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Diabetes Mellitus Testing

Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

THIS POLICY APPLIES TO IL ONLY.

1. For individuals with acute or persistent classic symptoms of diabetes mellitus, measurement of fasting plasma glucose (See **NOTE 1**) **may be considered medically necessary.**

2.   For individuals with a diagnosis of either Type 1 or Type 2 diabetes mellitus, measurement of hemoglobin A1c **may be considered medically necessary** in **any** of the following situations:
    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.

3. For prediabetic individuals, annual screening for type 2 diabetes with a fasting plasma glucose test or measurement of hemoglobin A1c **may be considered medically necessary.**

4. For asymptomatic individuals 18 years of age or older, screening once every three years for prediabetes or Type 2 diabetes with a fasting plasma glucose test **or** measurement of hemoglobin A1c **may be considered medically necessary** for individuals with **any** of the following risk factors:
   a. For individuals who are overweight or obese;
   b. For first-degree relatives (See **NOTE 2**) of individuals with diabetes;
   c. For individuals with a history of cardiovascular disease;
   d. For individuals with hypertension;
   e. For individuals with hypercholesterolemia;
   f. For individuals with metabolic syndrome;
   g. For individuals who are obese and have acanthosis nigricans;
   h. For individuals with polycystic ovary syndrome;
   i. For individuals who were previously diagnosed with gestational diabetes mellitus (GDM);

5. For individuals who are positive for HIV, screening for diabetes and prediabetes with a fasting plasma glucose test **may be considered medically necessary** in any of the following situations:
   a. For individuals starting antiretroviral therapy (ART);
   b. For individuals switching their ART;
   c. 3-6 months after starting or switching antiretroviral therapy;
   d. annually when screening results were initially normal.

6. For individuals 10 years of age and older who have been diagnosed with cystic fibrosis (CF) but not with CF-related diabetes, annual screening for CF-related diabetes with an OGTT **may be considered medically necessary.**

7. For overweight or obese children (after the onset of puberty **or** after 10 years of age, whichever occurs earlier), diabetes screening with a fasting plasma glucose test **or** an OGTT once every three years **may be considered medically necessary** for individuals with any of the following risk factors:
   a. The individual has a maternal history of diabetes or gestational diabetes mellitus during the child's gestation;
   b. The individual has a family history of type 2 diabetes in first-or second-degree relatives (See **NOTE 2**)
   c. The individual has signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small for gestational age birth weight).

8. For pregnant individuals, a fasting plasma test or an OGTT up to once per month during pregnancy **may be considered medically necessary.**

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9. For individuals diagnosed with GDM during pregnancy, an OGTT **may be considered medically necessary** in **any** of the following situations:
    a. To screen for persistent diabetes or prediabetes 4-12 weeks postpartum
    b. For individuals with a positive initial postpartum screening result, repeat screening to confirm a diagnosis of persistent diabetes of prediabetes.

10. For all other situations not previously addressed (See **NOTE 3**), measurement of hemoglobin A1c **is considered not medically necessary.**

Policy Guidelines

Note 1: While this policy provided evidence-based reasons for fasting or random plasma glucose testing in the diagnosis of diabetes, these tests have clinical use outside the scope of this policy and thus are not restricted to the criteria detailed above. According to the American Diabetes Association (ADA), measurement of plasma glucose is sufficient to diagnose diabetes mellitus in a patient with classic symptoms (polyuria, polyphagia, polydipsia).

Note 2: First-degree relatives include parents, full siblings, and children of the individual. Second-degree relatives include grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings of the individual.

Note 3: Measurement of hemoglobin A1c **should not** be performed in **any** of the following situations:
    1) In pregnant individuals not already diagnosed with diabetes.
    2) In individuals under 18 years of age not already diagnosed with diabetes.
    3) In conjunction with measurement of fructosamine.
    4) 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.

Description

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).

Fasting plasma glucose (FPG) and oral glucose tolerance testing (OGTT) can be used in the diagnosis of diabetes mellitus. FPG is obtained from blood after a typically overnight period of not eating, whereas the OGTT is performed to understand an individual's response to a concentrated solution of glucose after 2 hours, typically in the setting of pregnancy (MayoClinic, 2022). In an asymptomatic individual, fasting plasma glucose ≥ 126 mg/dL or two-hour plasma glucose values of ≥200 mg/dL during a 75 g OGTT establish a diagnosis of diabetes. In reference

to A1c values, a percentage ≥6.5% should raise clinical suspicion (Inzucchi & Lupsa, 2021). These assays are identified to be affordable alternatives to the more costly yet more convenient HbA1c level, and are more often used in the diagnosis of type 2 diabetes mellitus (Hayward & Selvin, 2022).

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, these levels correlate well with glycemic control over the previous eight to 12 weeks (Selvin, 2022). The measurement of hemoglobin A1c is recommended for diabetes management, including screening, diagnosis, and monitoring for diabetes and prediabetes.

Rationale

Diabetes is a major health concern in the United States. According to the Centers for Disease Control and Prevention:
- Prevalence: In 2019, 37.3 million Americans, or 11.3% of the population, had diabetes. Approximately 1.9 million American children and adults have type 1 diabetes, including about 244,000 children and adolescents.
- Diagnosed and undiagnosed: Of the 37.3 million, 28.7 million were diagnosed, and 8.5 million were undiagnosed.
- Prevalence in seniors: The percentage of Americans aged 65 and older remains high, at 29.2%, or 15.9 million seniors (diagnosed and undiagnosed).
- New cases: 1.4 million Americans are diagnosed with diabetes every year.
- Prediabetes: In 2019, 96 million Americans aged 18 and older had prediabetes.
- Deaths: Diabetes remains the 7th leading cause of death in the United States in 2019, with 87,647 death certificates listing it as the underlying cause of death, and a total of 282,801 death certificates listing diabetes as a cause of death.
- Total economic cost of diabetes care in the United States: $327 billion in 2017 (ADA, 2022; CDC, 2020).

Diabetes can be classified into the following 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 & Lupsa, 2021).

Glycated hemoglobin A1c (also known as HbA1c, A1c, glycohemoglobin, or 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 eight 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" (Selvin, 2022).

The HbA1c assay provides information about the degree of long-term glucose control (Nathan et al., 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 et al., 2021). Long term blood sugar control has been associated with decreased risk of retinopathy, nephropathy, neuropathy, and cardiovascular disease, peripheral arterial, cerebrovascular disease (Hanssen et al., 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).

Fasting plasma glucose is a method of glucose monitoring that measures an individual's glucose level typically in a period defined with no caloric intake for eight hours or more. Its usage in the diagnosis of diabetes lies primarily in gestational diabetes, along with the oral glucose tolerance test, but HbA1c, fasting plasma glucose, or oral glucose tolerance tests with their respective positive results can be used in diagnosing diabetes mellitus in nonpregnant individuals as well. To diagnose diabetes in asymptomatic individuals, a fasting plasma glucose has to be ≥ 126 mg/dL. For diagnosing prediabetes, an individual may have "impaired fasting glucose," which would present with a range of 100-125 mg/dL (Hayward & Selvin, 2022; Inzucchi & Lupsa, 2021).

The oral glucose tolerance test (OGTT) can be more inconvenient and used in the setting to diagnose gestational diabetes mellitus (GDM). Normally, 75g of glucose is ingested by the patient, and if the patient has a two-hour plasma glucose value of ≥200 mg/dL, a diagnosis of diabetes can be made. The test can also be performed at one hour with 50g oral glucose, with

positive GDM diagnostic results between 130-140 mg/dL as part of a two-step approach with the three-hour 100g test, which can be diagnostic of GDM with two elevated values. For prediabetes with an accompanied "impaired glucose tolerance," a two-hour plasma glucose value between 140-199 mg/dL is used. However, the WHO requires an additional FPG <126 in addition to the two hour plasma glucose value to establish impaired glucose tolerance (Durnwald, 2022; Hayward & Selvin, 2022).

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 two hour PG (Petersen et al., 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 et al., 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 Utility and Validity

Testing 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% cut point 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).

When using the reference diagnosis of diabetes being a two-hour blood glucose >200 mg/dL (11.1 mmol/L) during an OGTT, the specificity of FPG ≥126 mg/dL was >95% and sensitivity about 50%, with possibly lower sensitivities and specificities for individuals over 65 years (Blunt et al., 1991). With the same OGTT reference, the specificity and sensitivity of an A1c ≥6.5%, as per diagnosis of diabetes, were reported as 79% and 44%, respectively (Kramer et al., 2010).

Cowie et al. (2010) "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 et al., 2021).

Goodney et al. (2016) evaluated the consistency of A1c testing of diabetes patients and its effect on cardiovascular outcomes. The study included 1574415 Medicare patients with diabetes mellitus, 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 six 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 et al., 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 et al., 2019).

Mañé 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, the authors reported that the "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 et al. (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).

Xie et al. (2021) investigated the role of FPG and glucose fluctuation on the prognosis of COVID-19 patients who already had prior diagnoses of diabetes. Through a multivariate Cox analysis, the researchers found that FPG was "an independent prognostic factor of overall survival after adjustment for age, sex, diabetes, and severity of COVID-19 at admission (HR: 1.15, 95% CI: 1.06-1.25)." However, blood glucose fluctuation was associated with COVID-19 disease progression, as proven by the results found from the indices of the standard deviation of blood glucose and the largest amplitude of glycemic excursions. Both FPG and blood glucose fluctuation indices were also found to be positively associated with increased presence of inflammatory markers associated with COVID-19, such as the "white blood cell absolute count, neutrophil count, C-reactive protein (CRP), alkaline phosphatase, a-hydroxybutyrate

dehydrogenase (α-hbdh), gamma-glutamyl transferase (GGT), lactate dehydrogenase, [and] D-dimer." Ultimately, it was concluded that diabetes was not an independent risk factor for in-hospital death of COVID-19 patients, as these findings were identified regardless of diabetes status (Xie et al., 2021).

Yang et al. (2019) aimed to find the appropriate threshold for fasting plasma glucose for defining prediabetes among children and adolescents. The sample was selected from school-aged children in Taiwan via a nationwide survey administered between 1992-2000, who then underwent physical examinations and blood tests if they exhibited abnormal urine test findings. The researchers found that the incidence of pediatric diabetes increased with increasing fasting plasma glucose levels, and those with FPG > 5.6mmol/L had higher adjusted hazard ratios. Additionally, "the association between fasting plasma glucose and incident pediatric diabetes and the area under the receiver-operating characteristic curve were similar in boys and girls and were higher in the age group 12-18 years." In using 4.75 mmol/L as the optimal threshold for children 6-11 years, the sensitivity was 65% and specificity was 51%. For the threshold of 5.19 mmol/L among children 12-18 years, the sensitivity was 60% and the specificity was 73%. This supports utilizing FPG as a supplement for diagnosing prediabetes among pediatric patients, which may contribute to better disease management.

Geifman-Holtzman et al. (2010) assessed the correlation between fetal macrosomia and abnormal OGTT in pregnant women with term gestation and negative glucose challenge test (GCT) at 24-28 weeks. They recruited patients who had estimated fetal weights >90th percentile and a negative 50g GCT. From 170 women over a five-month period, they found that 10 patients or 5.9% had "impaired glucose metabolism at term." In this group, "we found no correlation between GCT values at 24-28 weeks, family history of diabetes mellitus, the patient's [body mass index] or weight at term, and the diagnosis of impaired glucose metabolism." Furthermore, there was no statistically significant difference in mean fetal weight between those with normal versus abnormal OGTT. This demonstrated the lack of clinical utility of using OGTT at term for predicting the incidence of fetal macrosomia. The researchers suggested utilizing a larger scale study to solidify or contradict these conclusions (Geifman-Holtzman et al., 2010).

Guidelines and Recommendations
The American Diabetes Association
The ADA publishes an extensive guideline encompassing the standards of medical care in diabetes. The 2022 recommendations state:
Screening for and diagnosis of diabetes (Chapter [Ch] 2) (American Diabetes Association Professional Practice, 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)
- 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 35 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.
    - People with HIV
- 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.

A1c
- "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 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 hemoglobinopathies, including 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**"
- "Adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to oral glucose tolerance testing as a screen for diabetes. Grade **A**"

Prediabetes and Type 2 Diabetes
- "Screening for prediabetes and type 2 diabetes with an informal assessment of risk factors or validated risk calculator should be done in asymptomatic adults. Grade **B**"

- "Testing for prediabetes and/ or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) who have one or more risk factors. Grade **B**"
- "For all people screening should begin at age 35 years. Grade **B**"
- "If tests are normal, repeat screening recommended at a minimum of 3-year intervals is reasonable, sooner with symptoms or change in risk (i.e., weight gain). Grade **C**"
- "To screen for prediabetes and type 2 diabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1C are each appropriate. Grade **B**"
- "When using oral glucose tolerance testing as a screen for diabetes, adequate carbohydrate intake (at least 150 g/ day) should be assured for 3 days prior to testing. Grade **A**"
- "In people with prediabetes and type 2 diabetes, identify and treat cardiovascular disease risk factors. Grade **A**"
- "Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more risk factor for diabetes. Grade **B**"
- "People with HIV should be screened for diabetes and prediabetes with a fasting glucose test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and 3-6 months after starting or switching antiretroviral therapy. If initial screening results are normal, fasting glucose should be checked annually. Grade **E**"

Cystic Fibrosis-Related Diabetes
- "Annual screening for cystic fibrosis-related diabetes with an oral glucose tolerance test should begin by age 10 years in all patients with cystic fibrosis not previously diagnosed with cystic fibrosis-related diabetes. 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. Grade **E**"

Gestational Diabetes Mellitus
- "In women who are planning pregnancy, screen those with risk factors (**Grade B**) and consider testing all women with undiagnosed diabetes (**Grade E**).
- "Before 15 weeks of gestation, test women with risk factors **B** and consider testing all women **E** for undiagnosed diabetes at the first prenatal visit using standard diagnostic criteria, if not screened preconception."
- "Before 15 weeks of gestation, screen for abnormal glucose metabolism to identify women who are at higher risk of adverse pregnancy and neonatal outcomes, are more likely to need insulin, and are at high risk of a later gestational diabetes mellitus diagnosis. Grade **B**."
- "Screen for early abnormal glucose metabolism using fasting glucose of 110–125 mg/dL (6.1 mmol/L) or A1C 5.9–6.4% (41–47 mmol/mol). Grade **B**"

- "Screen for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant women not previously found to have diabetes or high-risk abnormal glucose metabolism detected earlier in the current pregnancy. Grade **A**" (American Diabetes Association Professional Practice, 2021a).

On diagnostic tests for diabetes (Ch 2):
"The FPG and 2-h PG may be used to diagnose diabetes. The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose-based test. Compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with prediabetes and diabetes. In people in whom there is discordance between A1C values and glucose values, FPG and 2-h PG are more accurate."

"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. Point-of-care A1c assays may be NGSP certified and cleared by the U.S. Food and Drug Administration (FDA) for use in monitoring glycemic control in people with diabetes in both Clinical Laboratory Improvement Amendments (CLIA)-regulated and CLIA-waived settings. proficiency testing is not always mandated for performing the test. Point-of-care A1C assays have not been prospectively studied for the diagnosis of diabetes and are not recommended for diabetes diagnosis; if used, they should be confirmed with a validated measure. In the U.S., point-of-care A1C is a laboratory test that limits CLIA regulation…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 such as time in range or glucose management indicator) at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control). Grade **E**"
- "Assess glycemic status at least quarterly and as needed in patients whose therapy has recently changed and/or who are not meeting glycemic goals. Grade **E**"
- "An A1c goal for many non-pregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. Grade **A**"
- "On the basis of provider judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. Grade **B**"

- "Less stringent A1C goals (such as <8% [64 mmol/mol] may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. Grade **B**" (American Diabetes Association Professional Practice, 2021b).

<u>Children & Adolescents (Ch 13) (American Diabetes Association Professional Practice, 2021c)</u>
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 diabetes testing 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 screening is 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**"
- 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; American Diabetes Association Professional Practice, 2021c):
  - Criteria: Consider testing in youth "who have [sic] overweight (≥85th percentile) or obesity (≥95th percentile) and who have one or more additional risk factors for diabetes:
    - 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 blood glucose monitoring."
- "Fasting and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and preexisting diabetes in pregnancy to achieve optimal glucose levels. Glucose targets are fasting plasma glucose <95 mg/dL (5.3 mmol/L) and either 1-h postprandial glucose <140 mg/dL (7.8 mmol/L) or 2-h postprandial glucose

<120 mg/dL (6.7 mmol/L). Some women with preexisting diabetes should also test blood glucose preprandially. Grade **B**"

- "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. Grade **B"**
- "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 often represents previously undiagnosed prediabetes, type 2 diabetes, maturity-onset diabetes of the young, or even developing type 1 diabetes, women with GDM should be tested for persistent diabetes or prediabetes at 4–12 weeks postpartum with a fasting 75-g OGTT using nonpregnancy criteria as outlined in Section 2, "Classification and Diagnosis of Diabetes"."
- "In the absence of unequivocal hyperglycemia, a positive screen for diabetes requires two abnormal values. If both the fasting plasma glucose (≥126 mg/dL [7.0 mmol/L]) and 2-h plasma glucose (≥200 mg/dL [11.1 mmol/L]) are abnormal in a single screening test, then the diagnosis of diabetes is made. If only one abnormal value in the OGTT meets diabetes criteria, the test should be repeated to confirm that the abnormality persists."
- "Because GDM is associated with an increased lifetime maternal risk for diabetes estimated at 50–60%, [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)." (American Diabetes Association Professional Practice, 2021d).

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). The USPSTF has also provided guidelines pertaining to the screening of gestational diabetes. For asymptomatic pregnant persons at 24 weeks gestation or after, with a letter "B" grade, the USPSTF recommends screening for gestational diabetes in this population. However, in asymptomatic pregnant persons before 24 weeks gestation, the USPSTF states that "current evidence is insufficient to assess the balance of benefits and harms of screening" and has given it an "I" grade (USPSTF, 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 (NACB)
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)
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).

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)

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 (AACE)
The AACE provides the following inclusion criteria for individuals who should be screened for prediabetes or type 2 diabetes:
- Age ≥45 years without other risk factors
- CVD or family history of T2D
- Overweight or obese
- Sedentary lifestyle
- Member of an at-risk racial or ethnic group:
    o Asian
    o African American
    o Hispanic
    o Native American (Alaska Natives and American Indians)
    o Pacific Islander
- High-density lipoprotein cholesterol (HDL-C) <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
- Impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and/or metabolic syndrome
- Polycystic ovary syndrome (PCOS), acanthosis nigricans, or nonalcoholic fatty liver disease (NAFLD)
- Hypertension (blood pressure >140/90 mm Hg or on antihypertensive therapy)
- History of gestational diabetes or delivery of a baby weighing more than 4 kg (9 lb)
- Antipsychotic therapy for schizophrenia and/or severe bipolar disease
- Chronic glucocorticoid exposure

- Sleep disorders in the presence of glucose intolerance (A1C >5.7%, IGT, or IFG on previous testing), including obstructive sleep apnea (OSA), chronic sleep deprivation, and night-shift occupation

The AACE recommends repeat testing at least every 3 years for individuals with normal results. Consider annual screening for patients with 2 or more risk factors.

In a 2022 update focusing on developing a diabetes mellitus comprehensive care plan, the AACE expounds on how the diagnosis of diabetes mellitus should be made. According to the authors, the ELs refer to evidence levels established by AACE evidence ratings, where "descriptors of "must," "should," and "may" generally but not strictly correlate with Grade A (strong), Grade B (intermediate), and Grade C (weak) recommendations, respectively" (Blonde et al., 2022). The relevant recommendations are captured below.

"*Recommendation 1.1*
The diagnosis of DM is based on the following criteria…:
- FPG concentration ≥126 mg/dL (after ≥8 hours of an overnight fast), or
- Plasma glucose (PG) concentration ≥200 mg/dL 2 hours after ingesting a 75-g oral glucose load after an overnight fast of at least 8 hours, or
- Symptoms of hyperglycemia (eg, polyuria, polydipsia, polyphagia) and a random (nonfasting) PG concentration ≥200 mg/dL, or
- A1C level ≥6.5%

Diagnosis of DM requires 2 abnormal test results, either from the same sample or 2 abnormal results on samples drawn on different days. However, a glucose level ≥200 mg/dL in the presence of symptoms for DM confirms the diagnosis of DM.
Grade A; BEL 2 and expert opinion of task force

Recommendation 1.2
Prediabetes is identified by the presence of impaired fasting glucose (IFG) (100 to 125 mg/dL), impaired glucose tolerance (IGT), which is a PG value of 140 to 199 mg/dL 2 hours after ingesting 75 g of glucose, and/or A1C value between 5.7% and 6.4% (Table 4). A1C should be used only for screening for prediabetes. The diagnosis of prediabetes, which may manifest as either IFG or IGT, should be confirmed with glucose testing.
Grade B; BEL 2

Recommendation 1.3
T1D is characterized by marked insulin deficiency in the presence of hyperglycemia and positive autoantibody tests to glutamic acid decarboxylase (GAD65), pancreatic islet β cells (tyrosine phosphatase IA-2), and IA-2b zinc transporter (ZnT8), and/or insulin. The presence of immune markers and clinical presentation are needed to establish the correct diagnosis and to distinguish between T1D and T2D in children or adults, as well as to determine appropriate treatment.
Grade A; BEL 2

Recommendation 1.4
T2D is characterized by progressive loss of β-cell insulin secretion and variable defects in insulin sensitivity. T2D is often asymptomatic and can remain undiagnosed for many years; therefore, all adults ≥35 years of age with risk factors should be screened for DM (Table 5).
Grade A; BEL 1

Recommendation 1.5
GDM is defined as carbohydrate intolerance that begins or is first recognized during pregnancy and resolves postpartum. Pregnant women with risk factors for DM should be screened at the first prenatal visit for undiagnosed T2D using standard criteria (Table 4).
Grade B; BEL 1

Recommendation 1.6
Screen all pregnant women for GDM at 24 to 28 weeks' gestation. Diagnose GDM with either the one-step or the two-step approach.
- The one-step approach uses a 2-hour 75-g oral glucose tolerance test (OGTT) after ≥8 hours of fasting with diagnostic cutoffs of one or more FPG ≥92 mg/dL, 1-hour PG ≥180 mg/dL, or 2-hour PG ≥153 mg/dL.
- The two-step approach uses a nonfasting 1-hour 50-g glucose challenge test with 1-hour PG screening threshold of 130 or 140 mg/dL. For women with a positive screening test, the 3-hour 100-g OGTT is used for diagnosis with 2 or more PG tests that meet the following thresholds: FPG ≥95 mg/dL, 1-hour ≥180 mg/dL, 2-hour ≥155 mg/dL, 3-hour ≥140 mg/dL.

Grade A; BEL 1

Recommendation 1.7
Clinicians should consider evaluation for monogenic DM in any child or young adult with an atypical presentation, clinical course, or response to therapy. Monogenic DM includes neonatal diabetes and nonautoimmune diabetes of multiple genetic causes, also known as maturity-onset diabetes of the young (MODY). Most children with DM occurring under age 6 months of age have a monogenic cause as autoimmune T1D rarely occurs before 6 months of age. Other monogenic forms of diabetes are characterized by mutation of genes of transcription factors, genes regulating pancreatic development or atrophy, abnormal insulin genes, genes related to endoplasmic reticulum stress that impair insulin secretion, or abnormal glucokinase genes that cause impaired insulin signaling.
Grade B; BEL 2

Although not expressly listed as recommendations for diabetes screening, some additional information of note is that:
"A glucose level ≥200 mg/dL in the presence of hyperglycemia symptoms such as polyuria and polydipsia confirm the diagnosis of DM. In individuals with discordant results from 2 different tests, the test result that is above the diagnostic cut point should be repeated on a different day."

"In view of physiological changes in pregnancy that could affect glycated hemoglobin levels, A1C should not be used for GDM screening or diagnosis of DM."

"All pregnant women should be screened for GDM at 24 to 28 weeks' gestation. Universal screening is recommended, as selective screening (only in women with risk factors) would miss a significant number of women with GDM and universal screening has been shown to be cost-effective compared with selective screening" (Blonde et al., 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., 2020).

Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Working Group
The KDIGO group 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" (Rossing et al., 2022).

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	82951, 82952, 82985, 83036, 83037
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) may or may not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision	
Date	Description of Change
04/01/2024	New medical document. Diabetes mellitus testing may be considered medically necessary when criteria listed in Coverage are met.