospitalized due to COVID-19 by demonstrating that the mean Hb1Ac levels between those hospitalized (n=46, 7.75%, 95% CI: 7.17%-8.32%) and those not hospitalized (n=137, 6.83%, 95% CI: 6.54%-7.13%) were also statistically significant ($p<0.005$). Additionally, "In a multivariate logistic regression model adjusting for multiple potential risk factors and chronic conditions which may have a deleterious effect on disease outcomes (including age, sex, smoking, IHD, SES, depression/anxiety, schizophrenia, dementia, hypertension, CVA, CHF, chronic lung disease, and obesity), only HbA1c ≥ 9% remained a significant predictor for hospitalization." Given the evidence, the researchers urge "Paying special attention to patients with diabetes and an HbA1c ≥ 9 while allowing a more lenient approach to patients with well controlled disease", as this can reduce

economic, social, and patient burden, especially for those who are at the greatest risk for reacting severely to COVID-19 (Merzon et al., 2021).

VI. Guidelines and Recommendations

The American Diabetes Association

The ADA publishes an extensive guideline encompassing the standards of medical care in diabetes. The 2020 recommendations state:

Screening for and diagnosis of diabetes (Chapter [Ch] 2) (ADA, 2021a):

- Criteria for testing for diabetes or prediabetes in asymptomatic adult:
  - Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:
    - First-degree relative with diabetes
    - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
    - History of CVD
    - Hypertension (≥140/90 mmHg or on therapy for hypertension)
    - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
    - Individuals with polycystic ovary syndrome
    - Physical inactivity
    - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
  - Patients with prediabetes (A1c ≥5.7% [39 mmol/mol], IGT [impaired glucose tolerance], or IFG [impaired fasting glucose]) should be tested yearly.
  - Individuals who were diagnosed with GDM should have lifelong testing at least every 3 years.
  - For all other patients, testing should begin at age 45 years.
  - If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
  - HIV
- Testing for prediabetes and/or type 2 diabetes should be considered in individuals planning to become pregnant and who are overweight or obese and/or who have one more additional risk factors for diabetes
- Diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value after a 75-g oral glucose tolerance test (OGTT) or A1c criteria where A1c ≥6.5% (48 mmol/mol).
- "To avoid misdiagnosis or missed diagnosis, the A1c test should be performed using a method that is certified by the NGSP and standardized to the Diabetes Control and Complications Trial (DCCT) assay. Grade **B**"
- "Marked discordance between measured A1c and plasma glucose levels should raise the possibility of A1c assay interference due to hemoglobin variants (i.e., hemoglobinopathies) and consideration of using an assay without interference or plasma blood glucose criteria to diagnose diabetes. Grade **B**"
- "In conditions associated with an altered relationship between A1c and glycemia, such as sickle cell disease, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes. Grade **B**"

- "To test for prediabetes and type 2 diabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1c are equally appropriate. Grade **B**"
- "A1c is not recommended as a screening test for cystic fibrosis–related diabetes. Grade **B**"
- "Beginning 5 years after the diagnosis of cystic fibrosis–related diabetes, annual monitoring for complications of diabetes is recommended."
- "Test for undiagnosed diabetes at the first prenatal visit in those with risk factors using standard diagnostic criteria."
- "A1C is not recommended for diagnosis of diabetes in children with cystic fibrosis or symptoms suggestive of acute onset of type 1 diabetes and only A1C assays without interference are appropriate for children with hemoglobinopathies, the ADA continues to recommend A1C for diagnosis of type 2 diabetes in this cohort (ungraded)"
- "Test for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant [individuals] not previously known to have diabetes." (ADA, 2021a)

For management of diabetes (Ch 2):

"The A1c test should be performed using a method that is certified by the NGSP (www.ngsp.org) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Although point-of-care A1c assays may be NGSP certified or U.S. Food and Drug Administration approved for diagnosis, proficiency testing is not always mandated for performing the test. Therefore, point-of-care assays approved for diagnostic purposes should only be considered in settings licensed to perform moderate-to-high complexity tests… point-of-care A1C assays may be more generally applied for assessment of glycemic control in the clinic (ADA, 2021a)."

Comorbidities (Ch 4) (ADA, 2020a, 2021b)

"Individuals with HIV are at higher risk for developing prediabetes and diabetes on antiretroviral (ARV) therapies, so a screening protocol is recommended. The A1c test may underestimate glycemia in people with HIV; it is not recommended for diagnosis and may present challenges for monitoring." (ADA, 2021b)

Glycemic Targets (Ch 6) (ADA, 2020b, 2021c)

- "Assess glycemic status (A1C or other glycemic measurement) at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control).
- "Assess glycemic status at least quarterly, and as needed, in patients whose therapy has recently changed and/or who are not meeting glycemic goals."
- "Point-of-care testing for A1c provides the opportunity for more timely treatment changes." (ADA, 2021c)

Children & Adolescents (Ch 13) (ADA, 2020c, 2021d)

The traditional idea of type 2 diabetes occurring only in adults and type 1 diabetes occurring only in children is no longer accurate, as both diseases can occur in both age-groups. The recommendations concerning hemoglobin A1c for children and adolescents are as follows:

- "Fasting plasma glucose, 2-h plasma glucose during a 75-g oral glucose tolerance test, and A1c can be used to test for prediabetes or [type 2] diabetes in children and adolescents. Grade **B"**
- "Although A1c is not recommended for diagnosis of diabetes in children with cystic fibrosis or symptoms suggestive of acute onset of type 1 diabetes and only A1c assays without interference

are appropriate for children with hemoglobinopathies, ADA continues to recommend A1c for diagnosis of type 2 diabetes in this population (ungraded)"

- "If tests are normal, repeat testing at a minimum of 3-year intervals **E**, or more frequently if BMI is increasing. **C"**
- "A1C goals must be individualized and reassessed over time. An A1C of <7% (53 mmol/mol) is appropriate for many children. **B**" (ADA, 2021d)
- Concerning screening of asymptomatic children and adolescents (under the age of 18 but after the onset of puberty or after 10 years of age, whichever occurs earlier) for type 2 diabetes or prediabetes, the ADA recommends the following (ADA, 2021d):
    - Criteria: Consider testing in youth "who have [sic] overweight (≥85th percentile) or obesity (≥95th percentile) Grade **A**
    - Plus, one or more additional risk factors based on the strength of their association with diabetes as indicated by evidence grades:
        - Maternal history of diabetes or GDM during the child's gestation-Grade **A**
        - Family history of type 2 diabetes in first- or second-degree relative-Grade **A**
        - Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)-Grade **A**
        - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight)-Grade **B**

Pregnancy (Ch 14) (ADA, 2021e)

- "…although A1c may be useful, it should be used as a secondary measure of glycemic control in pregnancy, after self-monitoring of blood glucose."
- "Due to increased red blood cell turnover, A1c is slightly lower in normal pregnancy than in normal nonpregnant [individuals]. Ideally, the A1c target in pregnancy is <6% (42 mmol/mol) if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% (53 mmol/mol) if necessary to prevent hypoglycemia"
- "Given the alteration in red blood cell kinetics during pregnancy and physiological changes in glycemic parameters, A1c levels may need "to be monitored more frequently than usual (e.g., monthly)."
- "The OGTT is recommended over A1C at 4–12 weeks postpartum because A1C may be persistently impacted (lowered) by the increased red blood cell turnover related to pregnancy, by blood loss at delivery, or by the preceding 3-month glucose profile. The OGTT is more sensitive at detecting glucose intolerance, including both prediabetes and diabetes."
- "Because GDM is associated with an increased lifetime maternal risk for diabetes estimated at 50–70% after 15–25 years, [individuals] should also be tested every 1–3 years thereafter if the 4–12 weeks postpartum 75-g OGTT is normal. Ongoing evaluation may be performed with any recommended glycemic test (e.g., annual A1C, annual fasting plasma glucose, or triennial 75-g OGTT using nonpregnant thresholds)." (ADA, 2021e)

Diabetes Canada Clinical Practice Guidelines Expert Committee

This Expert Committee published a comprehensive guideline on the prevention and management of diabetes. Relevant items, recommendations, and comments—particularly those relating to the use of A1c testing—are captured below:

- "Screen for type 2 diabetes using a fasting plasma glucose and/or glycated hemoglobin (A1C) every 3 years in individuals ≥40 years of age or in individuals at high risk on a risk calculator (33% chance of developing diabetes over 10 years)."
- "In the absence of evidence for interventions to prevent or delay type 1 diabetes, routine screening for type 1 diabetes is not recommended."
- "For most individuals with diabetes, A1C should be measured approximately every 3 months to ensure that glycemic goals are being met or maintained. In some circumstances, such as when significant changes are made to therapy, or during pregnancy, it is appropriate to check A1C more frequently. Testing at least every 6 months should be performed in adults during periods of treatment and healthy behavior stability when glycemic targets have been consistently achieved."
- A1C can be misleading in various medical conditions ("e.g. hemoglobinopathies, iron deficiency, hemolytic anemia, severe hepatic or renal disease") and should not be used for "diagnostic use in children and adolescents (as the sole diagnostic test), pregnant [individuals] as part of routine screening for gestational diabetes, those with cystic fibrosis or those with suspected type 1 diabetes"
- Diabetes "should" be diagnosed at a level of A1C ≥6.5%.
- "Screening for diabetes using FPG and/or A1C should be performed every 3 years in individuals ≥40 years of age or at high risk using a risk calculator [Grade D, Consensus]. Earlier testing and/or more frequent follow up (every 6 to 12 months) with either FPG and/or A1C should be considered in those at very high risk using a risk calculator or in people with additional risk factors for diabetes [Grade D, Consensus]"

It should be mentioned that "Glycemic targets should be individualized [Grade D, Consensus]" based upon various considerations including, but not limited to, the patient's functional dependence, medical history, life expectancy, and life course stage. Moreover, the grading of recommendations above (e.g., "Grade D") reflect the methodological rigor used at arriving at the conclusion, such that lower grades reflect the presence of weaker evidence. But though the "paucity of clinical evidence addressing the areas of therapy, prevention, diagnosis or prognosis precluded the assignment of a higher grade", the authors recognize and note that many Grade D recommendations are "very important to the contemporary management of diabetes (Committee, 2018).

The United States Preventive Services Task Force (USPSTF)

The USPSTF recommends screening for prediabetes and type 2 diabetes in adults aged 35 to 70 years who are overweight or obese, and such "Screening tests for prediabetes and type 2 diabetes include measurement of fasting plasma glucose or HbA1c level or an oral glucose tolerance test". Recognizing that "The optimal screening interval for adults with an initial normal glucose test result is uncertain", the USPSTF suggests that "Screening every 3 years may be a reasonable approach for adults with normal blood glucose levels" (Davidson et al., 2021).

World Health Organization (WHO)

The Global Report on Diabetes (WHO, 2016) states that: "Glycated haemoglobin (HbA1c) is the method of choice for monitoring glycaemic control in diabetes. An advantage of using HbA1c is that the patient does not need to be in a fasting state. Ideally it should be measured twice a year in people with type 2 diabetes and more frequently in those with type 1 diabetes. However, HbA1c testing is more costly than glucose measurement, and therefore less readily available. If HbA1c testing is not available, fasting or post-meal blood glucose is an acceptable substitute."

The WHO also published a "module" titled "Hearts-D: Diagnosis and Management of Type 2 Diabetes in 2020. In it, a testing algorithm for "treatment of type 2 diabetes mellitus with insulin" is included at the bottom. The algorithm calls for an HbA1c assessment to be performed "in 3 months" if the patient is stabilized as a result of the insulin treatment. (WHO, 2020)

The National Academy of Clinical Biochemistry

The NACB guidelines (NACB, 2011) state:

- "Laboratories should use only Hb A1c assay methods that are certified by the National Glycohemoglobin Standardization Program (NGSP) as traceable to the DCCT reference. The manufacturers of Hb A1c assays should also show traceability to the IFCC reference method."
- "Laboratories that measure HbA1c should participate in a proficiency-testing program, such as the College of American Pathologists (CAP) HbA1c survey, that uses fresh blood samples with targets set by the NGSP Laboratory Network."
- "HbA1c 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."
- "HbA1c 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."
- "Point-of-care HbA1c assays are not sufficiently accurate to use for the diagnosis of diabetes."

American Academy of Family Physicians

In 2022, the AAFP published a clinical summary of the USPSTF recommendation for screening for prediabetes and type 2 diabetes mellitus. The document deferred to the USPSTF recommendations, with the testing audience being "Nonpregnant adults aged 35 to 70 years who have overweight or obesity and no symptoms of diabetes"—a move from 40 years of age in the previous recommendation—while deeming screening every 3 years to be a reasonable approach (AAFP, 2022).

International Society for Pediatric and Adolescent Diabetes (ISPAD)

IPSAD published a comprehensive set of guidelines for "children, adolescents, and young adults with diabetes". Some relevant chapters and recommendations include:

Chapter 5: Management of cystic fibrosis-related diabetes in children and adolescents

IPSAD recommends against use of HbA1c as a screening test for cystic fibrosis-related diabetes (CFRD) and states that screening for CFRD should be performed with the 2-hour 75 g (1.75 g/kg) OGTT instead. However, for patients already with CFRD, HbA1c measurement is recommended quarterly to guide insulin therapy decisions. (Moran et al., 2018)

Chapter 8: Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes

Although this guideline primarily focuses on glycemic targets for children with diabetes, a few relevant items are listed.

- IPSAD recommends hemoglobin A1c measurements “at least quarterly” for successful glycemic management.
- IPSAD also notes that fructosamine is used for “assessment of shorter periods of control than HbA1c” and “may be useful in monitoring glucose control in individuals with abnormal red cell survival time.” (DiMeglio et al., 2018)

Endocrine Society

The Endocrine Society published this guideline regarding management of diabetes in older adults. In it, they recommend screening for prediabetes or diabetes every 2 years for patients 65 years or older. Fasting plasma glucose and/or HbA1c may be used. However, the Society does recommend caution when interpreting HbA1c results, as older patients are more likely to have conditions that alter red blood cell turnover. (LeRoith et al., 2019)

National Institute for Health and Care Excellence

NICE published an update to their guideline on diabetes management. In it, they make the following recommendations:

“Measure HbA1c levels in adults with type 2 diabetes every:
- 3 to 6 months (tailored to individual needs) until HbA1c is stable on unchanging therapy
- 6 months once the HbA1c level and blood glucose lowering therapy are stable.”

“Measure HbA1c using methods calibrated according to International Federation of Clinical Chemistry (IFCC) standardisation.”

“If HbA1c monitoring is invalid because of disturbed erythrocyte turnover or abnormal haemoglobin type, estimate trends in blood glucose control using one of the following:
- quality-controlled plasma glucose profiles
- total glycated haemoglobin estimation (if abnormal haemoglobins)
- fructosamine estimation.”

“Investigate unexplained discrepancies between HbA1c and other glucose measurements. Seek advice from a team with specialist expertise in diabetes or clinical biochemistry.” (NICE, 2022)

American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE)

The 2020 Consensus Statement from the AACE/ACE on the Management of Type 2 Diabetes states:

- "The hemoglobin A1c (A1c) target should be individualized based on numerous factors such as age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia or adverse consequences from hypoglycemia, patient motivation, and adherence."
- “An A1c level of ≤6.5% is considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time.”

- "Therapy must be evaluated frequently (e.g., every 3 months) until stable using multiple criteria, including A1c, SMBG records (fasting and postprandial) or continuous glucose monitoring tracings, documented and suspected hypoglycemia events, lipid and BP values, adverse events (weight gain, fluid retention, hepatic or renal impairment, or CVD), comorbidities, other relevant laboratory data, concomitant drug administration, complications of diabetes, and psychosocial factors affecting patient care. Less frequent monitoring is acceptable once targets are achieved" (Garber et al., .

Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Working Group

KDIGO published recommendations on diabetes and chronic kidney disease (CKD). They recommend using HbA1c to monitor diabetic and CKD patients twice a year or as often as 4 times a year if glycemic target is not met or a change is made in therapy. KDIGO advises that "accuracy and precision of HbA1c measurement declines with advanced CKD, particularly among patients treated by dialysis, in whom HbA1c measurements have low reliability." They also recommend an "individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis" (de Boer et al., 2020).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

A search for "Hemoglobin A1c" on the FDA website yielded 42 results on April 28, 2022 (FDA, 2020, 2021). Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a guarantee of payment.

Code Number	Code Description
82985	Glycated protein
83036	Hemoglobin; glycosylated (A1C)
83037	Hemoglobin; glycosylated (A1C) by device cleared by FDA for home use

IX. Evidence-based Scientific References

AAFP.). Screening for Abnormal Blood Glucose and Type 2 Diabetes Mellitus: Recommendation Statement. *Am Fam Physician, 105*(1), Online. Retrieved from https://www.aafp.org/afp/2022/0100/od1.html

ADA. (2010). Diagnosis and classification of diabetes mellitus. *Diabetes Care, 33 Suppl 1*, S62-69. doi:10.2337/dc10-S062

ADA. (2017). Statistics About Diabetes. Retrieved from https://www.diabetes.org/resources/statistics/statistics-about-diabetes

ADA. (2020a). 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes—2020. *Diabetes Care, 43*(Supplement 1), S37. doi:10.2337/dc20-S004

ADA. (2020b). 6. Glycemic Targets: Standards of Medical Care in Diabetes—2020. *Diabetes Care, 43*(Supplement 1), S66. doi:10.2337/dc20-S006

ADA. (2020c). 13. Children and Adolescents: Standards of Medical Care in Diabetes−2020. *Diabetes Care, 43*(Supplement 1), S163. doi:10.2337/dc20-S013

ADA. (2021a). 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. *Diabetes Care, 43*(Supplement 1), S14. doi:10.2337/dc20-S002

ADA. (2021b). 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes—2021. *Diabetes Care, 43*(Supplement 1), S37. doi:10.2337/dc20-S004

ADA. (2021c). 6. Glycemic Targets: Standards of Medical Care in Diabetes—2021. *Diabetes Care, 43*(Supplement 1), S66. doi:10.2337/dc20-S006

ADA. (2021d). 13. Children and Adolescents: Standards of Medical Care in Diabetes−2021. *Diabetes Care, 43*(Supplement 1), S163. doi:10.2337/dc20-S013

ADA. (2021e). 14. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes—2021. *Diabetes Care, 43*(Supplement 1), S183. doi:10.2337/dc20-S014

Al-Badri, A., Hashmath, Z., Oldland, G. H., Miller, R., Javaid, K., Syed, A. A., . . . Chirinos, J. A. (2018). Poor Glycemic Control Is Associated With Increased Extracellular Volume Fraction in Diabetes. *Diabetes Care*. doi:10.2337/dc18-0324

Al Mansari, A., Obeid, Y., Islam, N., Fariduddin, M., Hassoun, A., Djaballah, K., . . . Chaudhury, T. (2018). GOAL study: clinical and non-clinical predictive factors for achieving glycemic control in people with type 2 diabetes in real clinical practice. *BMJ Open Diabetes Res Care, 6*(1), e000519. doi:10.1136/bmjdrc-2018-000519

Arbiol-Roca, A., Pérez-Hernández, E. A., Aisa-Abdellaoui, N., Valls-Guallar, T., Gálvez-Carmona, F., Mariano-Serrano, E., . . . Ruiz-Morer, M. R. (2021). The utility HBA1c test as a screening biomarker for detecting gestational diabetes mellitus. *Clinical Biochemistry, 90*, 58-61. doi:https://doi.org/10.1016/j.clinbiochem.2021.01.002

CDC. (2020). National Diabetes Statistics Report 2020 Estimates of Diabetes and Its Burden in the United States. Retrieved from https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

Committee, D. C. C. P. G. E. (2018). *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada.* Retrieved from http://guidelines.diabetes.ca/docs/CPG-2018-full-EN.pdf

Cowie, C. C., Rust, K. F., Byrd-Holt, D. D., Gregg, E. W., Ford, E. S., Geiss, L. S., . . . Fradkin, J. E. (2010). Prevalence of Diabetes and High Risk for Diabetes Using A1C Criteria in the U.S. Population in 1988–2006. *Diabetes Care, 33*(3), 562. doi:10.2337/dc09-1524

Darukhanavala, A., Van Dessel, F., Ho, J., Hansen, M., Kremer, T., & Alfego, D. (2021). Use of hemoglobin A1c to identify dysglycemia in cystic fibrosis. *PLoS One, 16*(4), e0250036. doi:10.1371/journal.pone.0250036

Davidson, K. W., Barry, M. J., Mangione, C. M., Cabana, M., Caughey, A. B., Davis, E. M., . . . Wong, J. B. (2021). Screening for Prediabetes and Type 2 Diabetes: US Preventive Services Task Force Recommendation Statement. *Jama, 326*(8), 736-743. doi:10.1001/jama.2021.12531

de Boer, I. H., Caramori, M. L., Chan, J. C. N., Heerspink, H. J. L., Hurst, C., Khunti, K., . . . Rossing, P. (2020). KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney International, 98*(4), S1-S115. doi:10.1016/j.kint.2020.06.019

DiMeglio, L. A., Acerini, C. L., Codner, E., Craig, M. E., Hofer, S. E., Pillay, K., & Maahs, D. M. (2018). ISPAD Clinical Practice Consensus Guidelines 2018: Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes. *Pediatr Diabetes, 19 Suppl 27*, 105-114. doi:10.1111/pedi.12737

FDA. (2020). Devices@FDA. Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm

FDA. (2021). Devices@FDA. Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm

Gambino, R. (2007). Glucose: a simple molecule that is not simple to quantify. *Clin Chem, 53*(12), 2040-2041. doi:10.1373/clinchem.2007.094466

Garber, A. J., Handelsman, Y., Grunberger, G., Einhorn, D., Abrahamson, M. J., Barzilay, J. I., . . . Umpierrez, G. E. CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - EXECUTIVE SUMMARY. *Endocr Pract,* (1), -139. doi:10.4158/cs--0472

Goodney, P. P., Newhall, K. A., Bekelis, K., Gottlieb, D., Comi, R., Chaudrain, S., . . . Skinner, J. S. (2016). Consistency of Hemoglobin A1c Testing and Cardiovascular Outcomes in Medicare Patients With Diabetes. *J Am Heart Assoc, 5*(8). doi:10.1161/jaha.116.003566

Gu, J., Pan, J. A., Fan, Y. Q., Zhang, H. L., Zhang, J. F., & Wang, C. Q. (2018). Prognostic impact of HbA1c variability on long-term outcomes in patients with heart failure and type 2 diabetes mellitus. *Cardiovasc Diabetol, 17*(1), 96. doi:10.1186/s12933-018-0739-3

Hanssen, K. F., Bangstad, H. J., Brinchmann-Hansen, O., & Dahl-Jorgensen, K. (1992). Blood glucose control and diabetic microvascular complications: long-term effects of near-normoglycaemia. *Diabet Med, 9*(8), 697-705. Retrieved from http://dx.doi.org/

Hoelzel, W., Weykamp, C., Jeppsson, J. O., Miedema, K., Barr, J. R., Goodall, I., . . . Wiedmeyer, H. M. (2004). 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, 50*(1), 166-174. doi:10.1373/clinchem.2003.024802

IEC. (2009). International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care, 32*(7), 1327-1334. doi:10.2337/dc09-9033

Inzucchi, S., Lupsa, Beatrice. (2021). Clinical presentation, diagnosis, and initial evaluation of diabetes mellitus in adults - UpToDate. Retrieved from https://www.uptodate.com/contents/clinical-presentation-and-diagnosis-of-diabetes-mellitus-in-adults?source=search_result&search=a1c&selectedTitle=5~150. https://www.uptodate.com/contents/clinical-presentation-and-diagnosis-of-diabetes-mellitus-in-adults?source=search_result&search=a1c&selectedTitle=5~150

Kanyal Butola, L., Ambad, R., Kanyal, D., & Vagga, A. (2021). Glycated Haemoglobin-Recent Developments and Review on Non-Glycemic Variables.

LeRoith, D., Biessels, G. J., Braithwaite, S. S., Casanueva, F. F., Draznin, B., Halter, J. B., . . . Sinclair, A. J. (2019). Treatment of Diabetes in Older Adults: An Endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism, 104*(5), 1520-1574. doi:10.1210/jc.2019-00198

Ludvigsson, J. F., Neovius, M., Söderling, J., Gudbjörnsdottir, S., Svensson, A. M., Franzén, S., . . . Pasternak, B. (2019). Maternal Glycemic Control in Type 1 Diabetes and the Risk for Preterm Birth: A Population-Based Cohort Study. *Ann Intern Med, 170*(10), 691-701. doi:10.7326/m18-1974

Malkani, S., & Mordes, J. P. (2011). The implications of using Hemoglobin A1C for diagnosing Diabetes Mellitus. *Am J Med, 124*(5), 395-401. doi:10.1016/j.amjmed.2010.11.025

Mamtora, S., Maghsoudlou, P., Hasan, H., Zhang, W., & El-Ashry, M. (2021). Assessing the Clinical Utility of Point of Care HbA1c in the Ophthalmology Outpatient Setting. *Clinical ophthalmology (Auckland, N.Z.), 15*, 41-47. doi:10.2147/OPTH.S287531

Mañé, L., Flores-Le Roux, J. A., Pedro-Botet, J., Gortazar, L., Chillarón, J. J., Llauradó, G., . . . Benaiges, D. (2019). Is fasting plasma glucose in early pregnancy a better predictor of adverse obstetric outcomes than glycated haemoglobin? *Eur J Obstet Gynecol Reprod Biol, 234*, 79-84. doi:10.1016/j.ejogrb.2018.12.036

Merzon, E., Green, I., Shpigelman, M., Vinker, S., Raz, I., Golan-Cohen, A., & Eldor, R. (2021). Haemoglobin A1c is a predictor of COVID-19 severity in patients with diabetes. *Diabetes Metab Res Rev, 37*(5), e3398. doi:10.1002/dmrr.3398

Miller, W. G., Myers, G. L., Ashwood, E. R., Killeen, A. A., Wang, E., Ehlers, G. W., . . . Toth, A. (2008). State of the art in trueness and interlaboratory harmonization for 10 analytes in general clinical chemistry. *Arch Pathol Lab Med, 132*(5), 838-846. doi:10.1043/1543-2165(2008)132[838:sotait]2.0.co;2

Mitsios, J. P., Ekinci, E. I., Mitsios, G. P., Churilov, L., & Thijs, V. (2018). Relationship Between Glycated Hemoglobin and Stroke Risk: A Systematic Review and Meta-Analysis. *J Am Heart Assoc, 7*(11). doi:10.1161/jaha.117.007858

Moran, A., Pillay, K., Becker, D., Granados, A., Hameed, S., & Acerini, C. L. (2018). ISPAD Clinical Practice Consensus Guidelines 2018: Management of cystic fibrosis-related diabetes in children and adolescents. *Pediatr Diabetes, 19 Suppl 27*, 64-74. doi:10.1111/pedi.12732

NACB. (2011). Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus. In D. Sacks (Ed.), *LABORATORY MEDICINE PRACTICE GUIDELINES*. Retrieved from https://www.aacc.org/science-and-practice/practice-guidelines/diabetes-mellitus

Nathan, D. M., Singer, D. E., Hurxthal, K., & Goodson, J. D. (1984). The clinical information value of the glycosylated hemoglobin assay. *N Engl J Med, 310*(6), 341-346. doi:10.1056/nejm198402093100602

NGSP. (2019, 06/2019). College of American Pathologists (CAP) GH5 Survey Data: . Retrieved from http://www.ngsp.org/CAP/CAP19a.pdf

NICE. , 3/31/2022). Type 2 diabetes in adults: management. Retrieved from https://www.nice.org.uk/guidance/ng28/chapter/1-Recommendations

Petersen, P. H., Jorgensen, L. G., Brandslund, I., De Fine Olivarius, N., & Stahl, M. (2005). Consequences of bias and imprecision in measurements of glucose and hba1c for the diagnosis and prognosis of diabetes mellitus. *Scand J Clin Lab Invest Suppl, 240*, 51-60. doi:10.1080/00365510500236135

Rohlfing, C., Wiedmeyer, H. M., Little, R., Grotz, V. L., Tennill, A., England, J., . . . Goldstein, D. (2002). Biological variation of glycohemoglobin. *Clin Chem, 48*(7), 1116-1118. Retrieved from http://dx.doi.org/

Saito, Y., Noto, H., Takahashi, O., & Kobayashi, D. (2019). Visit-to-Visit Hemoglobin A1c Variability Is Associated With Later Cancer Development in Patients With Diabetes Mellitus. *Cancer J, 25*(4), 237-240. doi:10.1097/ppo.0000000000000387

Selvin, E. (2022). Measurements of glycemic control in diabetes mellituss - UpToDate. Retrieved from https://www.uptodate.com/contents/measurements-of-glycemic-control-in-diabetes-mellitus. https://www.uptodate.com/contents/measurements-of-glycemic-control-in-diabetes-mellitus

Selvin, E., Crainiceanu, C. M., Brancati, F. L., & Coresh, J. (2007). Short-term variability in measures of glycemia and implications for the classification of diabetes. *Arch Intern Med, 167*(14), 1545-1551. doi:10.1001/archinte.167.14.1545

Skyler, J. S., Bakris, G. L., Bonifacio, E., Darsow, T., Eckel, R. H., Groop, L., . . . Ratner, R. E. (2017). Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis. *Diabetes, 66*(2), 241-255. doi:10.2337/db16-0806

van 't Riet, E., Alssema, M., Rijkelijkhuizen, J. M., Kostense, P. J., Nijpels, G., & Dekker, J. M. (2010). Relationship between A1C and glucose levels in the general Dutch population: the new Hoorn study. *Diabetes Care, 33*(1), 61-66. doi:10.2337/dc09-0677

Weykamp, C., John, W. G., Mosca, A., Hoshino, T., Little, R., Jeppsson, J. O., . . . Siebelder, C. (2008). The IFCC Reference Measurement System for HbA1c: a 6-year progress report. *Clin Chem, 54*(2), 240-248. doi:10.1373/clinchem.2007.097402

WHO. (2016). *Global Report on Diabetes*. Retrieved from http://www.who.int/diabetes/global-report/en/

WHO. (2020). Diagnosis and Management of Type 2 Diabetes. Retrieved from https://www.who.int/publications/i/item/who-ucn-ncd-20.1

Zhao, M. J. Y., Prentice, J. C., Mohr, D. C., & Conlin, P. R. (2021). Association between hemoglobin A1c variability and hypoglycemia-related hospitalizations in veterans with diabetes mellitus. *BMJ Open Diabetes Res Care, 9*(1). doi:10.1136/bmjdrc-2020-001797

X. Revision History

Revision Date	Summary of Changes
01/01/2022	Initial Effective Date
05/20/2022	Updated background, guidelines, and evidence-based scientific references.
09/14/2022	Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes to coverage criteria: Policy edited to remove gendered language. CC2a.vi now reads “Individuals with polycystic ovary syndrome; OR” and CC2b now reads “individuals who were previously diagnosed with gestational diabetes” Removed BMI “(BMI ≥25 kg/m2 or BMI ≥23 kg/m2 in Asian Americans)” from CC2a. Addition of “asymptomatic” to CC4, now reads “Diabetes screening with a hemoglobin A1c determination MEETS COVERAGE CRITERIA once every 3 years for asymptomatic children (age 10 years and older OR after the onset of puberty, whichever occurs earlier) with the following characteristics:”

	Addition of CC6a: “as the sole diagnostic test in children and adolescents, except as previously described; OR” Removed of CC6b: “in individuals who have been transfused within the past 120 days; OR” Addition of “of all ages” to CC6d “to diagnose the acute onset of type 1 diabetes in individuals of all ages; OR” Addition of new note- NOTE: The American Diabetes Association states that “to test for prediabetes and type 2 diabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1c are equally appropriate,” but also notes that “in a patient with classic symptoms, measurement of plasma glucose is sufficient to diagnose diabetes.” Revised code disclaimer statement