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Corporate Medical Policy

Hemoglobin A1c AHS – G2006

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Description of Procedure or Service

Glycated hemoglobin 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 (McCulloch, 2018). 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).

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for measurement of hemoglobin A1c when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When measurement of hemoglobin A1c is covered

1. Reimbursement for measurement of hemoglobin A1c is allowed 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. Reimbursement for measurement of hemoglobin A1c is allowed 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 (BMI >25 kg/m2 or BMI >23 kg/m2 in Asian Americans) 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. Women with polycystic ovary syndrome; OR
   vii. Physical inactivity; OR
   viii. Other clinical conditions associated with insulin resistance (eg. Severe obesity, acanthosis nigricans)

b) Women who were previously diagnosed with gestational diabetes

3. Reimbursement is allowed once per year in pre-diabetic individuals, to screen for type 2 diabetes using a hemoglobin A1c test.
4. Reimbursement is allowed once every 3 years for diabetes screening with a hemoglobin A1c determination in children (age 10 years and older OR after the onset of puberty, whichever occurs earlier) with the following characteristics:
   i. Overweight (BMI ≥85th percentile) or obese (BMI ≥95th percentile) as defined by ADA AND
   ii. Must have one or more of the following additional risk factors:
   iii. Maternal history of diabetes or gestational diabetes mellitus during the child's gestation; OR
   iv. Family history of type 2 diabetes in first- or second-degree relative; OR
   v. High-risk race/ethnicity (e.g., African American, Latino or Hispanics, Native American, Asian American, Pacific Islanders); OR
   vi. 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. Reimbursement is allowed once per month during pregnancy for measurement of hemoglobin A1c for pregnant individuals.

When measurement of hemoglobin A1c is not covered

Reimbursement is not allowed for measurement of hemoglobin A1c in the following circumstances:

a. in individuals who have been transfused within the past 120 days; 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 with symptoms of hyperglycemia; OR
e. as a screening test for cystic fibrosis-related diabetes.

Policy Guidelines

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 age 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 age 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, 2020a).

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, 2020).

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" (McCulloch, 2018).

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). 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; 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).

Clinical Utility

Goodney et al. 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. 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. evaluated the association between preterm birth risk and periconceptional HbA1c levels in women 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 women 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)"

Tommerdahl et al. 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)."

Saito et al. 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. evaluated the "suitability of first-trimester fasting plasma glucose and HbA1c levels in non-diabetic range to identify women 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. Women 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).

Guidelines and Recommendations

The American Diabetes Association (ADA, 2020a, 2020b, 2020c, 2020d, 2020e)
The ADA publishes an extensive yearly guideline encompassing the standards of medical care in diabetes. The 2020 recommendations state:

Screening for and diagnosis of diabetes (Chapter [Ch] 2) (ADA, 2020a):

- 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)
    - Women 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.
  - Women 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.
- 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 women not previously known to have diabetes." (ADA, 2020a)

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, 2020a)."

Comorbidities (Ch 4) (ADA, 2020b)

"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, 2020b)

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

- "Perform the A1c test *at least* two times a year in patients who are meeting treatment goals (and who have stable glycemic control)."
- "Perform the A1c test quarterly in patients whose therapy has changed or who are not meeting glycemic goals."
- "Point-of-care testing for A1c provides the opportunity for more timely treatment changes." (ADA, 2020c)

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

- The majority of patients diagnosed with autoimmune type 1 diabetes are under the age of 18. 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 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, 2020d)
- 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, 2020d):
  - 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, 2020e)

- "…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 women. 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, women 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, 2020e)

Diabetes Canada Committee (Committee, 2018)
This Expert Committee published a comprehensive guideline on the prevention and management of diabetes. Relevant items, recommendations, and comments include:

- "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 women 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%. (Committee, 2018)

The American College of Physicians (ACP) (Qaseem et al., 2018)
The ACP published guidelines (Qaseem et al., 2018) for glycemic control based on A1c which state:

Guidance Statement 1:
Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.

Guidance Statement 2:
Clinicians should aim to achieve an HbA_{1c} level between 7% and 8% in most patients with type 2 diabetes.

Guidance Statement 3:
Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA_{1c} levels less than 6.5%.

The United States Preventive Services Task Force (USPSTF, 2016)
The USPSTF recommends screening overweight or obese adults ages 40-70 years for abnormal blood glucose, with a grade B recommendation. In it, they recommend hemoglobin A1c as one of the screening tests (USPSTF, 2016).

World Health Organization (WHO) (WHO, 2016, 2020)
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 (NACB, 2011)
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 (AAFP, 2016)
The AAFP published the revised Summary of Recommendations for Clinical Preventive Services in 2016 that stated that "the AAFP recommends screening for abnormal blood glucose as part of cardiovascular risk assessment in adults aged 40 to 70 years who are overweight or obese. The AAFP noted that "glucose abnormalities can be detected by measuring HgbA1c, fasting plasma glucose, or oral glucose tolerance test. Abnormal results should be confirmed." The AAFP further stated that "there is limited evidence on the best rescreening interval for adults with normal results but screening every 3 years is a reasonable option."(AAFP, 2016)

International Society for Pediatric and Adolescent Diabetes (ISPAD) (DiMeglio et al., 2018)
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 (LeRoith et al., 2019)
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, 2019)

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

- "In adults with type 2 diabetes, measure HbA1c levels at: 3–6-monthly intervals (tailored to individual needs), until the HbA1c is stable on unchanging therapy and 6-monthly intervals once the HbA1c level and blood glucose lowering therapy are stable."
- "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) [or] fructosamine estimation." (NICE, 2019)

American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) (Garber et al., 2015; Garber et al., 2019)
The 2019 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., 2019)

State and Federal Regulations, as applicable
A search for "Hemoglobin A1c" on the FDA website yielded 42 results on August 4, 2020. (FDA, 2020). 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 82985, 83036, 83037

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

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Specialty Matched Consultant Advisory Panel review 2/2020

Policy Implementation/Update Information

4/1/19 New policy developed. BCBSNC will provide coverage for measurement of hemoglobin A1c when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 4/1/2019. Policy noticed 4/1/2019 for effective date 6/1/2019. (an)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed (gm)

12/10/19 Coding section updated to reflect new and deleted codes per Avalon Q3 CAB update. When covered section #5 added "Reimbursement is allowed once per month during pregnancy for measurement of hemoglobin A1c for pregnant individuals." When not covered section – removed pregnancy from bullet b and removed panel testing of biochemical markers for type 2 diabetes risk. (eel)

03/10/20 Specialty Matched Consultant Advisory Panel review 2/19/2020. No change to policy statement. (eel)

11/10/20 Coding section updated, deleted code 82947 per Avalon Q3 CAB update. Updated description and policy guidelines sections. When covered section #3 removed "fasting plasma glucose test" for clarity. When covered section #4 updated ADA definition of overweight and obese. (eel)

and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.